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About This Report

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**Peer Review**

The draft research report, *Organotin and Total Tin Levels in Danish Women of Reproductive Age*, was evaluated by the reviewers listed below. These reviewers served as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determined if the design and conditions of this NTP study were appropriate and ensured that this NTP Research Report presented the experimental results and conclusions fully and clearly.

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Abstract

Background: Organotin compounds (OTCs) are organic derivatives of tin (Sn) used in the plastics and communication industries, and as antifouling agents in agriculture. Some OTCs have been shown to produce endocrine disrupting effects in aquatic species and rodent models, raising concern for effects on human reproduction and development. Little is known about exposure levels in women of reproductive age.

Objective: To collect pilot data on levels of OTCs and total Sn among Danish women of reproductive age.

Methods: Serum, whole blood, and urine samples were collected pre-pregnancy and during pregnancy from 55 women participating in the Snart-Forældre/Milieu (Soon-Parents/Environment) Study between November 2011 and May 2012. Six OTC species were measured in 47 serum samples using mass spectrometry [monobutyltin (MBT), dibutyltin (DBT), tributyltin (TBT), monophenyltin (MPT), diphenyltin (DPT), and triphenyltin (TPT)]. In addition, the concentration of total Sn was determined in serum (n = 47), whole blood (n = 10), and urine (n = 29) study samples by mass spectrometry.

Results: The frequency of detection above the experimental level of quantitation (ELOQ) was 0% for MPT, TPT, DPT, and TBT, 2.1% for DBT, and 10.6% for MBT. Total Sn levels were above the limit of detection (LOD) in 100% of serum (median 1.51 ng/mL, average 1.86 ng/mL; n = 47) and whole blood (median 1.70 ng/mL, average 1.79 ng/mL; n = 10) samples. Total Sn concentrations were lower in urine samples compared with the blood-based measures.

Conclusions: OTCs were not readily detected in serum collected from Danish women of reproductive age. Total Sn concentrations, which include organic and inorganic species, were also low, suggesting the results of OTC analyses are not due to metabolic conversions or analyte stability issues.
Introduction

Background
Organotin compounds (OTCs) are organic derivatives of tin (Sn) widely used in the plastics and communication industries, and in several agricultural applications. Tri-substituted OTCs such as triphenyltin (TPT) and tributyltin (TBT) previously were used primarily as antifouling agents in ship hull paints until concerns for marine organism toxicity led to prohibitions on the application (ATSDR 2005; EU 2006; RPA 2005; WHO 2006). Most consumer exposure is assumed to occur through dietary sources (RPA 2005), especially fish, mussels, and other marine animals obtained from contaminated areas such as the vicinity of harbors and heavily used shipping routes. Tri-substituted OTCs might still be in use as active ingredients in biocides and pesticides for certain consumer products such as nonallergenic pillows, shoe insoles, cycling short padding, and athlete’s foot spray (ATSDR 2005; RPA 2005).

Mono- and di-substituted OTCs, including monobutyltin (MBT), dibutyltin (DBT), and dioctyltin (DOT), are used in a range of applications that could result in exposure from household and consumer products. These compounds often are used together as stabilizers in polyvinyl chloride (PVC) plastics, which can be found in drinking water pipes, flooring and wall coverings, shower curtains, prints on t-shirts and other clothing, gloves, sandals, food packaging, toys, and other household items (Antizar-Ladislao 2008; RPA 2005). Overall, use of OTCs as PVC stabilizers dominates, accounting for an estimated 66–80% of global consumption based on information from the late 1990s and early 2000s (ATSDR 2005; Fent 1996; RPA 2005); more recent information does not appear readily accessible. Beyond PVC stabilizers, mono- and di-substituted OTCs have been detected in Canadian drinking water distributed through PVC pipes (Sadiki and Williams 1999). Di-substituted OTCs also are used as catalysts in manufacturing of polyurethane foams and mattress filling, car seats, diapers, female hygiene products, paints, adhesives, and coatings on grease-proof and baking paper, among other items (RPA 2005).

Organotin compounds might be present in medical devices due to their use as PVC stabilizers and as catalysts in silicone production (EU 2006). Dibutyltin chloride is listed by the US FDA as an indirect food additive for use in polymers and polyurethane resins and bis(tributyltin)oxide is listed as an indirect food additive for use as a preservative (ATSDR 2005). A study of household dust in the United States reported levels of OTCs ranging from 390 to 28,000 ng/g (Kannan et al. 2010), and similar levels have been described in house dust in Germany (Fromme et al. 2005).

A 2005 analysis performed for the European Commission identified several scenarios in which estimated human intakes could approach 20% or more of the tolerable daily intake (TDI), assuming worst-case exposure conditions. Scenarios included exposure to tri-substituted tins (mostly TBT) from consumption of fish and fish products, exposure to di-substituted tins (DBT, DOT) from indoor air/dust in children, di-substituted tins used in flexible PVC products (t-shirts, PVC gloves, PVC sandals), di-substituted tins used in rigid PVC products (PVC food packaging), and di-substituted tins used in catalysts (diapers, feminine hygiene products, dental moldings) (RPA 2005). The ban on TBT for use as a biocide in consumer products and baking paper eliminated concern for certain exposure scenarios (e.g., food spray, insoles, cookies). Monte Carlo simulations of estimated adult and child exposures indicated that children were at a greater risk of exposure to OTCs; however, little data are available to confirm the modelled...
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exposure predictions, and most human biomonitoring data are based on samples collected prior to 2005 (Table 1, Table 4).

Concern over the toxicity of OTCs initially arose during the 1970s, when exposure to TBT in the marine environment was linked to the occurrence of imposex in marine mollusks (Antizar-Ladislao 2008; Okoro et al. 2011), presumably through elevated testosterone levels and abnormal modulation of the retinoid X receptor (RXR) in gastropods (Antizar-Ladislao 2008; Lima et al. 2011). TBT and TPT are considered highly toxic to aquatic organisms and have been shown to produce imposex in female snails and fish at water concentrations as low as 1 ng/L (EU 2006). In animal studies, several OTCs have been shown to exhibit a wide range of toxicity (WHO 2006). Effects include neurotoxicity (especially for methyltins), reproductive and developmental toxicity (with TPT, dimethyltin or DMT, DBT, and DOT exhibiting significantly greater effects than their corresponding mono-substituted compounds), hematological effects (DBT dichloride, TBT oxide, DOT dichloride), and immunotoxicity (ATSDR 2005; WHO 2006). Immunotoxicity, which has been the critical toxicological endpoint for several risk assessments, was used by the European Union as the basis for deriving a group TDI (EFSA 2004; EU 2006). More recent work has demonstrated effects on adipocytes, leading to references to TBT as an “obesogen” (Chamorro-Garcia et al. 2013; Janesick and Blumberg 2012). Reports of imposex in aquatic species including fish and snails, masculinization in fish, reproductive and developmental toxicity in rodents, inhibition of aromatase by TBT and DBT, and in vitro stimulation of placental estrogen biosynthesis and adipogenic effects in rodent models support the consideration of OTCs as endocrine-active compounds (Antizar-Ladislao 2008; EFSA 2004; WHO 2006).

Very few epidemiological studies assess the potential health impact of chronic low-level exposure to OTCs, although death and neurological effects following accidental poisoning have been reported (ATSDR 2005). Recent work reports a trend toward greater weight gain from birth to 3 months with increasing placental TBT concentrations in 110 newborn males from Finland (Rantakokko et al. 2014). Another study including many of the same newborns found increasing concentrations of four OTCs (MBT, DBT, TBT, TPT) had a negative association with cryptorchidism in Finland (56 cases, 56 control newborns) but a positive association in Denmark (39 cases, 129 control newborns) (Rantakokko et al. 2013).

