JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Determination of Bisphenol A and Bisphenol B Residues in Canned Peeled Tomatoes by Reversed-Phase Liquid Chromatography

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Bisphenol A (BPA) and bisphenol B (BPB) concentrations were determined in peeled canned tomatoes of different brands bought in Italian supermarkets. Tomato samples analyzed were packaged in cans coated with either epoxyphenolic lacquer or low BADGE enamel. A solid phase extraction (SPE) was performed on C-18 Strata E cartridge followed by a step on Florisil cartridge. Detection and quantitation were performed by a reversed phase high-performance liquid chromatography (RP-HPLC) method with both UV and fluorescence detection (FD). On the total of 42 tested tomato samples, BPA was detected in 22 samples (52.4%), while BPB was detected in 9 samples (21.4%). BPA and BPB were simultaneously present in 8 of the analyzed samples. The levels of BPA found in this study are much lower than the European Union migration limits of 3 mg/kg food and reasonably unable to produce a daily intake exceeding the limit of 0.05 mg/kg body weight, established by European Food Safety Authority.

KEYWORDS: Bisphenol A; bisphenol B; canned peeled tomatoes; endocrine disruptors; HPLC

INTRODUCTION

During past years endocrine disruptors (EDs) have been attracting the attention of the scientific world because of their possible negative effects on human health. This class includes many alkylphenols, such as bisphenol A (BPA) and bisphenol B (BPB), which have been recognized to be potent EDs (*1, 2*).

BPA (2,2-bis(4-hydroxyphenyl)propane) has an estrogen-like activity, and its blood levels in men and women are associated with reproduction dysfunctions, endometrial hyperplasia, recurrent miscarriages, abnormal karyotypes and polycystic ovarian syndrome (*3*−*7*). It is a small monomer (MW = 228.29 Da) used primarily in the production of polycarbonate plastic and epoxy resins and as a nonpolymer additive to other plastics. These materials are extensively used in the manufacture of consumer goods and products, including food containers and utensils, dental sealants, protective coatings in food and beverage metal cans, baby bottles, and water supply pipes. It is reasonable to suppose that the extensive diffusion of such goods and products can give rise to a high risk of human exposure (*8, 9*).

BPB (2,2-bis(4-hydroxyphenyl)butane) is a BPA derivative (MW = 242.32 Da) used in the manufacture of polycarbonate resin (*3*) with ED properties similar to those of BPA (*1, 10, 11*).

Some dispute has been in the past about the actual levels of bisphenols able to cause toxic effects on humans; indeed, recent reports (*7, 12, 13*) have indicated that health risks can result from exposure to doses much lower than the limit of 0.05 mg/kg body weight day, previously reported by chemical corporations and regulatory agencies (*14*). Therefore, to assess actual human health risks caused by BPA and BPB exposure, it is essential to achieve accurate data on their levels in foodstuffs even at very low concentrations.

Several studies have been dedicated to determine BPA levels in food, mainly foods stored in cans (*15*−*17*), but, to the better of our knowledge, to date no study evaluated the possible release of BPB in canned food. Indeed, BPA has been demonstrated to be released from epoxy resin linings utilized to prevent corrosion and migration of metals into food during heat stabilization and storage (*18*−*21*), and this may occur for BPB, too. Therefore, we have focused our attention on the simultaneous determination of both BPA and BPB levels in canned peeled tomatoes. The choice of the matrix was based on the fact that canned tomatoes can represent a non-negligible daily dietary source of EDs, due to their large use in the preparation of many dishes all over the world.

The aim of this work has been both the simultaneous monitoring of BPA and BPB levels in marketed canned tomatoes and the setup of a simple and fast method suitable for routine determination of bisphenol levels in the selected food matrix. The setup of the method has included the validation of high-performance liquid chromatography (HPLC) analyses performed with both fluorescence detection (FD) and ultraviolet (UV) detection; indeed, the latter has been taken into account because,

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10.1021/jf802297z CCC: $40.75
Published on Web 10/30/2008

although less sensitive than fluorescence, it is the most widespread detection method in HPLC.

EXPERIMENTAL PROCEDURES

Reagents and Chemicals. All chemicals and reagents were of either analytical or HPLC grade and were purchased from Sigma-Aldrich (Milan, Italy).

