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Levels and potential health risks of mercury in prescription, non-prescription medicines and dietary supplements in Poland

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ABSTRACT

Determination of mercury is important in the case of pharmaceuticals for which the European Union regulations have not defined the maximum permissible concentration of this metal. The aim of the study was to determine the levels of mercury in the following groups of drugs (n = 119): analgesics, diuretics, cardiacs, antihypertensives, anti-influenza, antibiotics, anti-allergics, tranquilizers, antibacterials and in dietary supplements (n = 33) available on the Polish market. Mercury was analyzed using cold vapor atomic fluorescence spectrometry CV-AFS. Its content in the samples varied in the range of 0.9 −476.1 ng g^{-1}. Higher mercury concentrations were reported for prescription drugs (Rx): 0.9 −476.1 ng g^{-1} (median: 7.4 ng g^{-1}), lower − for non-prescription medicines (OTC): 1.2−45.8 ng g^{-1} (median: 6.0 ng g^{-1}). In the analyzed dietary supplements the concentrations were: 0.9−16.7 ng g^{-1} (median: 5.9 ng g^{-1}). On the basis of the information contained in the leaflet accompanying the medicine, a daily dose of mercury taken into the body with an analyzed medicament was estimated and the health risk posed by using such medicines was assessed. The study indicates that it is justified to carry out measurements of mercury in pharmaceuticals due to its high, potentially harmful.

1. Introduction

Mercury is one of the most toxic substances for humans, animals, plants and microorganisms, alike. It has mutagenic and teratogenic properties and can be accumulated in the human body. Therefore, the concentration of mercury in food, as well as in medicines and dietary supplements should be limited. The most toxic form of mercury taken orally is methylmercury (Me−Hg), Hg^{+2} is less toxic, and Hg^{+1} and Hg^{0} are the least toxic forms (Abernethy et al., 2010; Syversen and Kaur, 2012; Park et al., 2014).

Elemental mercury is vaporous and hence very mobile. It can easily cross the blood brain barrier, but is also quickly oxidized to inorganic mercury in the blood and other tissues.

(Clarkson et al., 2007), leading to deposition of inorganic mercury in target organs such as liver or kidneys. Methylmercury is readily absorbed in the gut and distributes in all tissues, including the brain (Clarkson et al., 2007). The presence of methylmercury in pharmaceuticals is un-likely, however, it can occur in certain dietary supplements produced from fish (Abernethy et al., 2010; Smith and Guentzel, 2010). In medicine and pharmacy, mercury has been known for centuries. Various compounds and forms of mercury were used for the production of drops, powders, ointments, pills and slurries applied in the treatment of conjunctivitis, syphilis, psoriasis, ulcers, boils, pediculosis, eczema, lichens and acne, or as anti-inflammatory, antibacterial and antiseptic substances (Szcześniak et al., 2010). Thimerosal is currently still used (excluding Sweden) as a preservative in multi-dose vaccine vials and can be dangerous, especially for young children (Zahir et al., 2005).

Pharmaceuticals and dietary supplements can be a potential source of mercury ingested orally by consumers. In recent years, particularly in developed countries such as the USA, Canada and in Europe, an increase in the consumption of drugs and dietary supplements has been observed (Dolan et al., 2003; Ang and Lee, 2006; Harris et al., 2011; Genuis et al., 2012 Wolle et al., 2014). Dietary supplements are defined as products that are designed to supplement the normal diet with vitamins, minerals, amino acids and other substances which have a nutritional or physiological effect. Due to an easy access and low price, they are considered by a large number of consumers as an alternative to the various types of drugs (Genuis et al., 2012; Marrero et al., 2013). The increase in demand for dietary supplements is also caused by numerous reports about

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side effects of synthetic medicines, and by the fact that people who take the supplements believe they are harmless (Ang and Lee, 2006; Genuis et al., 2012). It is estimated that 25% of the prescribed drugs worldwide are of plant origin, and 121 active substances are used in them. According to the World Health Organization (WHO), 11% of the total 252 drugs are exclusively of plant origin, whereas the substances used in the production of dietary supplements are derived from about 200 plants (Sahoo et al., 2010). Environmental pollution, primarily associated with industrial activity, motor vehicle emission and agricultural use of chemicals, influences the plants which are used by manufacturers of the supplements and drugs, and leading to possible mercury contamination (Caldas and Machado, 2004; Ang and Lee, 2006). The amount of mercury in plant medicines depends on the part of the plant from which the medicine is prepared. Fruits and seeds accumulate less mercury than rhizomes and leaves. Contamination of pharmaceuticals can also be caused by low grade reagents, solvents, catalysts or heavy metals used in the process of production (Avula et al., 2011; Genuis et al., 2012). Low-quality raw materials, inadequate control during the production and drug counterfeiting (mainly in China, Malaysia and India) can lead to high concentrations of mercury in the final product, which can pose a health threat to consumers, poisoning and even death (Caldas and Machado, 2004; Ang and Lee, 2006; Huang et al., 2006; García-Rico et al., 2007; Sahoo et al., 2010; Genuis et al., 2012; Kumar et al., 2012). Pharmaceuticals from Asia, used in traditional medicine, containing mercury as the main ingredient or as an excipient should be regarded as particularly dangerous (Ang and Lee, 2006; Sahoo el al., 2010; Kumar et al., 2012). Medicines and dietary supplements produced from plants are most often used to treat chronic diseases, which means potential long-term exposure of patients to heavy metals. The WHO recommends that medicinal plants used as raw materials for drugs should be examined for the presence of heavy metals. The maximum permissible mercury concentration should not exceed 1.0 ppm (Sahoo et al., 2010). In some countries, permissible levels of mercury have been proposed for medicines and herbal products used in medicine (WHO, 2007). However, the regulations are not uniform and vary depending on the country (Table 1).