Objectives

Relatively little biomonitoring has been done to assess the levels of OTCs in blood or tissues, and additional measurement of OTC levels in humans is considered a research need (EU 2006). The primary objective of the current study was to collect pilot data on the levels of six OTCs (MBT, monophenyltin or MPT, DBT, diphenyltin or DPT, TBT, and TPT; see Figure 1) in serum samples from Danish women of reproductive age. The women were participating in a prospective cohort study to assess fertility, and the results of this pilot study were intended to inform whether OTCs should be measured in the broader cohort. As points of comparison, total Sn in serum, whole blood, and urine also were measured in the pilot study.
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Methods

Study Design and Population

This study focused on the first 55 women participating in the Snart-Forældre/Milieu (Soon-Parents/Environment) Study, a prospective cohort study of 129 Danish women between the ages of 18 and 40 years who had recently discontinued contraception to conceive. Milieu is a biospecimen collection substudy within the broader Snart-Forældre (SF) project, which has enrolled 3300 Danish women (https://www.snartforaeldre.dk/). The SF study is a continuation and expansion of a similar preconception cohort study, Snart-Gravid (Huybrechts et al. 2010; Mikkelsen et al. 2008).

The 55 participants in this report were women from Aalborg, Denmark who were asked to join the Milieu cohort after filling out an extensive online baseline questionnaire as part of the parent SF project. Enrollment in the Milieu substudy began in 2011, and blood and urine specimens were collected from each woman at up to three time points to measure concentrations of OTCs, phthalates, and other environmental chemicals (preconception within 1 month after completion of the baseline questionnaire, 1st trimester at 10–12 gestational weeks, and 2nd trimester at 20–22 gestational weeks) (Figure 2). The Milieu study protocol was approved by the Institutional Review Boards of Boston University (IRB number #H29427), the Danish Medical Research Council (IRB number N-20100087), and the Danish Data Protection Agency (J. nr. 2013-41-1922). The women provided written informed consent prior to the collection of blood and urine specimens for use in the study.

Sample Collection and Preparation

Participants were not instructed to fast before sample collection. For the serum OTC analysis, 6 mL of blood was collected by a medical laboratory assistant at the Clinical Research Laboratory at the Aalborg University Hospital via venipuncture. Samples were collected from 47 of the participating women directly into plastic collection tubes (serum collection tube containing increased silica clot activator and with silicone-coated interior walls, purchased from Becton Dickinson, BD# 367815). Selection of this collection tube for OTC analysis was based on a comparison of background Sn levels with other commercially available blood collection tubes, and multiple lot numbers of the same tube were analyzed to identify collection tubes with the lowest background Sn present. The background Sn levels were approximately 10 times lower in Becton Dickinson serum tubes (0.045 ng Sn/tube versus 0.590 ng Sn/tube). This screening prior to sample collection is an important consideration due to the ubiquity of Sn and its organic derivatives in consumer products. After collection, each tube was placed upright in a rack at room temperature to allow the blood to clot for at least 2 hours (clotting times varied between participants). Blood samples then were centrifuged at 3100 rpm for 15 min at room temperature and serum was transferred to 10-mL cryovials (SKS Natural Cryogenic, Ref # T310-10A) for storage at −20°C, which also were screened to minimize background Sn content prior to use. These cryovials were selected for storage because they had lower background levels of Sn (0.052 ng Sn/tube) compared to another vial considered (0.319 ng Sn/tube).

Whole blood samples were collected from the first 10 participants because an initial literature search of other human biomonitoring studies suggested that whole blood is the preferred matrix
for OTC analysis (Kannan et al. 1999; Rantakokko et al. 2008). Subsequent discussions between the co-authors and chemists at the Vrije Universiteit Institute for Environmental Studies, however, suggested that serum might be a better matrix for OTCs because they bind preferentially to serum proteins, which would be expected to result in lower concentrations in whole blood compared to serum (Shim et al. 2002; Yi et al. 2012). Thus, whole blood collection was abandoned and serum was collected in subsequent samples for the OTC analysis described above. The 10 whole blood samples were analyzed for total Sn (as discussed below) for comparison to total Sn in serum samples. Whole blood was collected using plastic collection tubes (Vacutainer Trace Element collection tube with potassium ETDA anticoagulant, Becton Dickinson, BD# 368381) that were screened to minimize background Sn. All blood samples were stored at −20°C.

All serum and blood samples were shipped on dry ice to RTI International (Research Triangle Park, NC, USA) for analysis. At RTI International, all samples were stored at −20 °C until time of analysis.

A spot urine sample was collected from all women in 50-mL polypropylene collection cups and stored at −20°C, shipped on dry ice to the US Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA), and stored at −20°C until time of analysis.

**Chemical Analyses**

**Serum OTCs**

Serum samples were analyzed for MBT, DBT, TBT, MPT, DPT, and TPT using a validated analytical method (Levine et al. 2015). Briefly, method performance was established over several analytical days using a series of spiked human serum matrix quality control samples. Major validation parameters included intra- and inter-day precision and accuracy, sensitivity, linearity, specificity, carryover, matrix impact and recovery, and stability under a variety of scenarios. Samples were analyzed within 2 weeks of receipt date at the analytical laboratory. In brief, the sample preparation involved a 1:4 dilution of serum with the eluent solution (0.5% triethylamine, 0.075% tropolone, 5.5% acetic acid, and 65% methanol in deionized water), followed by centrifugation. The analytical method used ion-pair, reversed-phase, ultrahigh pressure liquid chromatography coupled with sector field-inductively coupled plasma mass spectrometry detection (IPRP-UHPLC-SF-ICP-MS), and the chromatographic separation of all organotin species was achieved within 3 minutes. The experimental limit of quantitation (ELOQ) for the speciation method, defined as the lowest matrix standard concentration used, ranged from 1.25 to 1.71 ng/mL for different organotin species. The limits of detection (LOD), estimated as 3 times the standard deviation of ELOQ, ranged from 0.25 to 0.50 ng/mL for different organotin species (Levine et al. 2015). Spiked matrix quality control samples were interspersed throughout each analytical batch of study samples to ensure the method was performing as validated.

**Serum and Whole Blood Total Sn**

The concentration of total Sn was determined in serum and in selected whole blood samples at RTI International (Figure 2). Although the methodology for determining total Sn was not validated, study samples were processed with several quality control samples to ensure proper analytical method performance, including method and control matrix blank samples and spiked
blank and control matrix samples. Briefly, a 0.500-mL aliquot of each serum or whole blood sample was digested at elevated pressure and temperature in a microwave oven in the presence of high-purity acids (nitric, hydrochloric) and oxidants (nonstabilized hydrogen peroxide). After complete decomposition, the concentration of Sn was determined using a Thermo X-Series II ICP-MS (Bremen, Germany). For this assay, the LOD—conservatively defined as the lowest acceptable calibration standard on a batch-specific basis—was 0.200–0.400 ng Sn/mL for serum and 0.600 ng Sn/mL for whole blood.

**Urine Total Sn**

Urine samples also were analyzed for total Sn at the CDC Division of Laboratory Sciences. The analysis was performed using inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS) using an ELAN® DRCTM II ICP-MS (PerkinElmer SCIEX, Concord, ON, Canada) equipped with a Meinhard quartz nebulizer (Type TQ-30-A3), a DRC quartz cyclonic spray chamber, a 2.0-mm ID quartz injector, and nickel sampler and skimmer cones. Sn was measured using an ICP-DRC-MS method designed to monitor a 15-element panel (CDC 2012; Jarrett et al. 2008). Briefly, urine samples (0.5 mL) were diluted 1+9 with 2% (v/v) concentrated nitric acid containing iridium (Ir) and rhodium (Rh) as internal standards. Method accuracy was evaluated using National Institute of Standards Technology-Standard Reference material 2668 (Toxic Elements in Frozen Human Urine), levels 1 and 2. The LOD was 0.09 ng Sn/mL. Additional information regarding the sample preparation and analysis method have been described previously (Caudill et al. 2008).

