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Exposure of pregnant consumers to suspected endocrine disruptors -summary

In daily life, humans are exposed to chemical substances from various sources such as food, medical products, indoor environment, cosmetics and other consumer products surrounding us at home, in connection with hobbies, and at work. Among the thousands of chemical substances one could possibly be exposed to in daily life, some have been shown to act as endocrine disruptors in laboratory animals. These substances are also suspected of being endocrine disruptors in humans and to contribute to e.g. cryptorchidism (undescended testicles to scrotum) or hypospadias (birth defect of the penis) in baby boys, premature puberty in girls and low semen quality, increased occurrence of testicular cancer and reduced levels of the male sex hormones in men.

In this project the exposure of women in the child-bearing age to a number of selected suspected endocrine disrupters was investigated. Some of the most sensitive periods of human life are the fetal stage and childhood, because the human being and its organs during these stages undergo a significant development which requires a balance in the hormonal systems involved in regulating the various stages of the development. The pregnant woman was in focus in this project, because her exposure to suspected endocrine disruptors can give an impression of what her fetus may be exposed to in sensitive stages of its development. Women who wish to become pregnant are included in the target group for the subsequent information campaign, because they are typically pregnant two weeks before they know it, and because some suspected endocrine disruptors accumulate in the body and are only excreted very slowly. Exposure even a long time before pregnancy may therefore have an impact on the exposure of the fetus.

The project forms the basis for an information campaign which includes the conclusions of the report and gives advice to pregnant women and women who want to become pregnant.

A number of chemical substances suspected of being endocrine disruptors were selected. The endocrine disrupting effects included are antiandrogenic (reduce production of or block effects of male sex hormones), estrogenic (affects the balance of female sex hormone) and/or thyroid disrupting (disrupts the balance or effects of the thyroid gland's hormones).

The criteria for including a substance in the project were as follows:

- substances from group 1 and group 2a according to the criteria for identification of endocrine disruptors made by the Danish Centre for Endocrine Disruptors (CEHOS) for The Danish EPA (Danish EPA 2011),
- substances, where the endocrine disrupting effect is related to an antiandrogenic, estrogenic or thyroid hormone disrupting mode of action,

- substances, for which there is sufficient knowledge in animal studies to calculate the doses of the substance, which may be assumed to be safe for humans (with regard to the specific endocrine effect),
- substances expected to be present in products commonly used by the pregnant women,
- substances expected to contribute with a significant exposure,
- finally, it was considered that the selected substances should cover several different product groups and several different materials within the selected exposure situations/activities

The focus is thus on substances with antiandrogenic, estrogenic and thyroid disrupting mode of action. It should be noted that some substances have multiple modes of actions and that it is not always possible to categorise, whether, for example, changes in the reproductive system are due to an antiandrogenic or estrogenic mode of action.

The **Selected substances** are:

Substance name (CAS No.)	**Antiandro-genic**	**Estrogenic**	**thyroid disrupting**
Phthalates			
DEHP (di-ethyl-hexyl-phthalate) (117-81-7)	X		X
DiNP (di-iso-nonyl-phthalate) (28553-12-0)	X		
DBP (di-butyl-phthalate) (84-74-2)	X		
DiBP (di-iso-butyl-phthalate) (84-69-5)	X		
BBP (butyl-benzyl-phthalate) (85-68-7)	X		
DPP (dipentyl phthalate) (131-18-0)	X		
DnHP (di-n-hexyl phthalate) (84-75-3)	X		X
DnOP (Di-n-octyl phthalate) (117-84-0)	X		X
Other environmentally hazardous chemical substances			
Dioxin and dioxin-like PCBs	X		X
Bisphenol A (80-05-7)		X	
Nonylphenol (25154-52-3)		X	
TBBPA (Tetrabromobisphenol A) (79-94-7)		X	X
Perfluorooctanoate (PFOA) (335-67-1)	X		X
Perfluorooctane sulfonate (PFOS) (1763-23-1)	X		X
Octamethylcyclotetrasiloxane (D4) (556-67-2)		X	
Substances in cosmetic products			
Propylparaben (94-13-3)		X	
Butylparaben (94-26-8)		X	
Isobutylparaben (4247-02-3)		X	
Octyl methoxycinnamate, 2-ethylhexyl-4-methoxycinnamate (OMC) (5466-77-3)		X	X
3-Benzylidene camphor (3-BC) (15087-24-8)		X	
4-Methylbenzylidene camphor (4-MBC) (36861-47-9)		X	
Benzophenone 3 (BC-3) (131-57-7)		X	
Triclosan (3380-34-5)		X	X
Resorcinol (108-46-3)			X
Pesticides			
Chlorpyrifos (2921-88-2)	X		X
Dithiocarbamates: - Mancozeb (8018-01-7) - Maneb (12427-38-2) - Propineb (12071-83-9)	X		X
Imazalil (35554-44-0)	X		
Iprodione (36734-19-7)	X		
Pirimiphos-methyl (29232-93-7)	X		
Procymidon(32809-16-8)	X		
Propamocarb (24579-73-5)		X	
Tebuconazole (107534-96-3)	X		
Thiabendazole (148-79-8)	X		X