Bisphenol A standard (minimum purity ≥99%) was purchased from Sigma-Aldrich (U.K.) and bisphenol B standard (minimum purity ≥99%) from TCI Europe (Zwijndrecht, Belgium).

Sample Preparation. Tomato cans of different brands were purchased in Italian supermarkets. The expiration date of products ranged between three months and two years at the moment of the analyses (mean value = thirteen months). We analyzed three samples from three cans with the same batch number for each brand. The analyses were performed as follows: the whole content of each can was homogenized by a model 7011 Waring blender, and a representative aliquot (20.0 g) was taken for extraction. The remaining content of each can was frozen at −20 °C for further analyses. 150 mL of acetonitrile was added to each sample (20.0 g) and mixed in the blender at high speed for 30 s. The mixture was filtered under vacuum on a Büchner funnel through a filter paper. The filter cake was returned to the blender for a second extraction with a fresh 150 mL of acetonitrile. The two acetonitrile aliquots were put together and partitioned with hexane (60 mL × 3 times) by shaking vigorously for 1 min for fat removal. The phases were allowed to stand for about 10 min, and the hexane layer was removed and discarded. The acetonitrile extract was evaporated using a rotary evaporator at 40 °C, and the residue was dissolved in 6.0 mL of a water/acetonitrile 90:10 (v/v) mixture.

Control samples were prepared as follows: BPA and/or BPB was added to peeled tomatoes in glass bottles, previously verified bisphenol free, to obtain five concentration levels (200, 300, 400, 500 and 1000 μg/kg).

Glassware was used to avoid possible release of BPA and/or BPB from plastic equipment.

SPE Purification. C18 Strata E SPE cartridges (Phenomenex, Torrance, CA) were conditioned and equilibrated with 5.0 mL of acetonitrile followed by 5.0 mL of water/acetonitrile 90:10 (v/v). After the application of the extract (6.0 mL) onto the SPE cartridge and washing with 20.0 mL of a water/acetonitrile 80:20 (v/v) mixture, each sample was eluted with 5.0 mL of acetonitrile for four times. The combined acetonitrile phases were evaporated to dryness, and the residue, after dissolution in 6.0 mL of a mixture of hexane/ethyl acetate 96:4 (v/v), was loaded onto a Florisil cartridge (Chromabond, Düren, Germany) previously conditioned with 5.0 mL of a hexane/ethyl acetate 96:4 (v/v) mixture. After cartridge washing (20.0 mL of hexane/ethyl acetate 93:7 (v/v)), the sample was eluted with 20.0 mL of ethyl acetate (5.0 mL × 4 times). The combined ethyl acetate phases were evaporated to dryness, and the residue was reconstituted with 20.0 mL of acetonitrile for the HPLC analysis.

Equipment and Chromatographic Conditions. A liquid chromatograph (Waters 600 Controller, Milford, MA) equipped with a 7725 Rheodyne injection valve (fitted with a 20 μL loop) was used. The stainless-steel column was a reversed-phase Synergi 4 μ Fusion-RP80A (250 × 4.60 mm i.d.) (Phenomenex, Torrance, CA) equipped with a reversed-phase Synergi 4 μ guard column. The mobile phase was acetonitrile/water 50:50 (v/v). The analyses were carried out at room temperature (20 ± 2 °C) and at a flow rate of 1.0 mL/min. Detection was simultaneously performed by two detectors in series, namely, (i) a UV detector (Waters 486) set at the wavelength of 228 nm, and (ii) a fluorescence detector (Waters 470) (excitation wavelength 273 nm, emission wavelength 300 nm). The signals from UV detection were recorded by a 746 Data Module (Millipore, Bedford, MA), whereas the signals from fluorescence detection were recorded by PC software (Chromatoplus 2007, Shimadzu-Corporation, Kyoto, Japan). The analysis of each sample was performed in triplicate.

Samples of tomatoes in glass bottles were considered as blanks and used to verify the absence of interfering peaks and, after fortification, to confirm the assignment of peak identity to BPA and BPB, as well as the precision of the method and the recovery. The retention times (t_r) were 9.70 ± 0.30 min for BPA and 11.20 ± 0.40 min for BPB.

