



Alkylphenols in adipose tissues of Italian population

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ABSTRACT

Alkylphenols (APs) and AP ethoxylated compounds (APEs) were screened in human subcutaneous adipose tissue samples from Italy. The samples were collected during bariatric surgery from 16 subjects (three men and 13 women) and a total of seven alkylphenol compounds (APs) was detected. Nonylphenol (NP) was the compound found at the highest level (mean 122 ng g⁻¹ fresh weight; range 10–266 ng g⁻¹ fw). Several nonylphenol ethoxylates (NPEOs) were found in all the sample analysed though the frequency of detection decreased with the increasing number of ethoxylic groups. NP4EO was found only in four patients ranging from trace amounts to 41.3 ng g⁻¹ fw. Total nonylphenols (NPEs) ranged between 45 and 1131 ng g⁻¹ fw, whereas the concentration of total octylphenols (OPEs) was at least 10 times lower (range 6–80 ng g⁻¹ fw). Our findings show that the average concentration of NP is about two times higher than that found in women from Southern Spain and up to three times that of people from Switzerland. Similarly, OP mean level is two times that reported in Finland and Spain populations. This is the first study that reports the presence of alkylphenols in the Italian population adipose tissue and it draws a baseline for further researches in order to depict a trend in human exposure to these compounds and to investigate possible consequences for human health.

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1. Introduction

Alkylphenol ethoxylates (APEs) are the most widely used classes of non-ionic surfactants in industrial, agricultural and household applications (Ying et al., 2002; Vazquez-Duhalt et al., 2006). Nonylphenol ethoxylates represent around 80% of APEs, octylphenol ethoxylates most of the remaining (White et al., 1994). APEs are also used in the fabrication of plastic and rubber (Mutsuga et al., 2003; Nerín et al., 2003). Indeed, various plastic food containers and wrappings have been found to allow migration of alkylphenols residue into foodstuffs (Inoue et al., 2001; Loyó-Rosales et al., 2004). Some 60% of used APEs are discharged into the aquatic environment (Renner, 1997; Sole et al., 2000) where they are degraded to shorter-chain and more persistent alkylphenols (APs) (Giger et al., 1984; Jonkers et al., 2001) such as nonylphenol (NP) and octylphenol (OP). These products have been found as quite ubiquitous contaminants of biota and foodstuffs (Ahel et al., 1993; Tsuda et al., 2000; Guenther et al., 2002; Basheer et al., 2004; Lu et al., 2007).

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Alkylphenols and their ethoxylates exert endocrine disruption effects since they possess the ability to mimic natural hormones by interacting with estrogen receptors (Korach et al., 1991; Soto et al., 1991; Jobling and Sumpter, 1993; Jobling et al., 1996; Renner, 1997; Hong et al., 2004), nevertheless, they are weak estrogens (Paris et al., 2002; Bechi et al., 2006). Compared to 17 β -estradiol, in rainbow trout hepatocytes, OP, NP and NP2EO (nonylphenol di-ethoxylated) have relative potencies of 37×10^{-6} , 9×10^{-6} and 6×10^{-6} , respectively (Jobling and Sumpter, 1993). Besides, *p*-NP induces cell proliferation in estrogen-dependent breast cancer cells (MCF-7) (Soto et al., 1991), can cross the placenta and cause reproductive and developmental toxicity (Kwack et al., 2002; Hong et al., 2004). In a three generation study in rats, NP administered orally induced renal alteration in both sexes at a dose of 15 mg kg⁻¹ body weight (b.w.) (Cunny et al., 1997). A No Observed Adverse Effect Level (NOAEL) of 40 mg kg⁻¹ b.w. d⁻¹ has been reported from a 90-d feeding study in rats both for nonylphenol 4-ethoxylated (NP4EO) and NP9EO. The effects measured at higher doses were growth retardation and increased absolute and relative liver weight. In a study on dogs, after a technical mixture of NPEOs was administered by oral route, cardiotoxicity was observed at the dose of 40 mg kg⁻¹ d⁻¹ (Nielsen et al., 2000). In a two generation study on rats, after oral administration of OP, a NOAEL of 10 mg kg⁻¹ b.w. d⁻¹ for systemic and postnatal

toxicity was reported (Tyl et al., 1999). The Danish Environmental Agency has defined Tolerable Daily Intakes (TDIs) of 5 and 13 $\mu\text{g kg}^{-1}$ b.w. for NP and NPEO, respectively (Nielsen et al., 2000).