**Statistical Analysis**

The percentage of samples with detectable concentrations of Sn and the range of measured concentrations of each analyte were calculated in all three biological matrices. Mean and median concentrations of analytes were calculated when values were above ELOQ (serum OTC species) or LOD (total Sn in serum, whole blood, urine) in more than 40% of the samples. When presented, descriptive statistics were calculated based only on levels above ELOQ or LOD (i.e., values were not imputed).
Results

The results presented here describe OTCs and total Sn concentrations from the first 55 participants enrolled in Snart-Forældre/Milieu during August 2011 through May 2012. The number of serum, urine, and whole blood samples collected and analyzed varied among participants (Figure 2). For 12 of the 55 women, multiple samples were collected at different time points, but this analysis focused on the first sample collected from each subject, which was most often collected pre-pregnancy (n = 33) or very early in the first trimester (n = 13). Data from the repeated samples are available in Excel Supplemental Table S1 (https://doi.org/10.22427/NTP-DATA-RR-2). To help interpret the serum organotin results, data also are presented on total Sn in serum, whole blood, and urine.

Serum OTCs

Concentrations of individual organotin species above the ELOQ were infrequently detected (Table 2; individual subject data are presented in Table S1 available at https://doi.org/10.22427/NTP-DATA-RR-2). The detection frequency above the ELOQ in the first 47 first samples collected from each woman was 0% for MPT, TPT, DPT, and TBT, 2.1% for DBT, and 10.6% for MBT. The detection frequencies based on values above the LOD were 48.9% MBT, 6.4% MPT, 53.2% DBT, 29.8% DPT, 55.3% TBT, and 25.5% TPT (Table S1 available at https://doi.org/10.22427/NTP-DATA-RR-2).

Total Sn in Serum, Whole Blood, and Urine

Total Sn in serum was detected in 100% of samples (n = 47), with a median concentration of 1.51 ng/mL (Table 2). In whole blood, 100% of samples (n = 10) had detectable levels of Sn with a median concentration of 1.70 ng/mL, and 65.5% of the urine samples were found to contain Sn at a median concentration of 0.28 ng/mL.

Measured concentrations of total Sn in whole blood ranged from 1.16 to 2.82 ng Sn/mL. Similarly, total Sn concentrations in serum samples ranged from 0.69 to 6.07 ng/mL. In most samples, the serum total Sn level was 2 to 3 times higher than the ELOQs for individual organotin species, that is, the 95th-percentile value for serum total Sn was 3.83 ng Sn/mL and the ELOQs for individual organotin species ranged from 1.25 to 1.71 ng/mL. Total Sn concentrations reflect both organic and inorganic sources of Sn, so levels of total Sn in whole blood and serum that are near the ELOQ for individual organotin species can be interpreted as confirming the low organotin concentrations observed in serum samples, as discussed in more detail below.

Pre-pregnancy versus Pregnancy Levels

We did not attempt to characterize the correlation between serum or urine levels collected from women prior to pregnancy and during pregnancy, as the number of subjects with repeated measures was relatively small (range 7–10 women, depending on biological matrix, Figure 2) and because many of the OTC values were <ELOQ. Descriptive statistics for samples collected during pregnancy are summarized in Table S1 (https://doi.org/10.22427/NTP-DATA-RR-2).
Discussion

Comparison of Results with Other Human Biomonitoring Data and Sample Matrix Considerations

We attempted to discern whether time of exposure/collection, geographical patterns, or other trends were apparent for OTC levels across studies, but the data were too heterogeneous to reach clear conclusions because of differences in study design, especially with respect to sample matrix (whole blood, serum, urine, liver, placenta, breast milk), sensitivity of the analytical method, and timing or location of sample collection (Table 3; studies are described in more detail in Supplemental Tables S2 and S3 [https://doi.org/10.22427/NTP-DATA-RR-2], in tabular and spreadsheet format, respectively). Within a given sample matrix, only one to three studies were available. In addition, most studies did not report sample storage time, which is an important factor given that some OTCs exhibit signs of degradation even when stored at −20°C (Levine et al. 2015; Van et al. 2005). During method validation, the stability of OTCs in the serum matrix at several storage conditions (freezer, refrigerator, ultracold freezer) was investigated, and all six species studied here were shown to degrade by at least 15%, beginning as soon as day 7 of storage at freezer temperatures. Triphenyltin degraded the most rapidly, losing 80% of the nominal concentration by day 7 of freezer storage.

Our results are consistent with findings from the only other study we identified that reported serum levels of OTCs (Lo et al. 2003) in suggesting that levels are relatively low. The Lo et al. (2003) study analyzed eight samples collected from Germany during 2000–2002 using a method with lower LODs than the method used in the current study (0.02 ng organotin cation/mL versus 0.25–0.5 ng/mL). TBT and TPT were detected (≥LOD) in four and eight samples, respectively, and other OTCs were not detected (MBT, DBT, tetrabutyltin (TeBT), MOT, DOT) (Table 3, Table S1 available at https://doi.org/10.22427/NTP-DATA-RR-2, Table 4). In our study, the frequency of samples above the LOD was 48.9% (MBT), 53.2% (DBT), 55.3% (TBT), and 25.5% (TPT), but few samples were above the ELOQs of 1.25–1.71 ng/mL (10.6% MBT, 2.1% DBT, 0% for other OTCs). The highest level of TBT detected in Lo et al. (2003) (0.05 ng organotin cation/mL) was lower than the LOD in the current study (0.25 ng/mL), and the highest level of TPT (0.67 ng organotin cation/mL) fell between the LOD and ELOQ in the current study (0.30–1.25 ng/mL). In our study, the highest levels for commonly measured OTCs were 10.9 ng/mL for MBT, 4.50 ng/mL for DBT, 0.51 ng/mL for TBT, and 0.85 ng/mL for TPT. These levels can be considered relatively low compared to the highest levels measured in other studies using different sample matrices. For example, for TBT, whole blood levels of 85 ng/mL (Kannan et al. 1999) or placental levels of 1.24 ng/mL (Rantakokko et al. 2013) have been reported. Regarding comparison of the LODs used in our study with those reported in Lo et al. (2003), the analytical methods in that study used a sample preparation method with a combination derivatization and extraction step that was not validated (Kuballa et al. 1995), and the LOD was estimated as 3 times the standard deviation of the baseline noise, which can produce artificially lower LOD values. A limitation of our serum OTC analysis is that samples were stored for 2 months to 1 year; thus degradation of OTCs might have occurred given that losses have been reported following several weeks of storage at −20°C (Levine et al. 2015). This limitation, however, likely extends to most studies reporting OTC levels.
The highest levels of OTCs were reported in a Michigan-based study by Kannan et al. (1999) with median whole blood values for MBT of 8.0 ng/mL (maximum 27 ng/mL, 53.1% of samples >LOD), DBT of 4.35 ng/mL (maximum 16 ng/mL, 81.3% of samples >LOD), and TBT of 4.8 ng/mL (maximum 85 ng/mL, 78.1% of samples >LOD). Two other studies measuring OTCs in whole blood report infrequent detection (0 to <14.3% for each species) using methods with lower LODs or LOQs than reported in Kannan (Meijer et al. 2004; Peters 2004; Rantakokko et al. 2008) (Table S1 and Table S 3, available at https://doi.org/10.22427/NTP-DATA-RR-2). The basis for the high levels reported in Kannan et al. (1999), is unclear. Collection time might be a factor as the samples analyzed by Kannan et al. (1999) were collected in 1998, while Rantakokko et al. (2008) used samples collected during 2004–2005; sample collection time was not reported in the Meijer and Peters reports (Meijer et al. 2004; Peters 2004). All samples were collected from regions where relatively high fish consumption might occur (Michigan, United States; Netherlands; Helsinki and Turku, Finland), but other geographic factors or exposure from consumer products could be contributing factors in the Kannan et al. (1999) results. Also, Kannan et al. (1999) used gas chromatography-flame photometric detector (GC-FPD), while the other whole blood studies used gas chromatography-mass spectrometry (GC-MS).

