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Validation of a method to monitor the occurrence of 20 relevant pharmaceuticals and personal care products in 167 bottled waters

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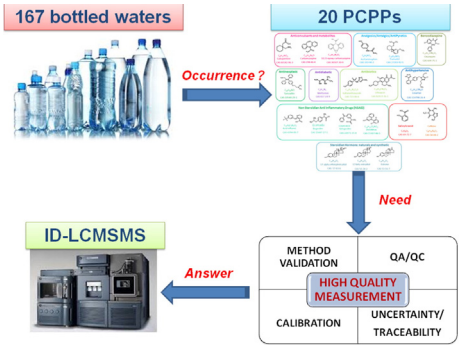
HIGHLIGHTS

- Measurements of quality in the water bottle market are needed.
- Quality of measurement implies accuracy and well stated uncertainty.
- Positive result shall be confirmed by a second analysis to avoid erroneous results.
- Scarce contamination of bottled water by the selected PCPPs is shown.

GRAPHICAL ABSTRACT



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ABSTRACT

Research on emerging substances in drinking water presents major interest and the possibility of trace contamination has seen increasing concern from the scientific community and the public authorities. More particularly, residues of pharmaceuticals and personal care products (PPCPs) in bottled water are a very important issue due to societal concerns and potential media impact. In this context, it has become necessary to carry out reliable monitoring. This requires measurements of high quality with demonstration of accuracy and well-defined uncertainty. In this study, 20 pharmaceutical compounds were targeted for the first time in 167 bottled waters from France and other European countries. An isotope dilution-solid phase extraction-liquid chromatography mass spectrometry method, together with stringent quality control and quality assurance protocols, was developed and validated according to French mandatory standards. Recoveries between 87% and 112% were obtained with coefficient of variation below 20%. Operational limits of quantification (LOQ) were comprised between 5 and 30 ng L^{-1}. Expanded uncertainties ($k = 2$) ranged between 16% and 43% and were below 35% for half of the compounds. The survey showed only four positive quantifications, thereby highlighting the rarity of contamination.

1. Introduction

Worldwide, the bottled water market is growing exponentially. The consumption of bottled water increased from 200% in 14 years,

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according to Rodwan (2013). In Mexico, the second largest market after the United States, consumption of bottled water is growing by 10% a year on average. In China, a jump of no <230% was observed between 2008 and 2012. In France, 175 bottles of water are sold every second and >11 billion liters of bottled water are produced annually. France is the world's largest exporter of natural mineral water, with average annual sales around 3.3 billion euros in 2012. In France, 40% of the population reports regular consumption of bottled water. This is motivated by the quality of tap water (poor taste, limestone content, and fear of pollutants) and by a preference for sparkling waters (Maïd et al., 2014). From the public's perspective, natural mineral water and spring water are associated with well-being, health, youth and a preserved natural environment. Moreover, they convey a very positive image of France abroad. The French bottled water industry is recognized as a reference in this sector that is careful to minimize its impact on the environment.

To answer, the societal demand for a water of quality, the demonstration of the need for effective chemical water monitoring is evident as the overall management and decision making system of European water policies is strongly dependent on monitoring data. Without accurate and comparable measurements, it cannot deliver a sound basis for proper decisions making. The challenge is to provide this information in a reliable, quick and yet affordable way for a steadily growing number of chemicals, which we can detect in the various.

Among emerging pollutants, pharmaceuticals receive significant interest because of increasing concern among the scientific community and the public authorities (Mompelat et al., 2009). Their pseudo ubiquity is currently demonstrated. Pharmaceuticals have been highlighted as of first concern for French aquatic system (Rosin et al., 2012; Botta and Lopez, 2016). In fact, they have been found in French groundwater (Lopez et al., 2015) and surface waters (Mompelat et al., 2011). Accordingly, it is reasonable to wonder if they can occur in bottled water considering that they are produced from natural waters. As the presence of pharmaceuticals in bottled water is also likely to have an impact on the positive image of these products, reliable data based on high quality measurements are essential and testing laboratories are required to provide these data. For substances of emerging concern, such as pharmaceuticals, there are no matrix certified reference materials and very few proficiency test schemes in place for laboratories to demonstrate their knowledge and abilities. Accreditation of laboratories according to the NF EN ISO/CEI 17025 (AFNOR, ISO/CEI 17025, 2000) standard helps to improve confidence in results, but is not always sufficient to guarantee reliable measurements.

