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Organochlorine levels in adipose tissue of women from a littoral region of Argentina ☆

Mónica Muñoz-de-Toro[a,*], Horacio R. Beldoménico[b], Silvia R. García[b], Cora Stoker[a], Juan J. De Jesús[b], Pablo M. Beldoménico[a], Jorge G. Ramos[a], Enrique H. Luque[a]

[a]*Laboratorio de Endocrinología y Tumores Hormonodependientes, School of Biochemistry and Biological Sciences, Universidad Nacional del Litoral, Santa Fe, Argentina*
[b]*Central Laboratory, Pesticide Division, School of Chemical Engineering, Universidad Nacional del Litoral, Santa Fe, Argentina*

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Abstract

Organochlorine compounds (OCCs), such as pesticides and polychlorinated biphenyls (PCBs), are persistent lipophilic chemicals identified as endocrine disruptors, mainly with estrogen-like effects. Northeastern Argentina, near the Paraná River, is characterized by intensive farming and agricultural activities and industrial development, and is therefore prone to high incidences of environmental and dietary exposure to OCCs. Hence, we conducted a study to (1) estimate the organochlorine residues present in mammary fat tissue in a population of women from this littoral region and (2) identify potential sources of exposure to OCCs. Our subjects were 76 women (residing in and around Santa Fe city and not occupationally exposed to organochlorines) who underwent excision biopsy of a breast lesion or had plastic surgery. Both frequency of occurrence and levels of organochlorine residues were high in breast adipose tissue of all the participants. The organochlorine residues most frequently found were *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE) in all the subjects analyzed, hexachlorobenzene (HCB) in 86.8%, and β-hexachlorocyclohexane (β-HCH) in 75.0%. The incidence of PCB congeners was very low. *p,p′*-DDE and β-HCH residues reached the highest levels, 4794 and 1780 ppb, respectively. The diet was a relevant source of exposure, consumption of animal fat and freshwater fish playing a significant role. Bioaccumulation was evidenced by the significant positive association between organochlorine levels and body mass index ($p = 0.0003$) and the age of the patient ($p = 0.0002$). The frequency and levels of OCCs found in our study population raise concerns regarding Argentinean exposure to these endocrine disruptors.

Keywords: Pesticides; Breast tissue; Environmental contamination; Diet exposure; Endocrine disruptors

1. Introduction

There is much evidence to show that organochlorine compounds (OCCs) interact with the endocrine system, resulting in numerous biologic effects (i.e., estrogenic, antiestrogenic, antiandrogenic) that may affect the health of humans and animals (Colborn et al., 1996). Most of these OCCs are agricultural pesticides or industrial compounds that also double as environmental pollutants. Chemically stable and strongly lipophilic, OCCs have low degradation rates and tend to bioaccumulate in lipid-rich tissues.

Most studies devoted to the assessment of the effects of OCCs on humans have been conducted mainly in highly developed countries. Not much research has been done in Argentina, a developing country. Although the only study on OCC body burden in the Argentinean population was carried out 30 years ago (García Fernandez, 1974), there have been later reports of the presence of OCCs in animal fat, freshwater fish, dairy products, maternal milk, and soil (Beldoménico et al., 1988; Lenardon et al., 1994; Maitre et al., 1994; Menone et al., 2000; Miglioranza et al.,

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*Corresponding author. Fax: +54 342 4575207.
E-mail address: monicamt@fbcb.unl.edu.ar (M. Muñoz-de-Toro).

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2003). Also, Oliva et al. (2001) reported an association between exposure to pesticides and infertility in male patients from a littoral region in northeastern Argentina, near the Paraná River. In recent years, OCCs have been proving to be a major threat to the health of Argentineans because of increased agricultural activities, industrial development, and lack of adherence to environmental protection rules.

In this background, we conducted a study to estimate the residues of OCCs present in mammary fat tissue in women living in a littoral region in Argentina and identify potential sources of exposure to OCCs. The study group consisted of women who underwent breast surgery and who also resided in and around Santa Fe city and nearby locations on the coast of the Paraná River. This area is characterized by intensive agricultural activities and thus is prone to higher incidences of environmental and dietary exposure to OCCs. Adipose tissue was the sample of choice because it gives adequate results with regard to accumulation status (Archibeque-Engle et al., 1997; Botella et al., 2004; Waliszewski et al., 2003).