In placental tissue collected between 1997 and 2001 from Finland (Turku) and Denmark (Copenhagen), Rantakokko et al. (2013; 2014) reported relatively infrequent detection of MBT in both locations (percentage of samples >LOQ ranged from 10 to 11%) and more frequent detection of DBT, TBT, and TPT (percentage of samples >LOQ ranged from 31 to 99%). Levels of DBT, TBT, and TPT were higher in samples collected from Turku, Finland compared to Copenhagen, Denmark, especially for TBT (99% versus 37%, respectively). In this study, fish consumption was surveyed, and fish consumption frequencies were not significantly correlated with TBT, sum of butylated species, or the sum of all measured OTC concentrations. The authors noted that the nature of fish consumption varied among participants (higher frequency of eating fish as part of hot meals in Finland; higher frequency of fish consumption on bread and salads in Denmark). After considering national fish consumption patterns, regional OTC contamination, and the differential correlation and ratios of TBT to DBT between the sites (more correlated and higher TBT to DBT ratio in Turku, Finland), the authors suggested sources of exposure other than fish (consumer products in particular) could be contributing to OTC intake in Denmark. The relatively small number of samples and the high frequency of samples <LOQ were identified as limitations of the analysis. Another Finnish study reported infrequent detection of OTCs in placenta (0–4.6%) collected from women living in an inland city (Kuopio) during 2004–2005 (Leino et al. 2013). In this case, the period of sample collection (1997–2001 versus 2004–2005), location (Turku is next to the Baltic Sea, an area known to have high OTC levels during the sampling period), and assay methodology (LOQ of 0.02–0.1 ng/g fresh weight versus 7.5–22 ng/g fat) could be factors. Although the sample matrix differs, a study by Rantakokko et al. (2008) suggests that OTC levels in people living in the Baltic Sea region could be decreasing subsequent to restrictions on use of TBT. Levels of MBT, DBT, TBT, and other OTCs were largely undetectable in the whole blood of 300 fishermen and their families collected during 2004–2005. The most commonly detected OTC was TPT, which was detected in 12.3% of samples (LOQ of 1.04 ng/mL, maximum 0.56 ng/mL).

Total urine Sn levels in this study of Danish women were lower (median = 0.34 ng/mL; 0.35 μg/g creatinine) than levels reported in the United States from the National Health and Nutrition Examination Survey (NHANES) for adult female non-smokers during the 2011–2012
surveys (median = 0.47 ng/mL; 0.743 μg/g creatinine) (CDC 2014). We did not analyze OTCs in urine, but methods have been reported that quantify OTCs in the urine matrix. Most of these studies focus on monomethyltin (MMT), dimethyltin (DMT), or trimethyltin (TMT) species (Cui et al. 2011; Ruan et al. 2011; Tang et al. 2013), but more recent analytical method development efforts overlap with species measured in the current study (MBT, DBT, TBT) (Table 3) (Valenzuela et al. 2014; Zachariadis and Rosenberg 2009). These studies had very low LODs (ranging from 0.0008 to 0.057 ng Sn/mL) and reported OTCs were not detected or were detected at lower concentrations than our serum ELOQs (Valenzuela et al. 2014; Zachariadis and Rosenberg 2009), including in samples collected from six workers employed at a harbor where ship-repairing and painting activities are frequently performed (Valenzuela et al. 2014). In Zachariadis and Rosenberg (2009), two of four urine samples collected from men aged 24–45 years had detectable concentrations of at least one organotin species (MBT, DBT, TBT, TeBT, MPT, DPT).

Very limited information is available to compare urine to blood for measurement of total Sn or OTCs in the same subjects. In the current study, total Sn levels in urine were above the LOD, but concentrations were lower in urine (median 0.28 ng/mL, average 0.34 ng/mL; n = 29) compared to serum (median 1.51 ng/mL, average 1.86 ng/mL; n = 47) or whole blood (median 1.70 ng/mL, average 1.79 ng/mL; n = 10). We did identify a study reporting higher concentrations of Sn in urine than in blood in Chinese patients who had been exposed to industrial lard cooking oil contaminated with OTCs (Gui-bin et al. 2000). Concentrations of DMT, TMT, and Sn(IV) were similar in urine samples, and TMT was the only analyte detected in blood samples.

Our main analysis of OTCs used serum samples, while other blood-based measurements focused on whole blood samples (Kannan et al. 1999; Meijer et al. 2004; Peters 2004; Rantakokko et al. 2008) (Table 3). The rationale for using serum was that OTCs have been reported to bind preferentially to proteins in the plasma portion of blood, which theoretically would result in a lower measured OTC concentration in whole blood compared with serum (Shim et al. 2002; Yi et al. 2012). We did have whole blood samples for 10 participants but did not conduct a comparative OTC speciation analysis for two reasons. First, the ELOQs for OTCs are similar (1.25–1.71 ng/mL) to the median and average levels of total Sn measured in whole blood (1.70 and 1.79 ng/mL, respectively), suggesting that quantification of individual OTCs in whole blood would be challenging, as the concentrations of each species would be even lower in whole blood than the already-low serum samples, possibly below the limit of detection. Second, the sample preparation method used here was designed, optimized, and validated in the serum matrix (Levine et al. 2015), and speciated analysis of whole blood would require some degree of re-optimization, cross-validation, or both.

**Contribution of OTCs to Total Sn Levels**

Total Sn content in serum and whole blood was analyzed to provide an estimate of the Sn species not accounted for in the speciation analysis or that might have degraded or converted to other chemical forms. Very little is known about the toxicokinetics of OTCs in humans or animals, and what is known indicates complex disposition patterns (ATSDR 2005; Appel 2004; Epstein et al. 1991; EU 2006; Valenzuela et al. 2014; WHO 2006). For example, in rats treated with dibutyltin dichloride, the parent compound and several acid-stable metabolites were detected in tissues (liver, kidney, brain, spleen) and four metabolites were found in urine, one of which was not
detected in tissues (Ishizaka et al. 1989). In another study, eight metabolites were measured in urine samples collected after treatment with tributyltin chloride (Matsuda et al. 1993).

To account for potential underestimation of tin species from the OTC analysis, two scenarios were assessed by summing the concentration for each OTC species expressed in concentration of Sn and comparing to the measured concentration of total tin.

A “worst-case” scenario was calculated to demonstrate what the measured total Sn concentration would have been if all species that were not detected by the speciation analysis were actually present at the LOD. This scenario was evaluated by summing the OTC species concentrations for each sample, using the measured value for samples >LOD and assuming all <LOD values contain a concentration of the species equivalent to the LOD (MBT: 0.50 ng/mL, DBT: 0.25 ng/mL, TBT: 0.25 ng/mL, MPT: 0.35 ng/mL, DPT: 0.25 ng/mL, TPT: 0.30 ng/mL).