To improve our knowledge, this study aimed at investigating the potential presence of emerging pharmaceutical and personal care product (PPCP) pollutants in 167 commercially bottled waters from France and other European countries. To do this and in view of certain sampling constraints (one L per sample), a single method of analysis that is able to meet the required limit of quantification (LOQ) was developed and validated. Given that very low concentrations are expected in these "pure matrices", and that low detection limits are obtained with the analytical procedures, it is important to be aware of the risk of false positive results. Accordingly, to ensure reliable data, the method relies on the implementation of isotope dilution/mass spectrometry (ID-MS), together with stringent quality control and quality assurance protocols. All these aspects are presented and discussed in the present paper.

2. Material and methods

2.1. Chemicals and reagents/reactants

2.1.1. Selection of target compounds

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) selected the target compounds based on national prioritization objectives and on the results of the previous national survey on drug residues in drinking water (Rosin et al., 2012) and recent bibliographic data (unpublished). The prioritization strategy developed was based on three relevant and accessible criteria: i) the prescribed and/or consumed quantity of pharmaceuticals in France; ii) the affinity for water based on physicochemical properties and iii) the activity through the acceptable daily intake for veterinary pharmaceuticals or minimum therapeutic dose for human ones. Finally, substances quantified in drinking water during the previous study were selected for this study (Rosin et al., 2012).

Twenty PPCPs belonging to ten chemical–therapeutic groups were selected (Fig. 1). As highlighted in Fig. 2, the 20 selected compounds – basic, neutral and acidic compounds – represent a wide range of physicochemical properties, especially regarding Log Kow and Log Dow that ranged between −2.51 for metformin and 7.88 for tamoxifen. As previously discussed, there is currently no European regulation on pharmaceutical compounds in drinking water neither bottled waters. Consequently, no performance requirements have been defined to monitor them. Accordingly, the required method performances, especially the limit of quantification, were set to achieve high level confidence measurements (accurate results with clear and controlled uncertainty), rather than the lowest achievable measurements of concentrations.

2.1.2. Selection of labelled analog standards

The selection of labelled analogs is a critical point (Petrovic, 2014). Each labelled compound was injected to check for the absence of unlabelled compound as an impurity and isotope ratios were verified and tracked. Isotope dilution was implemented for each analyte, using labelled analogs (deuterated or ^{13}C), except for the compound estrone.

The set of 20 selected compound standards and 19 labelled analog internal standards was purchased as pure standards. Information such as suppliers, CAS numbers, purity and physico-chemical properties is given in the Supplementary Information.

Acetonitrile (ultra gradient HPLC–grade, Baker HPLC analyzed) and methanol (Baker analyzed LC-MS reagent) were acquired from Atlantic Labo ICS (Bruges, France). High purity laboratory water was provided by a Milli-Q purification system (Millipore, Molsheim, France). Evian® water and Perrier® water (France Boissons, Rueil-Malmaison, France) were used as "reference" waters for still and sparkling water, respectively, during method development and validation because being considered as representative of both types of water and available in glass containers to prevent from contamination. Acetic acid (AnalaR Normapur®, purity = 100%), formic acid (AnalaR Normapur®, purity > 99%), hydrochloric acid 37% (Merck), sodium thiosulfate pentahydrate (AnalaR Normapur®, purity > 99.5%) and EDTA Na_2 (ethylenediaminetetraacetic acid disodium) 3.7% (0.1 M) in water (Merck, purity > 99.998%), potassium hydroxide KOH 47% (Merck), ammonia solution 25% (Ensure®, Merck), as well as ammonium hydroxide (ACS reagent 28–30% NH_3 basis) were purchased from VWR (Fontenay-sous-Bois, France) and from Sigma-Aldrich (Saint-Quentin-Fallavier, France).

2.2. Stock solution preparation

All stock solutions were prepared gravimetrically following the procedures of the French National Institute of Metrology (LNE). Each weighing was repeated five times for masses up to 5 mg and three times for higher masses. Individual stock solutions of each drug residue and its labelled analog were prepared at about 100 μg mL^{-1} in methanol. Mixed solutions of the 20 native surrogates and of the 19 isotopically labelled surrogates were then prepared in methanol at between 50 and 100 ng mL^{-1} and 100–200 ng mL^{-1}, respectively. All stock solutions were stored at −20 ± 6 °C in the dark. Their stability was checked and guaranteed throughout the five months of testing.

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