BPA and BPB quantitative analyses were performed on the basis of the respective calibration curves, peak area vs concentration (ng/mL). The calibration curves were obtained by the analysis of BPA and BPB acetonitrile standard solutions (final concentrations: 50, 100, 200, 500 and 1000 ng/mL). 60 μL of each standard solution, i.e. three times the loop volume, was injected, and the signals from UV and fluorescence detectors were simultaneously recorded. Straight lines were observed with both detection methods (UV detection, $r^2 = 0.9994$ for BPA and $r^2 = 0.9996$ for BPB; fluorescence detection, $r^2 = 0.9966$ for BPA and $r^2 = 0.9974$ for BPB) within the range of the concentrations considered.

Statistical Analysis. A commercially available statistical package for personal computer (Microsoft Excel 2000) was used. Data are expressed as mean ± standard deviation (mean ± SD).

Mass Spectrometry. Mass spectrometry was performed on samples obtained by collecting the chromatographic peaks corresponding to either BPA (t_r range: 9.20−10.20 min) or BPB (t_r range: 10.70−11.70 min) in 20 subsequent runs. Mass spectra were acquired using an API 2000 triple-quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source (Applied Biosystem, MDS Sciex, Foster City, CA).

All the mass spectra were recorded by infusion into the ESI source using acetonitrile as the solvent. For each analysis a full scan spectrum (mass range 100−600 *m/z*, scan time 1 s) was acquired for identification purposes. The ESI-MS was operated in the negative ion mode under the following conditions: ion spray voltage was kept at 5000 V; turbo gas temperature 250 °C; nebulizer gas (compressed air) 55 psi; curtain gas (N_2) 20 psi; declustering potential 40 V; focusing potential 200 V; entrance potential 10 V.

RESULTS

We analyzed forty-two samples of peeled canned tomatoes of different brands, bought in Italian supermarkets. Twenty-six samples had packaging coated with epoxyphenolic lacquer and sixteen with low BADGE enamel, as indicated by manufacturers. The results, achieved by FD, are reported in **Table 1**.

We tested several cleanup procedures for extraction from the matrix, employing different kinds of SPE cartridges (C-18 Strata E, Florisil, Chem-Elut, Oasis HLB), separately or in combination. We obtained the best results using two consecutive steps of purification, the first one with C-18 Strata E and the second one with Florisil SPE columns. Indeed, this procedure demonstrated effective to substantially reduce the concentrations of all the compounds eluting at the front of the chromatographic runs, sometimes so abundant in the crude matrix to interfere with bisphenol analysis. The procedure also allowed us to achieve high percentages of bisphenol recoveries, as calculated on spiked control samples. Excellent values were found for both analytes (94.3% for BPA and 95.7% for BPB; RSD 2.63% for BPA and 5.15% for BPB). Chromatograms were obtained by both UV and fluorescence detection. **Figure 1A** and **Figure 1B** show the chromatograms of a real sample pretreated with the selected cleanup procedure, with UV and fluorescence detection, respectively.

Qualitative analysis was performed by comparison with retention values observed for BPA and BPB in the control samples obtained by spiking tomatoes in glass bottles.

For quantitative analysis, calibration procedures were performed on BPA and BPB standard solutions and repeated every two weeks; within this period the coefficient of variation (CV) was <0.5%. The solutions were injected in the HPLC immediately after preparation, and no degradation product was observed in their analysis.

We also tested samples of tomatoes stored in glass bottles, in some cases from the same manufacturers of canned tomatoes,

Table 1. Results of BPA and BPB Analyses in Peeled Canned Tomatoes

sample	can type[a]	country of origin	concn (μg/kg)[b] BPA	BPB
1	EP	Italy	115.3	85.7
2	LB	Italy	41.3	
3	EP	Italy	53.3	55.9
4	LB	Italy	43.6	
5	LB	Italy	21.4	
6	EP	Italy	20.5	34.7
7	LB	Italy	28.0	
8	EP	Italy	36.7	
9	EP	Italy		
10	EP	Italy		29.0
11	EP	Italy	43.4	
12	EP	Italy		
13	EP	Italy	28.6	27.1
14	LB	Italy	30.5	
15	LB	Italy		
16	EP	Italy		
17	EP	Italy	33.5	
18	EP	Italy		
19	LB	Italy	34.4	31.3
20	EP	Italy		
21	EP	Italy		
22	EP	Italy	56.9	
23	LB	Italy	49.5	36.4
24	EP	Italy	27.6	34.9
25	EP	Italy	41.6	
26	LB	Italy	29.0	45.5
27	LB	Italy	30.7	
28	LB	Italy	28.3	
29	EP	China		
30	LB	Italy	30.3	
31	EP	China		
32	EP	Italy		
33	EP	Italy		
34	EP	Italy		
35	LB	Italy		
36	LB	Italy		
37	EP	Italy	27.4	
38	LB	Italy		
39	EP	China		
40	EP	China		
41	LB	Italy		
42	EP	Italy		