A “best-case” scenario also was calculated to demonstrate what the measured total Sn concentration would have been if all species that were not detected by the speciation analysis were not present at all. This scenario was evaluated by summing all species, assuming all <LOD values for each species are 0 and all values >LOD were as measured.

Most serum total Sn values (45 of 64 samples) are either lower than the best-case scenario, which means that the speciation values provide a conservative overestimate of OTC levels (22 of 64) or fall between the worst-case and best-case scenarios (23 of 64), suggesting the speciation analysis is a good estimate for these samples. In the remaining samples with total Sn values that fall above the worst-case scenario (19 of 64), the values obtained from speciation analysis benefit from complementary total Sn analysis, which provides an estimate of non-validated species and inorganic Sn due to degradation of samples. In these cases, however, the magnitude of potential underestimation resulting from the speciation analysis (which might account for other species or inorganic Sn) was not large, ranging from 0.03 to 2.26 ng Sn/mL. For the highest serum total Sn value measured in all 64 samples (6.07 ng Sn/mL in a sample where serum MBT was 4.20 ng Sn/mL), the worst-case estimate was 5.82 ng Sn/mL, a difference of 0.26 ng Sn/mL from the measured total Sn concentration, and the best-case estimate was 4.67 ng Sn/mL. Overall, the analysis of total Sn suggests that are OTCs levels are not substantially underestimated. Ideally, future analytical refinements would enable lower ELOQs for specific OTCs to increase the number of samples with quantifiable concentrations. Otherwise, based on the current results (similar concentrations of total Sn in serum and whole blood, Table 2), measuring only total Sn from whole blood or serum could be sufficient for an upper-bound estimate of OTCs.
Conclusions

Organotin compounds were not readily detected at quantifiable concentrations in serum collected during 2011–2012 from Danish women of reproductive age. The concentrations of total Sn, which reflect both organic and inorganic sources, also were low, suggesting that the OTC results are likely not a result of metabolic conversions or stability issues. Other studies also have reported relatively infrequent detection or low concentrations of OTCs in serum, whole blood, placenta, breast milk, or urine in samples collected after 2000 (Leino et al. 2013; Lo et al. 2003; Meijer et al. 2004; Mino et al. 2008; Peters 2004; Rantakokko et al. 2008; Valenzuela et al. 2014; Zachariadis and Rosenberg 2009), which provides support for low current levels of exposure. Of importance to note, however, is that OTCs are still widely used in consumer products and that organotin species bound to estuarine sediments can be released gradually, making them bioavailable under certain environmental conditions. As a result, periodic biomonitoring in humans and sentinel aquatic species is recommended. Also, the findings of low exposure levels in blood, urine, and placenta—despite widespread use in consumer products—suggest less routine sample matrices, such as hair or nails, should be considered.
References


European Union (EU). 2006. Revised assessment of the risks to health and the environment associated with the use of the four organotin compounds TBT, DBT, DOT and TPT.


Organotin and Total Tin Levels in Danish Women of Reproductive Age

http://dx.doi.org/10.1016/S0960-0760(03)00074-8


Organotin and Total Tin Levels in Danish Women of Reproductive Age


Table 1. Serum Concentrations of Organotins Measured in Samples Collected from Danish Women of Reproductive Age (ng Sn/mL)

<table>
<thead>
<tr>
<th>Monobutyltin (MBT)</th>
<th>Dibutyltin (DBT)</th>
<th>Tributyltin (TBT)</th>
<th>Monophenyltin (MPT)</th>
<th>Diphenyltin (DPT)</th>
<th>Triphenyltin (TPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOD: 0.50 ng/mL</td>
<td>LOD: 0.25 ng/mL</td>
<td>LOD: 0.25 ng/mL</td>
<td>LOD: 0.35 ng/mL</td>
<td>LOD: 0.25 ng/mL</td>
<td>LOD: 0.30 ng/mL</td>
</tr>
<tr>
<td>ELOQ: 1.71</td>
<td>ELOQ: 1.59</td>
<td>ELOQ: 1.48</td>
<td>ELOQ: 1.60</td>
<td>ELOQ: 1.40</td>
<td>ELOQ: 1.25</td>
</tr>
<tr>
<td>range: &lt;LOD–10.9</td>
<td>range: &lt;LOD–4.50</td>
<td>range: &lt;ELOQ</td>
<td>range: &lt;ELOQ</td>
<td>range: &lt;ELOQ</td>
<td>range: &lt;ELOQ</td>
</tr>
<tr>
<td>n &gt; LOD = 48.9% (23/47)</td>
<td>n &gt; LOD = 53.2% (25/47)</td>
<td>n &gt; LOD = 55.3% (26/47)</td>
<td>n &gt; LOD = 6.4% (3/47)</td>
<td>n &gt; LOD = 29.8% (14/47)</td>
<td>n &gt; LOD = 25.5% (12/47)</td>
</tr>
<tr>
<td>n &gt; ELOQ = 5/47 (10.9%)</td>
<td>n &gt; ELOQ = 1/47 (2.1%)</td>
<td>n &gt; ELOQ = 0/47 (0%)</td>
<td>n &gt; ELOQ = 0/47 (0%)</td>
<td>n &gt; ELOQ = 0/47 (0%)</td>
<td>n &gt; ELOQ = 0/47 (0%)</td>
</tr>
</tbody>
</table>

Table 2. Concentrations of Total Sn Measured in Samples Collected from Danish Women of Reproductive Age (ng Sn/mL)

<table>
<thead>
<tr>
<th>LOD</th>
<th>Serum (ng Sn/mL)</th>
<th>Whole Blood (ng Sn/mL)</th>
<th>Urine (ng Sn/mL)</th>
<th>Urine (μg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOD</td>
<td>0.200–0.400&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.600</td>
<td>0.09</td>
<td>N/A</td>
</tr>
</tbody>
</table>

First Sample Collected (either pre-pregnancy or early in the 1st trimester)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>47</td>
<td>10</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>% above LOD</td>
<td>100%</td>
<td>100%</td>
<td>65.5%</td>
<td>65.5%</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.69</td>
<td>1.16</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>Maximum</td>
<td>6.07</td>
<td>2.42</td>
<td>0.66</td>
<td>0.90</td>
</tr>
<tr>
<td>Average</td>
<td>1.86</td>
<td>1.79</td>
<td>0.34&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median</td>
<td>1.51</td>
<td>1.70</td>
<td>0.28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Represents the range of LODs from analysis of samples in two batches.

<sup>b</sup>Calculated based on values >LOD (samples <LOD were not imputed).

