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# Tidstrend 1996-2011: Bisfenol A (BPA) och andra fenolära ämnen i blod från förstföderskor i Uppsala


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**Sammanfattning**

Under perioden 1996 till 2011 har Livsmedelsverket samlat in blodserum från förstföderskor i Uppsala län. Ett av syftena med studierna är att undersöka hur halterna av vissa persistenta organiska miljögifter (POP) förändras med tiden. I denna rapport utvärderas blodserumnivåer för fem fenolära ämnen, bisfenol A (BPA), bisfenol S (BPS), bisfenol F (BPF), 4-nonylfenol (4-NP) och bensofenon-3 (BP-3).

Den fria formen av ämnena analyserades med hjälp av UPLC-MS/MS.

Resultaten tyder på att halterna av alla dessa ämnen är låga och ligger under kvantifieringsgränsen (LOQ = 0,1 ng/ml). Nivåer av fritt BPA som uppmättes i vissa prover kommer troligtvis från kontamination under provhanteringens gång och inte från faktiska nivåer i blodet. Slutsatsen är att halterna av fritt BPA, BPS, BPF, 4-NP och BP-3 har varit låga hos ammande kvinnor från Uppsala-regionen mellan åren 1996-2011. Studien antyder att det är tveksamt att använda biobankade blodprover för analys av BPA-exponering i befolkningen, om inte provtagning och provhantering genomförts på ett sätt som gör att BPA-kontamination av proverna kan uteslutas.

# INTRODUCTION

In this study the temporal trends of blood serum levels of bisphenol A (BPA) and four other phenolic compounds: bisphenol S (BPS), bisphenol F (BPF), 4-nonylphenol (4-NP), and benzophenone-3 (BP-3) were investigated among nursing women in the County of Uppsala. Even if a few studies have previously been published, the human exposure of these substances is not well known.

BPA is a phenolic substance used in high volumes by the industry. BPA is used mainly in the production of polycarbonate plastics, epoxy resins and thermo plastics, and is found in for example food and beverage containers, glues, materials for floor covering, varnishes and paints. BPA has been shown to leach from these materials due to incomplete polymerization and to degradation of the polymers by exposure to high temperatures, occurring under normal conditions of use (Biles et al., 1997). A certain type of BPA-containing varnish is used as a protective barrier on the inside of food tin cans (Chapin et al., 2008). Toxicological studies on cells and in experimental animals have shown that BPA act as hormone disrupter. BPA is estrogenic and affect the reproductive system in animals after exposure to high doses (Maffini et al., 2006). Some animal studies of BPA indicate that negative health effects occur even at very low doses (vom Saal and Hughes, 2005). These low-dose effects of BPA have however been questioned (Chapin et al., 2008; Hengstler et al., 2011; Myers et al., 2009).

BPS and BPF are BPA analogues and these compounds can be used to replace BPA in commercial products (Danzl et al., 2009; KEMI, 2012; Liao et al., 2012a). BPS and BPF have, similar to BPA, shown estrogenic activity *in vitro* (Hashimoto and Nakamura, 2000; Chen et al., 2002). Studies of these two analogues are not as frequent as BPA and information about both exposure and possible effects are scarce. Nonylphenol (NP) and BP-3 are two other phenolic compounds showing weak estrogenic activity both *in vitro* and *in vivo* (ECB, 2002; Suzuki et al., 2005; Krause et al., 2012). BP-3 has also shown antiandrogenic activity *in vitro* (Ma et al., 2003; Schreurs et al., 2005). NP is mainly used as a raw material for the production of plastics and of surface-active substances, so called nonylphenol-ethoxylates. The NP-ethoxylates can relatively easy degrade back to NP (Soares et al., 2008). BP-3 is a sunscreen agent commonly used in cosmetics and is also in plastic surface coatings for food packaging (Suzuki et al., 2005; Gonzalez et al., 2006).