The selection of the 35 substances reflects the knowledge available today. There are many other substances under suspicion of being endocrine disruptors. There are for instance almost 200 substances in category 1 on the EU list of potential endocrine disruptors, but many have not been included in this project. The reason may be that the exposure of pregnant women is expected to be very small or not occuring, that data available for risk assessment are inadequate or that the substance is part of a group of substances, represented by some of the selected substances. Furthermore, only a small part of the approximately 50.000 chemical substances, which surround us in daily life, are tested for endocrine disrupting effects. Consequently it cannot be ruled out that several other substances, which pregnant women are exposed to in daily life, may contribute to the risk of endocrine disrupting effects.

Based upon knowledge from previously completed surveys of consumer products from the Danish EPA, as well as a behaviour analysis focussing on the target group's use of consumer products, which might contain substances from above the table, new product groups were chosen for survey and analysis. A total of 8 product groups were included in this survey: cell phone covers, sleeping mats, work gloves, hand bags made of synthetic leather, sneakers, antibacterially treated clothes, moisturisers for full body/pregnant belly creams and sunscreens.
The survey gave insight into the number of products within the 8 product groups, types of material used in the product groups and for cosmetics the content of the selected substances. Within these 8 groups, products were selected for quantitative analyses of a number of the selected substances depending on the type of material of the product. For certain products in the different groups also migration analyses were performed.

The quantitative analyses gave the following results:

Phthalates were identified by analysing the content in the following product groups (the number between brackets indicates the number of products with detected content of the substance in question):

- 20 cell phone covers tested (DEHP in 5 products, DiNP in 1 product)
- 11 work gloves tested (DEHP in 1 product, DiNP in 2 products)
- 10 sleeping mats tested (DEHP in 1 product)
- 9 sneakers tested (DEHP in 1 product)
- 10 handbags tested (DEHP in 2 products, DBP in 1 product)

Chemical analyses identified traces of bisphenol A (i.e. concentrations under quantification limit) in 6 cell phone covers made of polycarbonate plastic, also known as PC.

The content of triclosan and nonylphenol were analysed in antibacterial clothes and sneakers. No triclosan or nonylphenol were identified in the analyses (including nonylphenolethoxylates with up to approx. 4 ethoxylate units in the chain).

The content of octamethylcyclotetrasiloxane (D4) was analysed in cell phone covers, work gloves, sneakers, antibacterial clothes and cosmetic products. The substance was only identified in cosmetic products. In 10 out of 15 cosmetic products a content of D4 above the detection limit was identified.

Migration tests with sweat simulators were performed. None of the phthalates DEHP or DiNP, or bisphenol A migrated out of the products under the conditions used – not even in trace amounts. Migration analyses were not performed for

triclosan and nonylphenol/nonylphenolethoxylates, as the quantitative analyses did not find any content of these substances. Migration analyses were not performed for D4, as no products apart from cosmetic products contained D4. For the cosmetic products a migration analysis is irrelevant, as the products are applied directly onto the skin. A dermal absorption factor is used instead in the subsequent exposure assessement, to estimate the amount of D4 expected to be absorbed through the skin.

A **hazard assessment** of the selected chemical substances was performed in order to determine the no or lowest adverse effect levels (NOAELs or LOAELs) of the substances based on their endocrine disrupting effect in laboratory animals. These were used both to assess the risk from exposure to each substance, and to calculate the combined risk from exposure to a group of substances with the same mode of action.