2. Materials and methods

2.1. Study subjects

The study sample comprised a group of women who underwent breast surgery either for cosmetic reasons or breast disease (benign and malignant lesions) between March 1998 and April 1999 in regional hospitals of Santa Fe city. All participants ($n = 76$) resided in and around Santa Fe city (Argentina) at the time of surgery and were not occupationally exposed to persistent OCCs. Each subject signed an informed consent form and 62 subjects completed questionnaires through telephonic interviews. The questionnaires requested information about the demographic profile, menopausal status, weight loss, height, parity, breast feeding, and dietary habits of the subject. The section on food frequency took into account dietary habits (intake of freshwater fish, dairy products, animal fat, etc.) that may contribute significantly to exposure to OCCs. Histopathological reports and medical records were available for all subjects. Approval for this study was obtained from the Institutional Review Board.

2.2. Tissue sample collection

At the time of surgery, 0.5–1.0 g of breast adipose tissue was collected and weighed for organochlorine analysis. Samples were labeled with identification numbers to conceal malignity status, frozen at −70 °C, and stored until analysis in a glass vial previously washed in hexane.

2.3. Detection of organochlorine in adipose tissue

Breast adipose tissue was analyzed for the presence of the following compounds: hexachlorobenzene (HCB), hexachlorocyclohexane isomers (α-HCH, β-HCH, and lindane), aldrin, oxychlordane, α-chlordane, γ-chlordane, heptachlor, heptachlor epoxide, dieldrin, endrin, mirex, metoxychlor, dichlorodiphenyldichloroethylene (*p,p*′-DDE and *o,p*′-DDE), tetrachlorodiphenylethane (*p,p*′-TDE, *o,p*′-TDE), dichlorodiphenyltrichloroethane (*p,p*′-DDT, *o,p*′-DDT), and eight polychlorinated biphenyl congeners (PCBs) (International Union of Pure and Applied Chemistry numbers 077, 118, 128, 138, 170, 180, 187, and 195). Concentrations of organochlorines were measured following the method of Beldoménico et al. (1989) with certain modifications. First, defrosted fatty tissue was weighed (at least 0.5 g) and minced on a glass container using a new scalpel blade. The tissue was then mixed with 2–5 g of anhydrous Na_2SO_4 (Merck, Germany) and drops of petroleum ether to obtain a fine dehydrated granular mass. A polar extract was obtained by heating the sample to boiling in 20 mL of acetone–petroleum ether (25:75, v/v) on a shaking water bath. The extract was filtered and the container rinsed twice with 10 mL of petroleum ether. All the petroleum ether fractions were collected and evaporated to dryness, and the percentage of fat in each tissue sample was calculated. Then an aliquot of 200 mg of fat from each sample was dissolved in 5 mL of petroleum ether. Solid-phase extraction cleanup was done using Supelclean LC-Alumina-N SPE tubes (Supelco, Bellefonte, PA, USA). One milliliter of extracted aliquot was eluted from a microcartridge with 10 mL of petroleum ether. The eluate was concentrated to 0.5 mL, and a second cleanup was performed using Supelclean Envi-Florisil SPE tubes (Supelco). Ten milliliters of ethylic ether–petroleum ether (15:85, v/v) was used to elute the chlorinated compounds from the microcartridge. Subsequently, the volume of solvent was reduced to 1 mL in a dry bath with a gentle nitrogen stream. A gas–liquid chromatograph (Varian Model 3400) equipped with a ^{63}Ni electron-capture detector was used for the analysis of residues. The gas chromatography (GC) columns used were Megabore Capillary GC Column DB 608 (30 m × 0.53 mm ID, film thickness 0.83 μm) (J&W Scientific, Taejon, Korea), GC Capillary Column CP-Sil 8 CB (50 m × 0.25 mm ID, film thickness 0.12 μm) (VWR International B.V., Amsterdam, the Netherlands), and a GC packed column (2 m × 2 mm) coated with 1.5% SP 2250 + 1.95% SP 2401 on a Supelcoport 100–120 ID mesh (VWR International B.V., West Chester, PA, USA). Organochlorine pesticide standards Pestanal (Honeywell Riedel–de Haën Fine Chemicals, Seelze, Germany) and PCB congener standards (Ultra Scientific, North Kingstown, RI, USA) were used. All the solvents used were of pesticide-grade quality (Merck, Darmstadt, Germany). OCCs presence and level were confirmed using a GC–MS system (VG Trio 2; VG Analytical, Manchester, UK) in randomly selected samples.