Abbreviation: LOD = limit of detection.
Table 3. Summary of Levels of Organotins (OTCs) Reported in Humans by Sample Matrix and Year of Sample Collection

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Years of Sample Collection (Region; n)</th>
<th>OTC Species Analyzed</th>
<th>Range of LODs or LOQs (Method)</th>
<th>Detection Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood</td>
<td>1998 (US, Michigan; n = 32)</td>
<td>MBT, DBT, TBT</td>
<td>LODs: 1–7 ng/mL (GC-FPD)</td>
<td>53.1–81.3% &gt; LOD</td>
<td>Kannan et al. (1999)</td>
</tr>
<tr>
<td></td>
<td>before 2004 (Netherlands; n = 91)</td>
<td>MBT, DBT, TBT, MOT, DOT, MPT, DPT, TPT</td>
<td>LODs: [0.11–0.42 ng/mL] (GC-MS)</td>
<td>0–14.3% &gt; LOD</td>
<td>Meijer et al. (2004); Peters (2004)</td>
</tr>
<tr>
<td></td>
<td>2004–2005 (Finland, near Helsinki &amp; Turku, n = 300)</td>
<td>MBT, DBT, TBT, DOT, MPT, DPT, TPT</td>
<td>LOQs: 0.03–0.72 ng/mL (GC-MS)</td>
<td>0–12.3% &gt; LOQ</td>
<td>Rantakokko et al. (2008)</td>
</tr>
<tr>
<td>Serum</td>
<td>2000–2002 (Germany; n = 8)</td>
<td>MBT, DBT, TBT, TeBT, MOT, DOT, TPT</td>
<td>LODs: 0.02 ng/mL (GC–MIP–AED)</td>
<td>0–100% &gt; LOD</td>
<td>Lo et al. (2003)</td>
</tr>
<tr>
<td></td>
<td>2011–2012 (Denmark, Aalborg; n = 47)</td>
<td>MBT, DBT, TBT, MPT, DPT, TPT</td>
<td>LODs: 0.25–0.5 ng/mL (GC-PFPD)</td>
<td>0–10.6% &gt; ELOQ</td>
<td>current study</td>
</tr>
<tr>
<td>Liver</td>
<td>1994 (Poland, Gdańsk; n = 9)</td>
<td>MBT, DBT, TBT</td>
<td>LODs: 1–5 ng/g wet weight (GC-FPD)</td>
<td>% &gt; LOD not reported; $\sum$OTCs range 4–11 ng/g wet weight</td>
<td>Kannan et al. (1999)</td>
</tr>
<tr>
<td></td>
<td>1997–1998 (Japan, Ehime; n = 4)</td>
<td>MBT, DBT, TBT</td>
<td>LODs: 2–4 ng/g wet weight (GC-FPD)</td>
<td>0–100% &gt; LOD; $\sum$OTCs range 59–96 ng/g wet weight</td>
<td>Takahashi et al. (1999)</td>
</tr>
<tr>
<td></td>
<td>1999–2000 (Denmark, Odense University; n = 18)</td>
<td>MBT, DBT, TBT, TPT</td>
<td>LODs: 0.3–3 ng/g wet weight (GC-PFPD)</td>
<td>0–100% &gt; LOD; $\sum$OTCs range 1.1–33 ng/g wet weight</td>
<td>Nielsen and Strand (2002)</td>
</tr>
<tr>
<td>Placenta</td>
<td>1997–1999 (Finland, Turku; n = 110)</td>
<td>MBT, DBT, TBT, TPT</td>
<td>LOQs: 0.02–0.1 ng/g wet weight (GC-MS)</td>
<td>10–99% &gt; LOQ; $\sum$OTCs median 0.39 ng/g wet weight</td>
<td>Rantakokko et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>1997–2001 (Denmark, Copenhagen; n = 168)</td>
<td>MBT, DBT, TBT, TPT</td>
<td>LOQs: 0.02–0.1 ng/g wet weight (GC-MS)</td>
<td>10–37% &gt; LOQ; $\sum$OTCs median 0.15 ng/g wet weight</td>
<td>Rantakokko et al. (2013)</td>
</tr>
<tr>
<td>Matrix</td>
<td>Years of Sample Collection (Region; n)</td>
<td>OTC Species Analyzed</td>
<td>Range of LODs or LOQs (Method)</td>
<td>Detection Frequency</td>
<td>Reference</td>
</tr>
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</tr>
<tr>
<td>Urine</td>
<td>2006 (Greece, Thessaloniki; n = 4)</td>
<td>MBT, DBT, TBT, TeBT, MPT, DPT</td>
<td>LODs: 0.009–0.057 ng/mL (HS-SPME, MIP-AED)</td>
<td>0–50% &gt; LOD</td>
<td>Zachariadis and Rosenberg (2009)</td>
</tr>
<tr>
<td>Breast Milk</td>
<td>2002 (Japan, Okayama &amp; Kagawa; n = 67)</td>
<td>MBT, DBT, TBT, TPT</td>
<td>LODs: 1.3–2.5 ng/mL (GC-FPD)</td>
<td>“undetected in vast majority of samples” – 16.4% &gt; LOD</td>
<td>Mino et al. (2008)</td>
</tr>
</tbody>
</table>

*a* Converted from ng/g to ng/mL by multiplying ng/g LOD × density of whole blood (1.06 g/cm³).

**Abbreviations:** ELOQ = estimated limit of quantitation; GC-FPD = gas chromatography-flame photometric detector; GC-PFPD = gas chromatography-pulse flame photometric detector; GC-MIP-AED = gas chromatography-microwave induced plasma-atomic emission detection; GC-MS = gas chromatography-mass spectrometry; HS-SPME = headspace solid-phase micro-extraction; LOD = limit of detection; LOQ = limit of quantitation.
Organotin and Total Tin Levels in Danish Women of Reproductive Age

### Table 4. Summary of Levels of Organotins (OTCs) Reported in Humans

<table>
<thead>
<tr>
<th>Study Information</th>
<th>Monobutyltin (MBT)</th>
<th>Dibutyltin (DBT)</th>
<th>Tributyltin (TBT)</th>
<th>Monophenyltin (MPT)</th>
<th>Diphenyltin (DPT)</th>
<th>Triphenyltin (TPT)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kannan and Falandysz (1997)</td>
<td>Subjects: ♂n = 5, ♀n = 3, sex unknown for 1 (autopsy), 45–83 y, n = 9</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>not measured</td>
<td>not measured</td>
<td>not measured</td>
</tr>
<tr>
<td></td>
<td>Years of collection: 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Country: Poland (Gdańsk)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Matrix: liver</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Analytics: GC-FPD</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kannan et al. (1999)</td>
<td>Subjects: ♂n = 17, ♀n = 15 (American Red Cross blood drive), 27–81 y, n = 32</td>
<td>LOD: 7 ng/mL mean: 8.17 median: 8.0 range: &lt;LOD–27</td>
<td>LOD: 2.5 ng/mL mean: 4.94 median: 4.35 range: &lt;LOD–16</td>
<td>LOD: 1 ng/mL mean: 8.18 median: 4.8 range: &lt;LOD–85</td>
<td>not measured</td>
<td>not measured</td>
<td>not measured</td>
</tr>
<tr>
<td></td>
<td>Years of collection: 1998</td>
<td>n &gt; LOD: 17/32 (53.1%)</td>
<td>n &gt; LOD: 26/32 (81.3%)</td>
<td>n &gt; LOD: 25/32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LOD: 17/32</td>
<td>LOD: 26/32</td>
<td>LOD: 25/32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Country: US (Michigan)</td>
<td></td>
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<td>Matrix: whole blood</td>
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<td></td>
<td>Analytics: GC-FPD</td>
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<tr>
<td>Study</td>
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<tr>
<td>Leino et al. (2013)</td>
<td>Subjects: ♀ (Protection against Allergy – Study in Rural Environments, PASTURE study: LUKAS-1, LUKAS-2), 29–81 y, n = 130</td>
<td>LOQ: 37 ng/g fat</td>
<td>LOQ: 22 ng/g fat</td>
<td>LOQ: 15 ng/g fat</td>
<td>LOQ: 30 ng/g fat</td>
<td>LOQ: 15 ng/g fat</td>
<td>LOQ: 7.5 ng/g fat</td>
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<tr>
<td></td>
<td>Years of collection: 2004–2005</td>
<td>mean: – median: – range: not reported n &gt; LOQ: 2/130 (1.5%)</td>
<td>mean: – median: – range: not reported n &gt; LOQ: 1/130 (0.8%)</td>
<td>mean: – median: – range: not reported n &gt; LOQ: 1/130 (0.8%)</td>
<td>mean: – median: – range: N/A n &gt; LOQ: 0/130 (0%)</td>
<td>mean: – median: – range: N/A n &gt; LOQ: 0/130 (0%)</td>
<td>mean: – median: – range: &lt;LOQ–280 n &gt; LOQ: 6/130 (4.6%)</td>
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<tr>
<td></td>
<td>Country: Finland (Kuopio)</td>
<td>Matrix: placenta</td>
<td>Analytics: GC–MS</td>
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<tr>
<td>Lo et al. (2003)</td>
<td>Subjects: ♂ n = 4, ♀ n = 4 (volunteers), 41–54 y, n = 8</td>
<td>LOD: 0.02 ng organotin cation/mL mean: – median: – range: &lt;LOD n &gt; LOD: 0/8 (0%)</td>
<td>LOD: 0.02 ng organotin cation/mL mean: – median: – range: &lt;LOD n &gt; LOD: 0/8 (0%)</td>
<td>LOD: 0.02 ng organotin cation/mL mean: – median: – range: &lt;LOD–0.05 n &gt; LOD: 4/8 (50%)</td>
<td>not measured</td>
<td>not measured</td>
<td>LOD: 0.02 ng organotin cation/mL mean: 0.31 median: 0.28 range: 0.17–0.67 n &gt; LOD: 8/8 (100%)</td>
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</tbody>
</table>