The **exposure** of pregnant women to the selected substances was assessed using a basis scenario, and with different other inputs to exposure such as a holiday scenario and a work scenario. The scenarios were divided into a medium and a maximum exposure respectively, with the approach that the exposure is evened out over a week's exposure, as the project assesses exposure for pregnant women. In the pregnancy period it is important to focus on a very short exposure period because of the several short critical windows of exposure, where the fetus is very vulnerable to endocrine disrupting effects, as shown in animal studies.
Medium exposure describes a situation, which many in the target group is expected to experience, i.e. a **realistic scenario**, whereas the maximum exposure describes a situation expected to be experienced by fewer in the target group, i.e. a **realistic worst case scenario**.

The starting point has been the available information and an estimate of which products a pregnant woman is expected to use during a week. A lot of women may use the products in other ways than described here, but the assumptions are made to be able to calculate an estimated exposure. Even though some of the assumptions in the scenarios may not cover all the women in the target group, it should be kept in mind that other women in the target group may also use other products not included here, but which may contain the selected substances and thereby add to the total exposure.

The **basis scenario** includes exposure to food, indoor environment and the activities normally practiced in daily life and includes contributions from toothbrushing, footwear/clothing, use of cream (including pregnant belly cream and body lotions), sex toys, bath soaps, bath mats etc. as well as sport, leisure and shopping. The exposure assessments are based on available data, i.e. for the consumer products, contributions from products with available migration data are included (e.g. oilcloth, pilates ball, rucksack, bath soap packaging and plastic sandal). Consequently, the exposures do not cover the contribution from all consumer products, which the target group is expected to be in contact with in daily life.

Apart from the basis scenario, an exposure in connection to a **holiday scenario** is estimated, where mainly the contribution from sunscreens is included in the assessment, a **work scenario**, where a risk of exposure from a few consumer products, such as hand cream and plastic sandals used by health staff and cashiers in work scenarios, is estimated. Also a risk from indoor environment in cars is estimated in a **transport scenario**.

Risk assessments of each of the selected substances showed that dioxins and dioxin-like PCBs (from foodstuff and dust), propyl- and butylparabens (from cream/sunscreen), OMC (from sunscreen), triclosan (from deodorant and toothpaste), nonylphenol (clothes) and phthalates (from various consumer products and dust) are the substances/substance groups with the highest contributions to exposure and the highest risk characterisation ratios (RCR). RCR describes the ratio between exposure and ”safe dose levels” with regard to endocrine disrupting effect of a substance. The higher the RCR, the higher the risk is assumed to be. In this project the total RCR values for substances with the same mode of action are also calculated. RCR values above 1 are interpreted as an indication that a risk of endocrine disrupting effects may occur at the estimated exposure levels, i.e. that the risk is not controlled, and that there is a need for a detailed assessment of whether the risk applies for a considerable part of the target group, and whether the exposure to the relevant substances can be limited.

Propyl- and butylparaben contribute considerably to the total RCR for estrogenic effects due to the use of sunscreens with parabens. Other products which are also used on a large surface area, such as for example body lotions, contribute considerably as well. The calculated RCR values are based on conservative estimates for no effect levels of propyl- and butylparabens, but even use of less conservative estimates for no effect levels lead to high RCR values at the estimated exposures to propyl- and butylparaben in the realistic worst case holiday scenario. The group of pesticides only contributes minimally to the RCR at the estimated exposure levels. It cannot be determined in this project if exposure to bisphenol A in food or products may cause endocrine disrupting effects in humans.

Normally a risk assessment is based upon an estimate of exposure from a single substance from a single product. However, we are exposed to many different products on a daily basis, of which several contain the same chemical substances, and thereby the same toxicological effect. This has been taken into account in this project by performing cumulative risk assessments and thereby including **combination effects** of the substances.

In this project, for all three effect types (antiandrogenic, estrogenic and thyroid disrupting effect), combined RCR values are between 0.5 and 0.8 for medium exposure in the basis scenario. For maximum exposure in the basis scenario, combined RCR values are between 1.4 and 3.1. In the holiday scenario the use of sunscreen containing propyl- and butylparabens contributes considerably to the combined RCR value for estrogenic effects. The combined RCR for propyl- and butylparabens alone is above 1 (1.1) at medium exposure in this scenario. Risk assessment of use of consumer products in work scenarios showed that e.g. use of extra hand cream containing propyl- and butylparabens during a work day will contribute to the RCR for estrogenic effects. Only an insignificant contribution was determined from indoor environment in cars.