Surrogate samples of bovine and equine abdominal and perirenal adipose tissue were prepared using known concentrations of organochlorine pesticides and PCBs. Recovery assays were run to compare the performance of both spiked matrix. As both assays were satisfactory (data not shown), bovine tissue was the matrix of choice. A certified reference sample of bovine fat tissue was supplied by the Department of Agriculture, Buenos Aires. The average recovery percentage in each sample was ⩾80%. The limit of detection, based on thrice the average SD of noise, was 2 ng/g of tissue for HCB, α-HCH, lindane, and *o,p*′-DDT, 4 ng/g for aldrin, oxychlordane, α-chlordane, γ-chlordane, heptachlor, heptachlor epoxide, dieldrin, *p,p*′-DDE, and *o,p*′-DDE, and 5 ng/g for the remaining chlorinated pesticides and all the PCB congeners assessed.

2.4. Statistical analysis

The variables evaluated were concentrations of OCCs, age at surgery (years), menopause status (pre or post), years lived in a rural area, weight loss (>3 kg) during the year prior to surgery (yes or no), body mass index (BMI, kg/m^2), number of children, months of lactation (average and categorized into three groups: less than 3 months, from 3 to 6 months, and more than 6 months), intake of animal fat (categorized into two groups: low, patients who ate lean red meat and processed meat [sausage, salami, etc.] infrequently; high, those who ate red meat regularly and processed meat frequently), intake of freshwater fish (less than once a week, at least once a week), and intake of dairy products (infrequent, at least once a week, every day). Each food type was evaluated individually and together with others for summation of scores.

The nondetectable level of OCCs was considered to be a value that was half the detection limit. The values of the OCCs were log-transformed when parametric tests were used and their central tendency reported as geometric means.

All possible pairs of variables were tested for association using appropriate statistical tests. Parametric tests were used when the assumptions were completely met, and nonparametric tests when they did not (i.e., Mann–Whitney tests to compare two groups, Kruskal–Wallis tests to compare three or more groups of a nominal variable, Jonckheere–Terpstra tests to compare three or more groups of an ordinal variable, and Spearman's *p* correlation to compare two continuous variables). Pearson and Mantel–Haenszel χ^2 tests and Fisher's exact tests were used to compare proportions. Although multivariable analysis was not possible because of the limited sample size, to account for confounding and interaction effects stratification was conducted every time an assessment of associations with values of a third variable was required.

3. Results

3.1. Characteristics of the subjects

According to histopathological reports, 54 patients were diagnosed with invasive breast carcinoma and 17 with benign breast disease. Five patients underwent plastic surgery of the breasts for cosmetic purposes; these subjects neither had breast cancer nor a family history of one. Table 1 summarizes the characteristics of the subjects studied. The mean age of the subjects was 59 years and most were in the postmenopausal stage. A high proportion of the subjects (79.7%) had children, and around half had breastfed for less than 6 months. The subjects presented an average degree of adiposity, in line with the BMI results (mean = 25.2 ± 4.6). It is important to note that all subjects lived in an urban area at the time of surgery. Even though 42% of the participants reported having resided in a rural area for different periods of time (21.6 ± 17.8 years) early in their lives, they had never been involved in rural work.