[a] EP = epoxyphenolic lining; LB = low BADGE coating; can surface area for all samples is 2.4 dm^2. [b] All concentration data were obtained by fluorescence detection. Cans with epoxyphenolic lining: mean concentration values, BPA 38.7 μg/kg ($\pm$19.7), BPB 33.4 μg/kg ($\pm$8.2). Cans with low BADGE coating: mean concentration value, BPA 42.3 μg/kg ($\pm$18.6), BPB 37.7 μg/kg ($\pm$7.2). Where no concentration value is reported it is intended below LOD or below LOQ.

to exclude that BPA and BPB were already present in tomatoes and confirming their release from can lining material. Neither BPA nor BPB were detected in their analyses.

Since only BPA, but not BPB, was previously reported to be released in food samples from can lining materials (*15*−*18, 21*−*25*), we performed mass spectrometry on the nine samples found positive for BPB to further confirm the identity of both BPA and BPB.

Figure 2a and **Figure 2b** show the mass spectra of two chromatographic peaks of a real sample, eluting at the retention times of BPA and BPB, respectively. The correspondence of the signals of molecular ions to those of BPA and BPB standards (*m*/*z* 227 $[M - H]^-$ for BPA and *m*/*z* 241 $[M - H]^-$ for BPB) confirmed their identity.

Method Validation. All procedures for method validation were performed on Synergi 4 μ Fusion-RP80A column.

Linearity was assessed by inspecting the detection signals as a function of analyte concentrations, with the aid of a regression line by the method of least-squares. The two analytes were evaluated for linearity using solutions at concentration levels of 50 (for only FD), 100, 200, 500 and 1000 ng/mL, and triplicate injections were made for each concentration level. The correlation coefficients obtained were all $\geq$0.999.

The limits of detection (LOD) of the analytical procedure are the lowest concentrations of analytes that can be measured with definable statistical certainty in a sample, and were calculated from the levels of the various analytes equivalent to three times the standard deviation of noise on analysis, whereas the limits of quantitation (LOQ) were calculated from the concentration of the analytes that provided signals equal to 10 times the noise signal of analysis. Using UV detection, LOQ were 66.9 μg/kg and 51.3 μg/kg, for BPA and BPB, respectively; LOD were 20.0 μg/kg and 15.4 μg/kg for BPA and BPB, respectively. Using fluorescence detection, LOQ were 3.7 μg/kg and 2.3 μg/kg, for BPA and BPB, respectively; LOD were 1.1 μg/kg and 0.7 μg/kg for BPA and BPB, respectively.

The robustness of the analytical method has been established on three different reversed-phase columns at different HPLC elution conditions: Synergi 4 μ Fusion-RP80A 250 x 4.60 mm i.d., water/acetonitrile 50:50 (v/v); Onyx monolithic C_{18} 100 $\times$ 4.6 mm i.d. (Phenomenex, Torrance, CA) water/acetonitrile 65:35 (v/v); Sphereclone 5 μ ODS 2 250 $\times$ 4.6 mm (Phenomenex, Torrance, CA) water/acetonitrile 50:50 (v/v). Peak resolution remained similar despite the different tested conditions.

Precision is the measure of how close results are to one another, and it is evaluated by making repetitive measurements for the entire method. Very good interday precision data (n = 10) and intraday precision data (n = 5) were obtained on control samples with FD. The RSD (relative standard deviation) ranged from 0.20% to 2.96% for the interday precision tests, and 0.04% to 2.82% for the intraday precision tests. The RSD % was calculated by dividing the standard deviation by the mean, and multiplying the value by 100. Even better precision was observed with UV detection (interday RSD % = 0.14 − 2.20; intraday RSD % = 0.04−1.84).