BPA has been analysed in blood serum in populations from around the world with median levels below the limit of quantification (LOQ) to 2 ng/ml and with large variations between participants and studies (Dekant and Völkel, 2008; Mielke and Gundert-Remy, 2009; Vandenberg et al., 2010). Most studies have analysed total BPA, both conjugated and free BPA, which includes an deconjugation step in the analysis. In a study from the County of Uppsala, Sweden, serum BPA levels were analysed in serum from 1016 individuals at the age of 70, showing a median concentration of  total BPA of 3.76 ng/ml

(interquartile range: 2.02-6.52) (Lind and Lind, 2011). Much lower median levels of free and total BPA were detected among nursing women from Uppsala County, where respectively 25 % and 22 %, had levels over the limit of detection (LOD) of 0.5 ng free BPA/g serum and 0.8 ng total BPA/g serum (Gyllenhammar et al., 2012). These exposure studies indicate that humans are constantly exposed to BPA as the half life of BPA in humans is very short, just a few hours in blood (Volkel et al., 2002).

For 4-NP, BPS, BPF, and BP-3 to our knowledge no studies of levels in blood serum excist. 4-NP was found in 51 % of urine samples from 394 adult americans, with the limit of detection (LOD) 0.1 ng/ml (Calafat et al., 2005). Total BPS (free and conjugated) was analyzed in urine from 315 individuals from the United States and seven Asian countries. BPS was detected in 81% of the samples at concentrations ranging from below the limit of quantitation (LOQ; 0.02 ng/mL) to 21 ng/mL (geometric mean: 0.168 ng/mL) (Liao et al., 2012b). BP-3 was detected in 97 % of 2 517 urine samples from americans, with LOD 0.34 ng/ml (Calafat et al., 2008).

The overall aim of the present study was to investigate temporal trends of BPA, BPS, BPF, 4-NP and BP-3 in serum från nursing women in Uppsala. Also individual serum samples of BPA were evaluated in order to ascertain the results of the temporal trend study. Another aim was to investigate possible contamination risks of BPA from blood sampling equipment and the tubes used for storage.

## MATERIAL AND METHODS

**Recruitment of primiparas**
Serum was sampled from primipara women. From 1996-1999, 395 pregnant women, having their first child, and living and seeking prenatal care in Uppsala County, Sweden, were asked to participate in a study of environmental pollutant exposure during pregnancy. The women participated as controls in a case-control study of risk factors for early miscarriages. All women were Swedish speaking and had completed 6-12 weeks of pregnancy when entering the study. After delivery, 211 women (53%) donated a blood sample 3 weeks after delivery. From year 2000, primiparous mothers were randomly recruited every second year and from 2007-2011 every year, among women who delivered at Uppsala University Hospital. They were asked within a few days after giving birth to donate a blood sample 3 weeks after delivery. At each sampling period 30-32 women (46-63% of all women who were asked) participated in the study.

**Blood serum sampling**
A midwife visited the women in their homes three weeks after delivery and a blood sample was taken for chemical analysis. The samples were centrifuged for separation of serum. The serum samples were aliquoted and frozen immediately

in acetone-washed glass tubes at -20 °C. For the temporal trend study, serum samples were pooled by thawing one aliquot from each participating woman and pipetting a fixed volume of serum into a new aceton-washed glass tube. Three pooled samples from each year were produced. Each pool contained serum from 5-25 individuals. The pooled samples were stored at -20 °C before analyses. Individual samples from 208 women sampled between 1996 and 2008 were also analyzed. The individual serum samples had been aliquoted and stored at -20 °C and -70°C at the time of sampling.

**Tests of sampling equipment**
Possible contamination risks of BPA from the blood sampling equipment and the tubes were evaluated using a single batch of serum with non-detectable BPA levels, purchased from Uppsala University Hospital. Untreated serum was compared with serum that had gone through the whole process from blood sampling to storage in -20°C and -70°C. Ten samples were taken using BD PrecisionGlide™ needles (BD Medical Surgical Systems), the needles used for the women in the present study. Another ten samples were made using BD Valu-Set™ winged infusion needle set, which is the needle used for sampling of some of the first-born children at 3 weeks and 3 months of age. VACUETTE® blood collection tubes (greiner-bio-one) were used with both needle types. Samples were left in room temperature in about 30 min and thereafter centrifuged at 1320 g in 15 min. One aliquot of the serum were put into a glass tube and stored at -20 °C and another aliquot were placed in a cryotube and stored at -70 °C. After one week all 40 samples were analyzed together with ten blank samples and three spiked samples at 0.1 ng BPA/ml and three at 0.5 ng BPA/ml.