According to the United States Pharmacopeia (USP), mercury concentrations in medicines should not exceed 3 μg g^{-1} (Karolewicz et al., 2010). Permissible limits for mercury in drugs have not been defined in current regulations of the European-Union however, concentrations of total mercury (THg) in dietary supplements were set to be not higher than 0.1 mg kg^{-1} (EC, 2008). Nevertheless, there is no information on the content of different mercury forms, e.g. methylmercury, in THg. The European Medicines Agency (EMA) and the European Pharmacopeia provides guidelines on mercury limits in plant products – they should not exceed 0.1 mg kg^{-1} (Karolewicz et al., 2010). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) set the provisional tolerable weekly intake (PTWI) by a healthy human for inorganic mercury at 4 μg kg^{-1} per week – and for methylmercury, especially for pregnant women the PTWI is 1.6 μg kg^{-1} per week (JECFA, 2010). The European Food Safety Authority (EFSA), Scientific Panel on Contaminants in the Food Chain (CONTAM Panel), however, proposed different PTWI for methylmercury – 1.3 μg kg^{-1} bw per week (EFSA, 2012). For mercuric chloride (II), the Agency for Toxic Substances and Disease Registry (ATSDR) established the Minimal Risk Levels (MRLs) for the acute exposure (1–14 days) – 7 μg kg^{-1} day^{-1}, and for the intermediate duration exposure (15–364 days) – 2 μg kg^{-1} day^{-1} (ATSDR, 2013). The EPA's reference dose (RfD) for mercury is 0.3 μg Hg day^{-1} (EPA, 2007a).

In Poland, according to data of the Central Statistical Office (GUS, 2011), the number of people taking different pharmaceuticals increased from 54% in 2004 to 71% in 2009. The report also noted a growth of *over-the-counter drugs* (OTC) in the survey period of 2004–2009, from 10% to 24%, while the use of medications prescribed by a doctor (Rx) decreased from 32% to 21% in the same period (GUS, 2011). IMS Health Poland reported that in 2007 the market of OTC products and medicines increased by 15.9% (the sales of Rx drugs – by 7.6%) as compared to the same period in 2006. At the same time, an excessive consumption was observed. The increase in consumption of such products can be associated not only with an easy access to them (in pharmacies and other sales outlets, e.g. internet pharmacies) and with the limited access to doctors – but it is also a result of the growing wealth and the belief that OTC medicines are completely harmless. Similarly as in other industrialized countries, a growing consumption of dietary supplements has been observed in Poland during recent years (Reguła et al., 2011). The legal requirements in many countries and the recommendations of the WHO/FAO regarding the permissible limits of mercury in pharmaceuticals are intended to control the concentrations at different stages of the production process: beginning from raw materials used to produce the drugs and ending at the final products. The aim of current study was to: (1) determine the levels of mercury in Rx and OTC medicines as well as in dietary supplements available on the Polish market; (2) estimate the daily dose of mercury taken with a single medicine; (3) assess the health risks, on the basis of the provisional tolerable weekly intake of mercury by a human, according to the WHO/FAO recommendations.

2. Materials and methods

2.1. Reagents

The acids of analytical grade (Sigma-Aldrich, USA), dedicated to the determination of mercury, were used in the analysis. Tin (II) chloride applied in the preparation of the reducing solution was of low mercury content (Merck, Darmstadt, Germany). Working standard solutions were prepared every day by diluting the stock

Table 1
Permissible limit for mercury in herbal drugs (WHO, 2007).

Mercury limit		
Herbal medicines		
Canada	Raw herbal materials	0.2 ppm
	Finished herbal products	0.02 mg day^{-1}
China	Herbal materials	0.5 ppm
Malaysia	Finished herbal products	0.5 mg kg^{-1}
Health Science Authority (HSA) Singapore	Finished herbal products	0.5 ppm
US Food and Drug Administration (FDA)	Herbal drugs	1.0 ppm
Department of Ayurveda, Unani, Sidhha and Homoeopathy (AYUSH) India	Herbal drugs	1.0 ppm
Other herbal products		
National Sanitation Foundation draft proposal	(Finished Dietary Supplement)	0.02 mg day^{-1}