Due to their potential interference with estrogens receptors, bioaccumulation in organisms, widespread environmental contamination, since 1995 the use of NPEs in Europe was reduced in line with PARCOM Recommendation 92/8 (PARCOMM 92/8, 2000; OSPAR Commission, 2002); octylphenol and nonylphenol were designated as priority hazardous substances in the Water Framework Directive (European Parliament, 2000) and in 2003 the European Parliament and the Council with the 2003/53/EC Directive established new restrictions on the marketing and use of NPEs as a substance or constituent of preparations in a number of applications (European Parliament, 2003).

Direct human exposures to these compounds include contact with personal care products and detergents (Talmage, 1994) and the use of spermicides in contraceptives (Brooke et al., 2005). Yet, the main route of exposure to these compounds is probably represented by ingestion of contaminated food and drinking water (Ying et al., 2002; Soares et al., 2008). The following average daily intakes for NP have been estimated in Germany, New Zealand, Taiwan and Italy: 7.5; 3.6; 31.4; 4.7–12.2 $\mu\text{g d}^{-1}$ (Ferrara et al., 2001, 2005, 2008; Guenther et al., 2002; Thomson et al., 2003; Lu et al., 2007). Furthermore, average daily intakes of 0.1–0.2 $\mu\text{g d}^{-1}$ have been estimated for OP and much higher intakes, up to 100 $\mu\text{g d}^{-1}$ for NP and 1.7 $\mu\text{g d}^{-1}$ for OP, have been derived in people with a high seafood consumption (Ferrara et al., 2001, 2005, 2008).

On the basis of the available data, even in the worst cases, NP estimated daily intakes do not seem to represent a threat to human health (e.g., 100 $\mu\text{g d}^{-1}$ versus 300 $\mu\text{g d}^{-1}$ for NP in an adult of 60 kg of body weight). On the other hand, APs and more generally mixtures of EDCs have been shown to induce effects where the individual substance concentrations in the mixture had no statistically significant effect in vitro and in vivo (Silva et al., 2002; Brian et al., 2005; Hass et al., 2007).

Lu et al. (2007) reported that rice was the predominant source of NP in the Taiwanese population, accounting for 21.5% of total daily intake, together with aquatic products and livestock, with percentages of 18.0% and 17.4%, respectively. The highest levels of NP were found in oysters (235.8 \pm 90.7 ng g^{-1} wet weight) and salmon (123.8 \pm 116.2 ng g^{-1} ww), though other APs were found in all the analysed foodstuffs (vegetables, fruits, meats, eggs, etc.). In particular OP ranged between non-detected (nd) and 63.7 ng g^{-1} ww (median = 6.7 ng g^{-1} ww) with higher levels in salmon and cod, two saltwater fishes (63.7 and 39.8 ng g^{-1} ww respectively) and chicken (23.0 ng g^{-1} ww). In Germany, NP was detected in several foodstuffs and beverages, including fruits and vegetables, dairy products, fish and meat, bread, pasta, beer, coffee, and chocolates, within the range of 0.1–19.4 ng g^{-1} . The highest concentrations were found in apples, tomatoes, and fatty foods such as fish and meat (Guenther et al., 2002).

In previous studies on Italian seafood we found levels of NP higher than those reported by Guenther et al. (Ferrara et al., 2001, 2005, 2008). In particular pelagic fishes and top predators species, as well as some benthic seafood (e.g. mantis shrimps) showed levels of nonylphenol never reported before in scientific literature (up to more than 1 $\mu\text{g g}^{-1}$).