In order to test equipment for repeated sampling from the same individual, blood samples were taken using BD Venflon™ intravenous cannula (BD Medical Surgical Systems) from two individuals. This cannula has a tap that enables taking repeated blood samples. The samples followed the same procedure as described above. Three samples were taken in separate VACUETTE® blood collection tubes immediately after each other from each person. Serum samples were stored at -20 °C.

**Analysis**
The phenolic substances were analyzed using a UPLC-MS/MS system. In order to precipitate proteins 200 µl serum was diluted in 1200 µl acetonitrile. All samples contained internal standards BPA-D16 and 4-NP-D4. The samples were centrifuged for 10 min at 1320 g and 1 ml of the supernatant was transferred into glass tubes and evaporated for 1 h in a SpeedVac Concentrator SPD2010 (Thermo Scientific). Thereafter 1 ml of 20% methanol in water was put into the tubes. After vortexing, the whole sample was transferred to vials and analysed using UPLC-MS/MS (Waters, Xevo TQ-S) with an Acquity UPLC BEH (C18, 1.7µm id, 2.1x50mm) column. In order to prevent contamination of BPA from the mobile phases an Acquity UPLC BEH (C18, 1.7µm id, 3.0x30mm) column was also used and placed before the injection site in the UPLC. Matrix matched

standard curves, with analyte concentrations in the range 0.1-10 ng/ml serum, were used for quantification. Peak areas relative to internal standard were used for quantifications of BPA and 4-NP, for which deuterium labeled standards were available, while absolute peak areas were used for BPS, BPF and BP-3. NPs are a group of chemicals with different isomers and in this study only the straight chained 4-NP was analyzed, which is also named 4n-NP. The method performance and quality control data for determination of BPA, BPS, BPF, 4-NP, and BP-3 in blood serum are presented in Table 1. LOQ was set to 0.1 ng/ml for all substances.

**Table 1.** Method performance and quality control data for determination of BPA, BPS, BPF, 4-NP and BP-3 in blood serum.

*a) Intra-batch*

| Analyte | Spiked conc. ng/ml | n | Mean ±SD ng/ml | CV % | Recovery % |
|---|---|---|---|---|---|
| BPA | 0.1 | 6 | 0.10 ±0.13 | 123 | 105 |
| | 0.2 | 6 | 0.19 ±0.05 | 24 | 97 |
| | 5 | 6 | 6.02 ±0.62 | 10 | 120 |
| BPS | 0.1 | 6 | 0.10 ±0.02 | 16 | 97 |
| | 0.2 | 6 | 0.21 ±0.04 | 21 | 105 |
| | 5 | 6 | 5.06 ±0.67 | 13 | 101 |
| BPF | 0.1 | 6 | 0.09 ±0.07 | 84 | 89 |
| | 0.2 | 6 | 0.14 ±0.08 | 59 | 71 |
| | 5 | 6 | 2.99 ±1.41 | 47 | 60 |
| 4-NP | 0.1 | 6 | 0.10 ±0.03 | 33 | 101 |
| | 0.2 | 6 | 0.18 ±0.02 | 12 | 90 |
| | 5 | 6 | 5.13 ±0.28 | 6 | 103 |
| BP-3 | 0.1 | 6 | 0.09 ±0.01 | 15 | 91 |
| | 0.2 | 6 | 0.24 ±0.14 | 58 | 122 |
| | 5 | 6 | 4.23 ±0.54 | 13 | 85 |

*b) Inter-batch*

| Analyte | Spiked conc. ng/ml | n | Mean ±SD ng/ml | CV % | Recovery % |
|---|---|---|---|---|---|
| BPA | 0.4 | 28 | 0.33 ±0.07 | 23 | 82 |
| BPS | 0.4 | 28 | 0.44 ±0.12 | 27 | 109 |
| BPF | 0.4 | 28 | 0.41 ±0.10 | 25 | 102 |
| 4-NP | 0.4 | 28 | 0.43 ±0.06 | 14 | 108 |
| BP-3 | 0.4 | 28 | 0.38 ±0.17 | 44 | 95 |

# RESULTS

## Temporal trends

The results from the pooled serum samples between 1996-2011 showed BPA-concentrations from <0.1 to 1.1 ng/ml (median <0.1 ng/ml) after reanalysis of all samples from the same aliquots. No clear temporal trend could be distinguished. In total 13 out of 39 samples (33 %) had levels >LOQ at both analyses and 5 samples (13 %) had levels >LOQ only at the first or the second analysis. For BPS, BPF, 4-NP and BP-3 no trends were seen between 1996 and 2011 as almost all samples (97 %) were below LOQ.