Table 1
Characteristics of subjects studied

Age (years), mean ± SD	58.8 ± 11.8 ($n = 68$)
Body mass index (kg/m^2), mean ± SD	25.2 ± 4.6 ($n = 62$)
Menopausal status (% postmenopausal)	74 ($n = 66$)
Number of children, mean ± SD	2.1 ± 1.7 ($n = 64$)
Breastfeeding (%)	($n = 61$)
For <3 months total	34.4
For >3 and <6 months total	14.8
For >6 months total	50.8
Rural residence (%)	($n = 62$)
Never	58
At least for one year	42[a]
Weight loss (>3 kg) during the year prior to biopsy (%)	29.8 ($n = 57$)

[a]Mean ± SD rural residence period (years): 21.6 ± 17.8.

3.2. Organochlorine levels in breast adipose tissue

As the levels of OCCs were similar among subjects who underwent plastic surgery and those who were treated for benign and malign breast lesions (geometric means: 950, 1034, and 832 ppb, respectively) (Kruskal–Wallis $p = 0.873$), we considered all subjects as belonging to a single population.

A high frequency of occurrence and elevated concentrations of OCC residues were found in breast adipose tissue of all the participants ($n = 76$) (Table 2). The highest concentrations of the OCC residues were 4794 ppb for *p,p′*-DDE, 1780 ppb for *β*-HCH, 252 ppb for HCB, 975 ppb for oxychlordane, and 222 ppb for heptachlor epoxide. The incidence of PCB congeners was very low (only one patient showed positive levels). The residues found most frequently were *p,p′*-DDE in all the participants studied, HCB in 86.8%, *β*-HCH in 75%, oxychlordane in 32.9%, heptachlor epoxide in 34.2%, and heptachlor in 22.4%. *p,p′*-DDT was detected in five patients (6.6%).

The total concentration of OCC residues measured showed a positive correlation with the age of the patient (Spearman's *p* correlation $p = 0.0002$) (Fig. 1A). Consistent with this, women in the postmenopausal stage had higher concentrations of total organochlorine residues (geometric mean = 1091.0) than women in the premenopausal stage (geometric mean = 382.6) (Mann–Whitney test $p = 0.0001$). BMI and concentration of OCC residues were positively correlated (Spearman's *p* correlation $p = 0.0003$) (Fig. 1B).

Significantly, high consumption of animal fat was associated with high levels of residues of OCCs in adipose tissue, whereas the association between freshwater fish

Table 2
Concentrations (ppb) of organochlorine residues in breast adipose tissue

Compound	Above detection limit frequency (%)	GM (95% CI)	AM ± SD	Range
p,p′-DDE	100	554.3 (431.6–711.8)	918.8 ± 935.5	20–4794
HCB	86.8	32.2 (22.4–46.4)	68.3 ± 65.2	BDL–252
β-HCH	75.0	83.1 (48.7–142.0)	367.4 ± 470.2	BDL–1780
Oxychlordane	32.9	6.7 (4.4–10.2)	50.9 ± 141.2	BDL–975.0
Heptachlor epoxide	34.2	5.2 (3.8–7.2)	16.9 ± 33.9	BDL–222.0
Heptachlor	22.4	3.1 (2.5–3.8)	7.3 ± 20.8	BDL–130
p,p′-DDT	6.6	2.5 (2.0–3.1)	7.9 ± 25.7	BDL–159
o,p′-DDE	1.3	2.1 (1.9–2.4)	5.3 ± 29.0	BDL–255
Dieldrin	1.3	2.1 (1.9–2.2)	2.4 ± 3.7	BDL–34
Total PCBs	1.3	2.1 (1.9–2.3)	3.0 ± 9.0	BDL–81
Total organochlorines	100	906.6 (705.4–1165.2)	1435.7 ± 1258.4	20.0–5861

Note: number of samples evaluated: 76. GM, geometric mean; CI, confidence interval, AM, arithmetic mean, BDL, below detection limit.