DISCUSSION

Hormonally active agents, the so-called "endocrine disruptors", represent a widely debated issue due to concerns that exposure, mainly in early life, may lead to developmental and reproductive toxicities. For these reasons, there is great interest in these xenoestrogens and it appears necessary to assess human exposure to dietary BPA and BPB (*24, 26*).

In the present study we found BPA and/or BPB in several samples of peeled tomato cans of various brands. They are not present in any tomato glass bottle confirming, as previously indicated by other studies (*15*−*17, 22*−*24, 27*), that the presence of bisphenols in canned tomatoes is due to a release from packaging. However, we found at least one of the two considered bisphenols in only about half of the samples, although at low level. This implies that the presence of bisphenols in peeled tomatoes does not necessarily arise from their being packaged in cans. Moreover, in this study we also found that no significant difference in bisphenol content exists between epoxyphenolic and low BADGE coated cans. Although we did not investigate on the effect of contact time between tomatoes and cans, other authors reported that storage time did not show any effect on BPA migration in food content (*21*). Therefore, to date it is not clear which are the factors governing the passage of bisphenols from cans to food. It may be related to can material quality, and/or to the temperature of heat preserving process, and/or to the pH of the content.

Due to their chemical similarity, it is reasonable to assume that BPA and BPB can synergistically act with the same

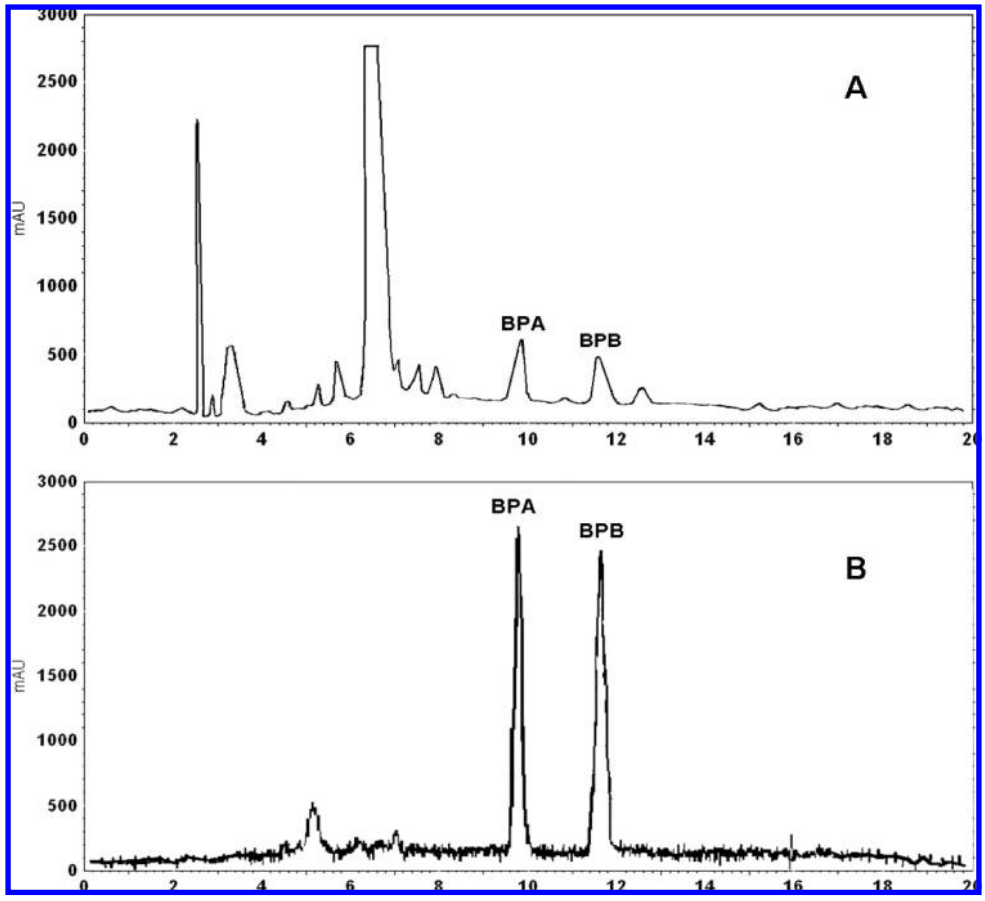

Figure 1. HPLC chromatograms of a real tomato sample purified by C-18 Strata E and Florisil SPE cartridges with UV detection (**A**) and fluorescence detection (**B**).