## Contamination risk of BPA

The contamination risk during sample handling was estimated to about 10 % in our laboratory. In total over 200 BPA spiked calibration samples were analyzed and 11 % were shown to be considerably higher than could be explained by the random error of the method, having residuals of more than 75 % in relation to the regression line of the standard curve. At the same time, none of the spiked samples gave a notably low of false negative result. Therefore, these occasional very high results were considered to be outliers caused by exogenous BPA contamination. As a consequence we enlarged the standard curve to include three replicates in the lower part of the concentration interval and repeated analyzes when levels were >LOQ. The blood sampling equipment and the tubes that were used when sampling the women and storing the samples have been tested and were shown not leaking BPA (Fig. 1).

## BPA in individual samples

Among the 208 individual samples 16 % had BPA-levels above LOQ (0.1 ng BPA/g serum). In order to check the repeatability of the results in cases of BPA levels >LOQ, 16 samples were taken from the same serum aliquot as the first sample and were reanalyzed. None of the samples had measurable BPA levels (Table 2). Similar results were obtained when 13 samples with levels >LOQ were reanalyzed with serum taken from a different aliquot (Table 3). From the sampling 2008, serum from ten individuals was analyzed from aliquots stored at both -20 $^{o}$C and -70 $^{o}$C with similar results (Table 4).

**Table 2.** Individual samples from 1996-2011 that had BPA concentrations over LOQ the first analysis. When reanalyzing the same serum sample from the same aliquot the concentrations did not correspond.

| Sample nr | Year | BPA concentration (ng/ml) | BPA concentration second analysis (ng/ml) |
|---|---|---|---|
| 222325 | 1996 | 0.12 | <0.1 |
| 222303 | 1997 | 0.81 | <0.1 |
| 222312 | 1997 | 0.45 | <0.1 |
| 222394 | 1997 | 0.13 | <0.1 |
| 222516 | 1997 | 2.7 | <0.1 |
| 2542089 | 1998 | 1.7 | <0.1 |
| 2542155 | 1998 | 0.10 | <0.1 |
| 2514586 | 2000 | 0.22 | <0.1 |
| 2514588 | 2000 | 0.18 | <0.1 |
| 2514483 | 2001 | 0.22 | <0.1 |
| 5424457 | 2006 | 0.11 | <0.1 |
| 5424460 | 2006 | 0.10 | <0.1 |
| 5424470 | 2006 | 0.63 | <0.1 |
| 5424476 | 2006 | 5.3 | <0.1 |
| 5424565 | 2008 | 0.36 | <0.1 |
| 5424598 | 2008 | 1 | <0.1 |

**Table 3.** Individual samples that had BPA concentrations over LOQ the first analysis. When analyzing the same serum sample from another aliquot the concentrations did not correspond.

| Sample nr | Year | BPA concentration (ng/ml) | BPA concentration second analysis (ng/ml) |
|---|---|---|---|
| 222303 | 1997 | 0.81 | <0.1 |
| 222312 | 1997 | 0.45 | <0.1 |
| 222367 | 1997 | 0.47 | <0.1 |
| 222370 | 1997 | 0.16 | <0.1 |
| 222371 | 1997 | 0.51 | <0.1 |
| 222382 | 1997 | 3 | <0.1 |
| 222394 | 1997 | 85 | 0.13 |
| 222545 | 1997 | 0.30 | <0.1 |
| 222561 | 1997 | 0.18 | <0.1 |
| 222595 | 1997 | 1.4 | <0.1 |
| 2542210 | 1998 | 0.30 | <0.1 |
| 2542290 | 1998 | 0.22 | <0.1 |
| 5424432 | 2007 | 55 | <0.1 |