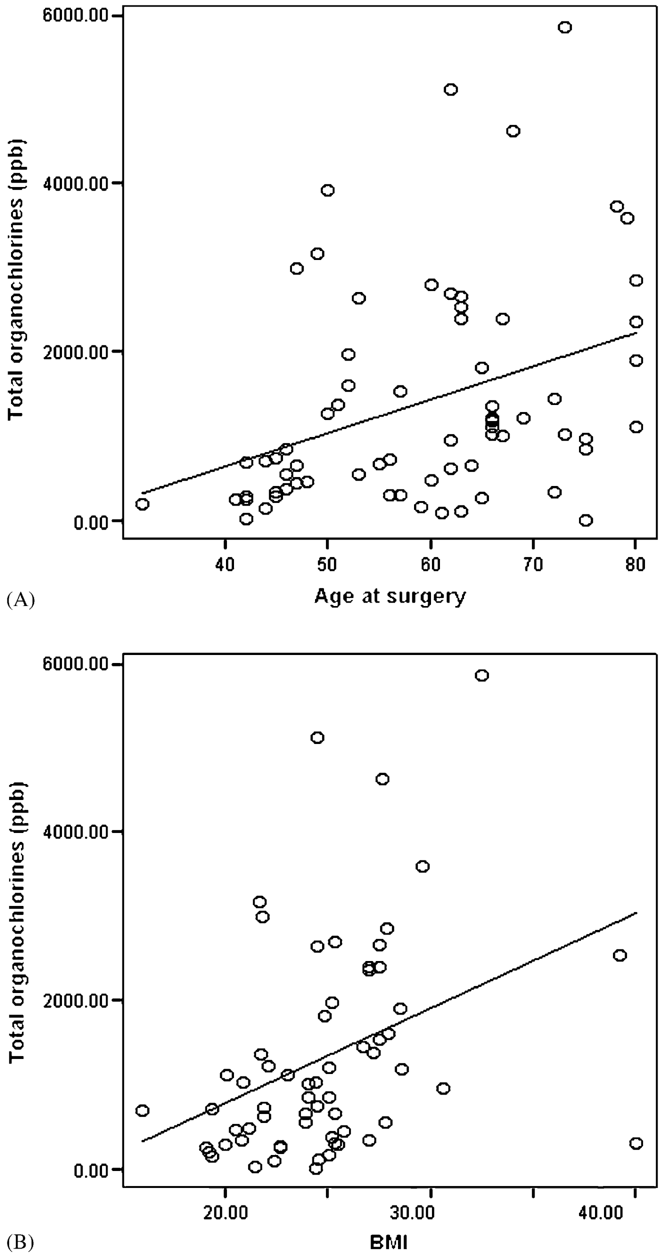

Fig. 1. Levels of total organochlorine residues in adipose tissue according to (A) age of the patients at surgery and (B) body mass index (BMI). The associations between organochlorine levels and BMI or age of the patients were estimated by Spearman's p correlation.

consumption and OCCs levels showed a positive trend (Table 3).

4. Discussion

In the present study, we describe the frequency distribution and concentrations of organochlorine residues in breast adipose tissue of women living in an urban area of an agricultural and industrial region of Argentina. Moreover, it is seen that dietary habits might be a significant source of exposure to OCCs.

Table 3
Dietary habits—with focus on potential sources of exposure to organochlorines and their relationship with organochlorine adipose levels

Consumption characteristic	Organochlorine levels (ppb)[a] (n)	P value
Freshwater fish		0.065[b]
Less than once a week	654 (44)	
At least once a week	1215 (18)	
Dairy products		0.530[c]
Infrequent	972 (3)	
At least once a week	837 (11)	
every day	777 (48)	
Animal fat intake		0.042[b]
Low	540 (19)	
High	971 (38)	

[a]Geometric mean.
[b]Mann–Whitney test.
[c]Jonckheere–Terpstra test.