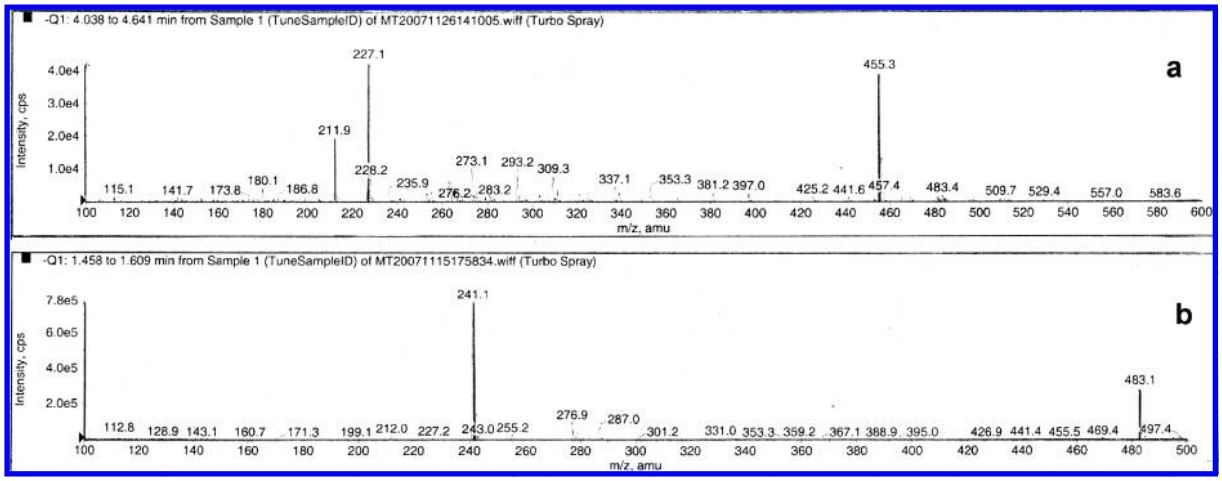

Figure 2. Mass spectra of BPA (**a**) and BPB (**b**) in a real sample of peeled canned tomatoes, acquired in full scan ESI-MS in negative mode.

mechanism of action at the same receptor sites. Therefore, the analytical procedure we propose, allowing their simultaneous determination, can be advantageous. Moreover, it is important to underline that the method includes a fast and simple cleanup procedure for tomato matrix, able to produce samples for HPLC analysis with minimal interfering signals and optimized to save analytical column life. Finally, a HPLC method with UV detection has been also validated. This detection method shows a slightly higher level of chromatographic interferences and is less sensitive than FD detection; indeed, LOD and LOQ values observed by FD are comparable with those already reported in the literature (*15*−*17*), whereas the values found with UV detection are about 20-fold higher. Nevertheless, UV detection, the most widespread detection method in HPLC, is anyway suitable for determination of bisphenol levels exceeding the legal limits (*28, 29*).

Our data show that the concentrations of BPA in the samples analyzed are far below the current specific migration limits of 3 mg/kg food for BPA, as imposed by the European Commission (*28, 29*). No information exists about BPB migration limits.

European Food Safety Authority (EFSA) indicates the dose of 0.05 mg/kg body weight as a full tolerable BPA daily intake from various sources (*14*). However, it is now widely recognized that toxic effects of bisphenols can arise from chronic exposure to doses much lower than those reported for acute exposure by chemical corporations and regulatory agencies. Indeed, following

a near continuous daily exposure, and due to the high lipophilicity (clog P is 3.32 and 4.20 for BPA and BPB, respectively) (*30*), bisphenols can accumulate in the adipose tissue giving rise to persistent, although low, serum levels (*12*). Moreover, it should be taken into account the possible synergistic action with other xenoestrogens or with endogenous steroids that should cause toxicity even at concentrations of each individual xenoestrogen that alone would not produce measurable effects (*13*). These considerations indicate the need of a continuous and accurate inspection of all possible sources of these substances, including dietary sources.

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Received for review July 25, 2008. Revised manuscript received September 30, 2008. Accepted October 1, 2008.

JF802297Z