**Table 4.** BPA concentrations (ng/ml) in serum from ten individuals stored at different temperatures from 2008.

| Sample nr | - 20 °C | -70 °C |
|---|---|---|
| 5424392 | <0.1 | <0.1 |
| 5424398 | <0.1 | 1.4 |
| 5424444 | <0.1 | <0.1 |
| 5424446 | <0.1 | <0.1 |
| 5424566 | 0.44 | <0.1 |
| 5424593 | <0.1 | <0.1 |
| 5424320 | <0.1 | 7.8 |
| 7134061 | <0.1 | <0.1 |
| 7134045 | <0.1 | <0.1 |
| 7134027 | <0.1 | <0.1 |

**Test of sampling equipment**

The results from the evaluation of possible contamination from the blood sampling equipment is shown in Fig. 1 and Table 5. The equipment used for the blood sampling of the mothers in the present study was shown not leaking BPA (Fig. 1). The use of BD Valu-Set™ winged infusion needle set, that is used for blood sampling of children, are shown to be leaking BPA. The results showed higher response values with a large variation, compared to the blank samples. The three blood samples taken with BD Venflon™ intravenous cannula had all high levels of free BPA (Table 5). The leakage of BPA from the cannula was decreasing when taking samples in a sequence as the three samples were declining in BPA-concentration.

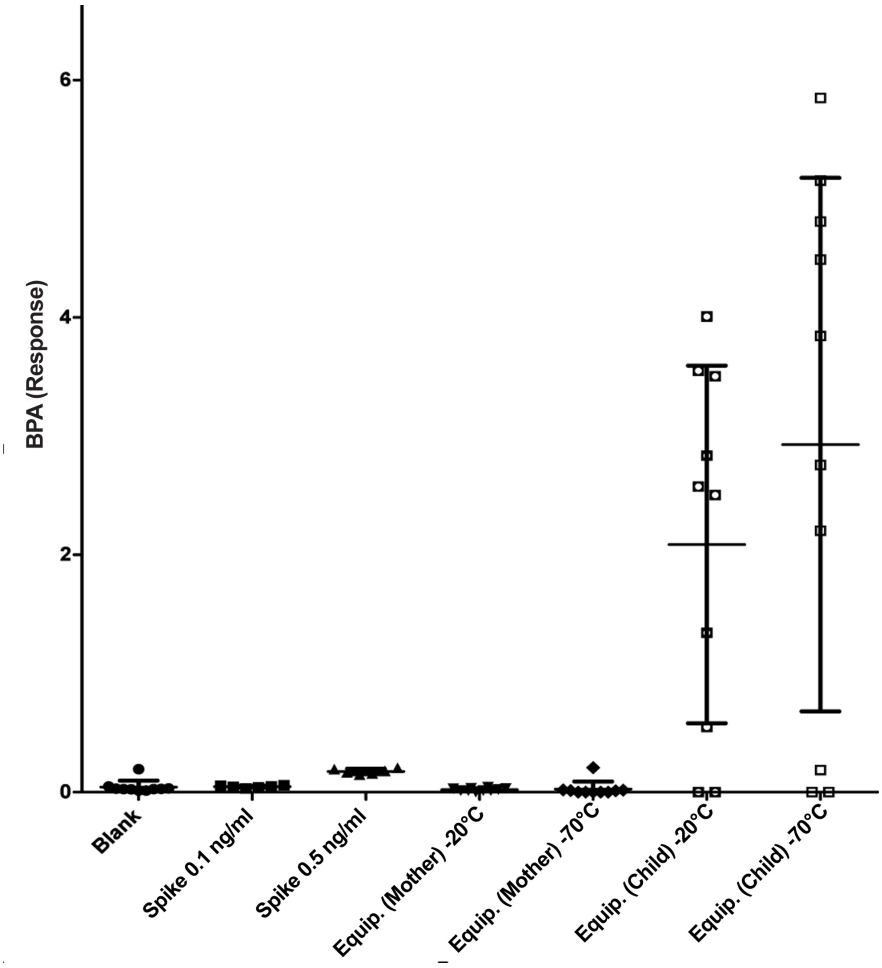


**Figure 1.** Peak response of BPA in blank serum (n=10), BPA-spiked serum (n=3) and serum that had been run through the blood sampling procedure (n=10). Equipment for mothers using BD PrecisionGlide™ needles and for children using BD Valu-Set™ winged infusion needle set. Samples were stored at two different temperatures, -20°C and -70°C. Response = BPA peak area/ BPA-D16 peak area.