Data concerning human exposure monitoring to APs are scarce. APs have been detected in human blood, breast milk, and urine samples from several countries. In a Malaysian study on cord blood, NP was the endocrine disruptor found with the highest frequency (86%) (Tan et al., 2003). In Taiwan, NP and OP were found in all plasma samples ($n = 33$) from a population occupationally exposed (Chen et al., 2005). NP was also detected in 26% and 76% of umbilical cords samples from populations living in the Central ($n = 124$) and Northern ($n = 50$) part of Taiwan, with higher

concentrations found in residents from metropolitan areas (Chen et al., 2008). Trace levels of APs in human blood have been reported in various Japanese and Chinese studies (Inoue et al., 2000; Kawaguchi et al., 2004; Liu et al., 2006). NP has been found in human breast milk, at levels of 0.65–1.4 ng g^{-1} in Japan ($n = 3$) (Otaka et al., 2003), and of 13.4–56.3 ng mL^{-1} in Italy ($n = 10$) (Ademollo et al., 2008). In this study OP levels ranging from non-detected (n.d.) to 0.2 ng mL^{-1} were also reported (Ademollo et al., 2008), whereas levels of OP (tert-OP) ranging from n.d. to 7.6 ng mL^{-1} were registered in human breast milk from lactating mother living in the USA ($n = 20$) (Ye et al., 2006). NP was also detected in urine samples from 394 adults in the United States. In 51% of the samples NP levels were $\geq 0.1 \mu\text{g L}^{-1}$ and the 95th percentile concentration was of 1.57 $\mu\text{g L}^{-1}$ (Calafat et al., 2005).

The occurrence of some APs has been also investigated in human adipose tissues samples from Switzerland, Finland and Spain. A median NP concentration of 57 ng g^{-1} was recorded in women from Southern Spain (Lopez-Espinosa et al., 2009). This value is quite similar to that found in adipose tissue from cadavers ($n = 25$) in Switzerland (37 ng g^{-1} adipose tissue) (Muller et al., 1998a). OP was detected in adipose tissue samples from medicolegal autopsies in Finland ($n = 2/13$: 1.6 and 4.6 ng g^{-1} adipose tissue, respectively) (Smeds and Saukko, 2003) at concentrations similar to those reported by Lopez-Espinosa et al. (2009) (range 0.58–4.1 ng g^{-1} adipose tissue).

Adipose tissues are reservoirs of many lipophilic, persistent chemicals, where they accumulate. Their concentrations in these tissues represent an overall value of external human exposure that often is difficult to estimate specially because data on some minor sources are missing. The occurrence of other persistent compounds in human adipose tissue has been widely investigated and the results have been used to compare the exposure among different countries and examine some possible anomalies and trend within the countries (Meironyté Guvenius et al., 2001; Smeds and Saukko, 2001; Choi et al., 2003; Johnson-Restrepo et al., 2005; Nakata et al., 2005; Tan et al., 2008).

This study was undertaken to investigate the concentration of NP and OP residues in adipose tissue in the Italian population and to compare these levels with those found in other countries.

2. Materials and methods

2.1. Human adipose tissue samples

A total of 16 samples of human subcutaneous adipose tissue, obtained from patients (three males and 13 females) aged from 34 to 68 years during bariatric surgery and stored at -80°C in air-tight glass vials, were analysed for OP, OP1EO, NP and its corresponding ethoxylates (n . EO = 1–4). Seven samples were taken in 2003, the others in 2005 and 2007. Information on patients were limited to sex and age. All patients were informed that the surgical piece would be used for research purposes.

2.2. Reagents

Acetone, *n*-hexane and diethyl ether (HPLC grade) were obtained from Merck (Darmstadt, Germany). Orthophosphoric acid (85%) was purchased from BDH Laboratories Supply (Poole, England). Sodium chloride, Na_2SO_4 anhydrous and deactivated glass wool were from Carlo Erba Reagenti (Italy). Trifluoroacetic anhydride (TFAA) was from ICN Biomedical Inc. (Ohio, USA). An aliquot of 2 mL of all solvents (HPLC grade) was pre-concentrated to 1/20th of the volume and tested for purity by injecting in the GC/MS both in full SCAN and in SIM mode, monitoring the typical fragment ions of each of the APE's analysed.

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