Organotin and Total Tin Levels in Danish Women of Reproductive Age
## Organotin and Total Tin Levels in Danish Women of Reproductive Age

<table>
<thead>
<tr>
<th>Study</th>
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<th>Monobutyltin (MBT)</th>
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<th>Diphenyltin (DPT)</th>
<th>Triphenyltin (TPT)</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td><strong>Meijer et al.</strong></td>
<td><strong>(2004); Peters</strong></td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
<td>LOD: 0.2 ng/g median &gt; LOD: 0.2</td>
<td>LOD: 0.2 ng/g median &gt; LOD: 0.2</td>
<td>LOD: 0.4 ng/g median &gt; LOD: 0.4</td>
<td>not reported</td>
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<tr>
<td>Subjects: ♂ n = 48, ♂ n = 43, (volunteers), 19–78 y, n = 91</td>
<td>Years of collection: prior to 2004</td>
<td>range: &lt; LOD 0.1</td>
<td>range: &lt; LOD 0.1</td>
<td>range: &lt; LOD 0.1</td>
<td>range: &lt; LOD 0.1</td>
<td>range: &lt; LOD 0.1</td>
<td>range: &lt; LOD 0.1</td>
<td>LOD: 3/91 (3.3%)</td>
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<td></td>
<td>Country: Netherlands</td>
<td>n &gt; LOD: 3/91 (3.3%)</td>
<td>n &gt; LOD: 0/91 (0%)</td>
<td>n &gt; LOD: 0/91 (0%)</td>
<td>n &gt; LOD: 0/91 (0%)</td>
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<td>LOD: 0/91 (0%)</td>
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<td></td>
<td>Matrix: whole blood</td>
<td>Analytics: GC-MS</td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
<td>LOD: 0.1 ng/g median &gt; LOD: 0.1</td>
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<td>LOD: 0.2 ng/g median &gt; LOD: 0.2</td>
<td>LOD: 0.2 ng/g median &gt; LOD: 0.2</td>
<td>LOD: 0.2 ng/g median &gt; LOD: 0.2</td>
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<td>range: &lt; LOD 0.1</td>
<td>range: &lt; LOD 0.1</td>
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<td>n &gt; LOD: 0/91 (0%)</td>
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<tr>
<td><strong>Mino et al.</strong></td>
<td><strong>(2008)</strong></td>
<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
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<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
<td>not reported</td>
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<tr>
<td>Subjects: ♂ (gave birth in previous week), age not reported, n = 67</td>
<td>Years of collection: 2002</td>
<td>range: not reported</td>
<td>range: not reported</td>
<td>range: not reported</td>
<td>range: not reported</td>
<td>range: not reported</td>
<td>range: not reported</td>
<td>LOD: 2.5 ng/mL mean: – median: –</td>
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<tr>
<td></td>
<td>Country: Japan (Okayama, Kagawa)</td>
<td>LOD: 2.5 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
<td>LOD: 2.5 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
<td>LOD: 2.5 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
<td>LOD: 2.5 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
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<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
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<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
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<td>LOD: 1.3 ng/mL mean: – median: – range: not reported n &gt; LOD: “undetected in vast majority of samples”</td>
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### Organization and Total Tin Levels in Danish Women of Reproductive Age

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<th>Triphenyltin (TPT)</th>
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</thead>
<tbody>
<tr>
<td><strong>Nielsen and Strand (2002)</strong></td>
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<tr>
<td>Subjects: ♂ (autopsy), 21–82 y, n = 18</td>
<td>LOD: 0.3 ng/g wet weight mean: 9.0 median: 4.6 range: 0.8–28.3 n &gt; LOD: 18 (100%)</td>
<td>LOD: 0.3 ng/g wet weight mean: 1.6 median: 1.4 range: 0.3–4.7 n &gt; LOD: 18 (100%)</td>
<td>LOD: 0.3 ng/g wet weight mean: – median: – range: &lt;LOD n (%) &gt; LOD: 0 (0%)</td>
<td>not measured</td>
<td>not measured</td>
<td>LOD: 3 ng/g wet weight mean: – median: – range: &lt;LOD n &gt; LOD: 0 (0%)</td>
<td>mean: 10.6 ng/g wet weight median: 6.2 range: 1.1–33</td>
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<tr>
<td><strong>Rantakokko et al. (2008)</strong></td>
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<tr>
<td>Subjects: ♂ n = 138, ♀ n = 162, (male fishermen, wives, other family), 18–79 y, n = 300</td>
<td>LOQ: 0.2 ng/mL mean: – median: – range: &lt;LOQ n &gt; LOQ: 0/300 (0%)</td>
<td>LOQ: 0.18 ng/mL mean &gt;LOQ: 0.32 median &gt;LOQ: 0.32 range: &lt;LOQ n &gt; LOQ: 0/300 (0%)</td>
<td>LOQ: 0.32 ng/mL mean &gt;LOQ: 0.38 median &gt;LOQ: 0.38 range: &lt;LOQ n &gt; LOQ: 2/300 (0.7%)</td>
<td>LOQ: 0.35 ng/mL mean &gt;LOQ: 0.38 median &gt;LOQ: 0.38 range: &lt;LOQ n &gt; LOQ: 0/300 (0%)</td>
<td>LOQ: 0.35 ng/mL mean &gt;LOQ: 0.35 median &gt;LOQ: 0.35 range: &lt;LOQ n &gt; LOQ: 0/300 (0%)</td>
<td>LOQ: 0.03 ng/mL mean &gt;LOQ: 0.03 median &gt;LOQ: 0.03 range: &lt;LOQ n &gt; LOQ: 0/300 (0%)</td>
<td>LOQ: 0.04 ng/mL mean &gt;LOQ: 0.04 median &gt;LOQ: 0.04 range: &lt;LOQ n &gt; LOQ: 0/300 (0%)</td>
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**References**

- Nielsen and Strand (2002)
- Rantakokko et al. (2008)
### Organotin and Total Tin Levels in Danish Women of Reproductive Age