**Table 5.** BPA concentration in serum from two individuals after blood sampling using BD Venflon™ intravenous cannula (BD Medical Surgical Systems) taken in three separate tubes in a sequence.

| | Individual A BPA conc. ng/ml | Individual B BPA conc. ng/ml |
|---|---|---|
| Tube 1 | 7 | 44 |
| Tube 2 | 0.6 | 5 |
| Tube 3 | 0.3 | 2 |

# DISCUSSION

Our results show that the concentration of free BPA, BPS, BPF, 4-NP, and BP-3 in blood serum is low in Swedish nursing women. The majority of BPA levels above LOQ (0.1 ng/ml) found in some serum samples in the temporal trend study are probably from exogenous sources. The contamination of BPA has probably occurred during the pooling and handling of samples since the sampling equipment used when taking blood samples from the women and the tubes used for storage and processing of samples did not show any BPA leakage.

BPA is a widespread used chemical and can be found at trace levels in the environment, for example in dust, in analytical solvents, and in laboratory equipment. The method used for analyzing free BPA was therefore designed to minimize contamination from exogenous sources. Nevertheless the majority of the individual samples with BPA levels >LOQ in the first analyses had levels <LOQ when reanalyzed. Consequently, in cases of levels >LOQ, contamination during handling when preparing samples for analysis, but also during previous handling of biobanked samples, is likely. The blood sampling equipment and the materials used in the processing and storage of the samples from the women in the study were not leaking BPA. However the two other types of needles examined, used for sampling of children and for repeated blood sampling, seriously contaminated the serum and are not possible to use in order to analyze BPA levels. The results from the present study show the difficulties in analyzing compounds where samples are easily contaminated from exogenous sources. It also points out that it is questionable to use biobanked samples unless sampling and handling of samples specifically were made with emphasis to minimize BPA contamination.

In the present study, only the free forms of the different phenolic contaminants were analyzed. It is the free molecule that is biological active and is therefore interesting when evaluating human risks. Most studies found in the literature have investigated the total concentration in urine or blood and that could be valuable when estimating the total exposure, if sampling and handling of the samples are done with special precautions to avoid contamination. It is known that BPA, 4-NP, and BP-3 is rapidly metabolized in the body and excreted in the urine (Okereke et al., 1993; Kadry et al., 1995; Müller et al., 1998; Volkel et al., 2002). So even if those chemicals could be detected in urine, the free form could be very low in the blood (Ye et al, 2012).

In many of the reports of BPA-levels in blood and urine the efforts to avoid contamination problem are poorly described and it cannot be ascertained if the reported levels are due to external contamination or not (Markham et al., 2010). When serum from biobanks have been used in order to analyze BPA levels, our data show that the results could be questioned, especially when levels >0.5 ng/ml is consistently reported (Dekant and Völkel, 2008; Lind and Lind, 2011; Gyllenhammar et al., 2012). The results in the present study are in agreement

with recent reports where total and free BPA was not detected or only at low concentrations in a few of the serum samples evaluated (Teeguarden et al., 2011; Koch et al., 2012; Ye et al., 2012; Liao and Kannan, 2012). Liao and Kannan (2012) have shown that free BPA only contributed to average 19% of the total BPA levels in blood serum and that glucuronide conjugated BPA is the dominating species of BPA (average: 43%). In this study free BPA levels in blood serum from 14 adult US volunteers were detected and almost all samples were under the LOQ of the present study (0.1 ng/ml). In order to analyze free BPA in serum it is necessary to use a method with very low LOQ and a sampling methodology and a laboratory that prevents contamination.

The low levels of free BPA, and the other phenolic compounds, in serum from nursing women in Uppsala County are an important observation. The total BPA concentration in urine reported in other studies gives a valuable measure of the total exposure, however, it does not provide the information of free and biologically active BPA in the blood, which is important for the risk assessment. In addition, the present study points to the uncertainty in using biobanked samples unless absence of BPA contamination from the sampling materials, and during handling of the samples can be proven.

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