Over the past three decades, most countries have observed a steady decline in the level of exposure to OCCs, reflecting a reduction in the use of these compounds and a corresponding decrease in environmental pollution (Kutz et al., 1991). The concentrations and frequencies of organochlorine residues in adipose tissue reported in this study are higher than those reported in developed countries (Jaga and Dharmani, 2005). Consistent with the increased agricultural activity and industrial development in the studied region, high levels of organochlorine pesticides and very low levels of PCBs were detected in the adipose tissue of our subjects. However, comparison of our results with those reported by García Fernandez (1974) reveals that there has been a decrease in concentration levels of OCCs also in Argentina. OCC residues were detected in animal fat, freshwater fish, dairy products, maternal milk, water-courses, soil, and wildlife (Beldoménico et al., 1988; Lajmanovich et al., 2002; Lenardon et al., 1994; Maitre et al., 1994; Menone et al., 2000; Miglioranza et al., 2003; Rovedatti et al., 2001). Therefore, fish, particularly fatty varieties caught in local rivers, as well as meat of animals raised on contaminated soil, can be significant sources of exposure. Although residing in a rural area did not seem to have an effect on the levels of OCC residues in our subjects, dietary habits could be a reason for the presence of high levels of OCC residues. In contrast with the results of Sanz-Gallardo et al. (1999), who reported that in five cities of Europe there was no association between p,p'-DDE concentration and any dietary component, our results show positive associations between organochlorine adipose levels and intake of animal fat and freshwater fish. In accordance with the Argentinean lifestyle, 70% of patients partake of a regular diet rich in red meat and processed meat (significant sources of animal fat). Similar results were reported with regard to the Inuit of Greenland, whose diet is mainly fish; the high concentrations of several OCCs showed a significant positive association with a marine diet (Bjerregaard et al., 2001).

In the present study, a marked bioaccumulation process was clearly seen in the positive association between organochlorine residue levels and BMI or patient age, results that are in accordance with previous reports (Muscat et al., 2003; Schildkraut et al., 1999; Stellman et al., 2000). Unlike results from other studies (Romieu et al., 2000; Soliman et al., 2003), in our study no correlation was found between breast-feeding periods and levels of OCC residues. The age of our subjects, higher than those included in the above-mentioned reports, together with their continuous exposure to OCCs, could explain the differences, because bioaccumulation for an extended period could mask OCCs lost through breast milk. Further, participants included in our study exhibited shorter periods of lactation than those included in earlier studies (Romieu et al., 2000; Soliman et al., 2003).

In Argentina, SENASA and ANMAT are responsible for the regulation of pesticides. Although the use of DDT on livestock was banned in 1968 (SENASA 2143/68), it remained in use as a household insecticide until 1998 (ANMAT 7292/98) (http://www.senasa.gov.ar/agroquimicos/principios.php). Regarding the concentrations of *p,p*′-DDE, our mean value (551.9 ng/g) is similar to that reported by Aronson et al. (2000), who, however, did not record data on the frequency of occurrence of different compounds in their study subjects. Other differences in data (arithmetic vs. geometric means, etc.) make it difficult to compare the organochlorine levels in our subjects with those recorded in other studies (Botella et al., 2004; Muscat et al., 2003; Stellman et al., 2000). Pesticides such as lindane and aldrin, frequently found by Botella et al. (2004), were below detection limits in our subjects. Regional differences in the use of pesticides might also explain the different frequencies of exposure.

Even though our study had the limitation of a small sample size, the data were sufficient to determine a significant positive correlation between levels of OCC residues and BMI or age, and to establish a link between intake of animal fat and OCC levels in adipose tissue.

In summary, this is the first full-fledged report from Argentina on the concentrations of OCC residues in women in the last 30 years. The present work shows that our study subjects (not occupationally exposed to organochlorines) have high levels of organochlorine residues in their breast fat tissue. More significantly, *p,p*′-DDE was present in all subjects and at high concentrations. Diet was a major factor that influenced the concentration of organochlorine residues in adipose tissue, with consumption of animal fat and freshwater fish playing a significant role. Despite the possible downward trend, the frequency and levels of OCCs found in our study population raise concerns regarding exposure of Argentineans to these endocrine disruptors. The persistence of DDT and mainly DDE in the food chain might be a concern to public health, especially considering the vulnerability of the fetus and breast-fed infants. Organochlorines accumulated in the mother could be transferred transplacentally to the developing fetus and from breast milk to the nursing infant (Dorea et al., 2001; Rogan et al., 1987, 1996). Results from our group on laboratory animals and wildlife showed significant long-term effects in hormone-dependent tissues because of prenatal exposure to low doses of xenoestrogens (Markey et al., 2001; Muñoz-de-Toro et al., 2005; Ramos et al., 2001, 2003; Stoker et al., 2003).

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Appendix A. Supplementary Material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2005.12.017.

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