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<tbody>
<tr>
<td>Rantakokko et al. (2013)</td>
<td>LOQ: 0.1 ng/g fresh weight mean: 0.06 median: 0.05 2.5th–97.5th percentile: 0.05–0.18 n &gt; LOQ: 12/112 (11%)</td>
<td>LOQ: 0.1 ng/g fresh weight mean: 0.14 median: 0.13 2.5th–97.5th percentile: 0.05–0.36 n &gt; LOQ: 74/112 (66%)</td>
<td>LOQ: 0.02 ng/g fresh weight mean: 0.32 median: 0.18 2.5th–97.5th percentile: 0.03–1.24 n &gt; LOQ: 111/112 (99%)</td>
<td>not measured</td>
<td>not measured</td>
<td>LOQ: 0.02 ng/g fresh weight mean: 0.05 median: 0.01 2.5th–97.5th percentile: 0.01–0.31 n &gt; LOQ: 49/112 (43%)</td>
<td>∑MBT + DBT + TBT mean: 0.57 ng/g median: 0.40 2.5th–97.5th percentile: 0.14–1.83</td>
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</tbody>
</table>

**Subjects:** ♀ (mothers of controls, n = 56, and cases of boys with cryptorchidism, n = 56), 28.1–29.1 y (median age in groups), n = 112

**Years of collection:** 1997–2001

**Country:** Finland (Turku)

**Matrix:** placenta

**Analytics:** GC–MS
## Organotin and Total Tin Levels in Danish Women of Reproductive Age

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<tr>
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<tbody>
<tr>
<td><strong>Rantakokko et al. (2013)</strong>&lt;br&gt;Subjects: &lt;♀ (mothers of controls, n = 129, and cases of boys with cryptorchidism, n = 39), 31.0–29.5 y (median age in groups), n = 168&lt;br&gt;Years of collection: 1997–2001&lt;br&gt;Country: Denmark (Copenhagen)&lt;br&gt;Matrix: placenta&lt;br&gt;Analytics: GC–MS</td>
<td>LOQ: 0.1 ng/g fresh weight&lt;br&gt;mean: 0.07&lt;br&gt;median: 0.05&lt;br&gt;2.5th–97.5th percentile: 0.05–0.30&lt;br&gt;n &gt; LOQ: 17/168 (10%)</td>
<td>LOQ: 0.1 ng/g fresh weight&lt;br&gt;mean: 0.09&lt;br&gt;median: 0.05&lt;br&gt;2.5th–97.5th percentile: 0.05–0.36&lt;br&gt;n &gt; LOQ: 62/168 (37%)</td>
<td>LOQ: 0.02 ng/g fresh weight&lt;br&gt;not measured&lt;br&gt;not measured</td>
<td>not measured</td>
<td>LOQ: 0.02 ng/g fresh weight&lt;br&gt;mean: 0.05&lt;br&gt;median: 0.01&lt;br&gt;2.5th–97.5th percentile: 0.01–0.32&lt;br&gt;n &gt; LOQ: 62/168 (37%)</td>
<td>LOQ: 0.02 ng/g fresh weight&lt;br&gt;mean: 0.22&lt;br&gt;median: 0.15&lt;br&gt;2.5th–97.5th percentile: 0.12–0.69&lt;br&gt;LOQ: 62/168 (37%)</td>
<td>LOQ: 0.1 ng/g fresh weight&lt;br&gt;mean: 0.06&lt;br&gt;median: 0.05&lt;br&gt;2.5th–97.5th percentile: 0.05–0.18&lt;br&gt;n &gt; LOQ: 99/110 (10%)</td>
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<tr>
<td>Study</td>
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<tr>
<td>Takahashi et al. (1999)</td>
<td>Subjects: ♂ (autopsy), 47–73 y, n = 4</td>
<td>LOD: 4 ng/g wet weight mean: 18 range: 14–22 n &gt; LOD: 4 (100%)</td>
<td>LOD: 3 ng/g wet weight mean: 66 range: 45–78 n &gt; LOD: 4 (100%)</td>
<td>LOD: 2 ng/g wet weight mean: – range: &lt;LOD n &gt; LOD: 0 (0%)</td>
<td>not measured</td>
<td>not measured</td>
<td>not measured</td>
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<tr>
<td>(Thayer et al. 2015)</td>
<td>Subjects: ♀ (Snart-Foreldre/ Milieu “Soon-Parents/Environment” study), 18–40 y, n = 47 (pre-pregnancy or early 1st trimester samples)</td>
<td>LOD: 0.50 ng/mL ELOQ: 1.71 mean: – median: – range: &lt;LOD–10.9 n &gt; ELOQ = 5/4 7 (10.9%)</td>
<td>LOD: 0.25 g/mL ELOQ: 1.59 mean: – median: – range: &lt;LOD–4.50 n &gt; ELOQ = 1/4 7 (2.1%)</td>
<td>LOD: 0.25 ng/mL ELOQ: 1.48 mean: – median: – range: &lt;ELOQ n &gt; ELOQ = 0/4 7 (0%)</td>
<td>LOD: 0.35 ng/mL ELOQ: 1.60 mean: – median: – range: &lt;ELOQ n &gt; ELOQ = 0/4 7 (0%)</td>
<td>LOD: 0.25 ng/mL ELOQ: 1.40 mean: – median: – range: &lt;ELOQ n &gt; ELOQ = 0/4 7 (0%)</td>
<td>LOD: 0.30 ng/mL ELOQ: 1.25 mean: – median: – range: &lt;ELOQ n &gt; ELOQ = 0/4 7 (0%)</td>
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</table>
### Study Information

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<th>Study</th>
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<tbody>
<tr>
<td><strong>Valenzuela et al. (2014)</strong></td>
<td>♂ workers in a harbor where ship repairing and painting activities are common, 30–50 y, n = 6</td>
<td>LOD: 0.013 ng/mL mean: – median: – range: &lt;LOD–0.034 n &gt; LOD: 1/4 (25%)</td>
<td>LOD: 0.009 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 0/4 (0%)</td>
<td>LOD: 0.009 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 2/4 (50%)</td>
<td>LOD: 0.015 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 0/4 (0%)</td>
<td>LOD: 0.057 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 0/4 (0%)</td>
<td>not measured</td>
<td>not reported</td>
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<tr>
<td><strong>Zachariadis and Rosenberg (2009)</strong></td>
<td>♂, 24–45 y, n = 4</td>
<td>LOD: 0.013 ng/mL mean: – median: – range: &lt;LOD–0.034 n &gt; LOD: 1/4 (25%)</td>
<td>LOD: 0.009 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 0/4 (0%)</td>
<td>LOD: 0.009 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 2/4 (50%)</td>
<td>LOD: 0.015 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 0/4 (0%)</td>
<td>LOD: 0.057 ng/mL mean: – median: – range: &lt;LOD–0.049 n &gt; LOD: 0/4 (0%)</td>
<td>not measured</td>
<td>not reported</td>
</tr>
</tbody>
</table>

**Years of collection:** 2012

**Country:** Chile (Valparaíso region)

**Matrix:** urine

**Analytics:** HS-SPME, GC-PFPD

**Abbreviations:** ELOQ = estimated limit of quantitation; GC-FPD = gas chromatography-flame photometric detector; GC-PFPD = gas chromatography-pulse flame photometric detector; GC-MIP-AED = gas chromatography-microwave induced plasma-atomic emission detection; GC-MS = gas chromatography-mass spectrometry; HS-SPME = headspace solid-phase micro-extraction; LOD = limit of detection; LOQ = limit of quantitation.
Figure 1. Structures of Organotin Compounds Analyzed in the Current Study
Figure 2. Sample Availability and Chemical Analysis

A significant number of urine samples were excluded from the analysis because of (1) insufficient volume (urine was also used to measure a large number of other analytes) and (2) 19 urine samples were inadvertently thawed during shipment.
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