Since it is realistic to also be exposed to food and other sources from the basis scenario during a holiday, the combined values for holiday+basis scenarios were also calculated. This resulted in an RCR above 1 for both antiandrogenic and estrogenic effects at medium exposure. For the combined values for basis+work+transport, RCR values below 1 were observed at medium exposure.

	Medium Exposure						Maximum Esposure					
Effect	RCR_{BASIS}	$RCR_{HOLIDAY}$	RCR_{WORK}	RCR TRANSPORT	$RCR_{BASIS+HOLIDAY}$	$RCR_{BASIS+WORK+TRANSPORT}$	RCR_{BASIS}	$RCR_{HOLIDAY}$	RCR_{WORK}	RCR TRANSPORT	$RCR_{BASIS+HOLIDAY}$	$RCR_{BASIS+WORK+TRANSPORT}$
Anti-androgen	0.72	0.56	0.08	<0.00	1.28	0.80	2.23	1.12	0.15	<0.00	3.35	2.39
Estrogen	0.76	1.41	0.21	0	2.17	0.97	3.10	9.96	0.81	0	13.04	3.88
Thyroid	0.47	0.36	<0.0	<0.00	0.84	0.48	1.43	1.33	<0.00	<0.00	2.76	1.43

All in all this indicates that an increased risk of endocrine disrupting effects may exist for women, who because of their consumption pattern are in contact with many suspected endocrine disruptors at the same time. It appears to be of major importance that a cumulative risk assessment is made instead of a risk assessment for each single substance. It is clearly the combined contribution from the various substance groups that leads to RCR values above 1 at maximum exposure in the basis scenario, since the RCR for each individual substance is below 1. The only exception from this is that the RCR for dioxin and dioxin-like PCBs, at maximum exposure in the basis scenario is 1.1.

The estimated exposure levels from the consumer products, food and indoor environment are compared with actual measured concentrations of the substances, as observed in a **biomonitoring study**, measuring some of the substances in urine samples from Danish pregnant women. Neither the estimated nor the measured exposure levels constitute a complete picture of which exposure levels the individuals experience. For the estimated exposures this is due to the fact that not all exposure sources are known and included. For the biomonitoring study there are both big individual differences in exposure levels and big differences in exposure between different days for the same individual. Therefore also the levels that are observed in the biomonitoring study differ remarkably between individuals. Since only a certain number of women are included in the biomonitoring study, it cannot be ruled out that other levels may be observed in other pregnant women who did not participate in the study.
The estimated exposures and the biomonitoring study, however, give a combined picture of the exposure that at least some individuals experience. For several of the specific substances included in this project, there is coherence between the exposure levels found in the realistic worst case estimations (maximum exposure) and the highest levels measured in the urine samples. The substances, (DEHP, DBP, propylparaben and triclosan), which in the project contribute the most to the combined RCR, are also the substances, which in the biomonitoring study correspond best to the estimated realistic worst case exposure levels.

All in all it can be concluded that for some pregnant women there is a need to reduce the exposure to suspected endocrine disruptors. Substances with antiandrogenic, estrogenic and thyroid disrupting effects may increase the risk of endocrine disrupting effects for the group of pregnant women, who are exposed to high levels of the substances from food, indoor environment and consumer products. Based on the estimated exposures to suspected endocrine disruptors included in this project, it seems that the majority of pregnant women are not exposed to endocrine disrupting chemicals at levels that lead to immediate concerns. However, several sources of suspected endocrine disruptors are not included in the risk assessment of this project, such as e.g. phytoestrogens in food,

medical products and food supplements. Furthermore, there is still a high level of uncertainty as to which substances are endocrine disruptors and how are we exposed to them. Consequently, it cannot be ruled out that several other substances, to which pregnant women are exposed in daily life, may contribute further to the risk of endocrine disrupting effects. It is not possible to avoid all exposures to endocrine disruptors (e.g. exposure to dioxins and dioxin-like PCBs in food), but for certain substance groups it is possible to limit the exposure, for example by avoiding propyl- and butylparabens in cream and sunscreens, OMC in sunscreens, triclosan in deodorant and toothpaste, nonylphenol by washing new clothes and phthalates in various consumer product as well as in dust.