Survey of human pharmaceuticals in drinking water in the Czech Republic

Frantisek Kozisek, Ivana Pomykacova, Hana Jeligova, Vaclav Cadek and Veronika Svobodova

ABSTRACT

The first large-scale assessment of pharmaceuticals in drinking water in the Czech Republic (CR) focused on the detection of five substances. Samples were collected from public water systems supplying 5.3 million people, 50.5% of the Czech population. In the initial survey of tap water from 92 major supply zones using mostly surface water, no pharmaceutical exceeded the limit of quantification (LOQ = 0.5 ng/L). In a second survey, samples were collected from the outlet of 23 water treatment plants (WTPs) considered of high risk because they use surface waters influenced by wastewater. Ibuprofen was the most frequently found pharmaceutical (19 samples), followed by carbamazepine (12), naproxen (8), and diclofenac (3); concentrations ranged from 0.5 to 20.7 ng/L, with medians below 6 ng/L. Concentrations of 17α-ethinylestradiol were below the LOQ. A follow-up survey included tap and outlet samples from eight of the 23 WTPs with the highest concentrations. Pharmaceuticals were quantified in only three tap water samples. Regarding risks to consumers, these results suggest that a relatively small population (<10%) in the CR is exposed to quantifiable concentrations of pharmaceuticals in tap water and that an extremely high margin of safety (several thousand-fold to several million-fold) is associated with these exposures.

Key words | Czech Republic, drinking water, health risk, human pharmaceuticals, tap water

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INTRODUCTION

The occurrence of pharmaceuticals in the environment and water cycle, especially in municipal wastewater and its treated effluent and receiving surface waters, has been reported in a number of studies and summary monographs (e.g. Kümmerer 2004; Ternes & Joss 2006; Anonymous 2008; Snyder et al. 2008; Halden 2010; WHO (World Health Organization) 2011a). Increasing consumption and release of unmetabolized or unused pharmaceutical residues into the environment and advances in the detection of trace amounts of organic substances underlie the increased reports of pharmaceuticals in drinking water. These substances have been detected in drinking water in relatively low concentrations, generally below 50 ng/L (KNAPPE (Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters) project 2008; Snyder et al.

2008). However, few systematic surveys have been conducted to help estimate the proportion of the population exposed to these pharmaceuticals and the range of concentrations to which this population is exposed (WHO 2011a).

Detection of pharmaceuticals in the environment has attracted the attention of the mass media, arousing health concerns of consumers. The mass media in the Czech Republic (CR) have covered this issue poorly. They mistakenly reported drug concentrations found in waste water as if they were present in drinking water, and they reported data from other countries as if it were applicable to the CR without considering that local conditions may differ. Reasons for not extrapolating drinking water quality data from one country to another include differences among countries in drug consumption and types of drugs prescribed

by physicians, protection of water sources, proportions of surface and ground water used for the production of drinking water, and water treatment technologies.

In 2010, 93.1% (9.787 million) of the 10.51 million people in the CR, received drinking water from public water supply systems; the remaining households used water from private wells. Some 41.3% of population supplied from public water supplies received drinking water produced only from groundwater sources, 30.7% received water produced only from surface sources and 28% were supplied with a mixture of ground and surface water (NIPH (National Institute of Public Health) 2011). In the same year, 49.7% of water distributed through public supplies was obtained from ground sources and 50.3% from surface sources (MoA (Ministry of Agriculture) 2011). About 80% of the volume of water from surface sources is obtained from protected water supply reservoirs situated at the upper reaches of the rivers that do not receive, or receive only minimal amounts of, wastewater discharges (SOVAK CR (Water Supply and Sewerage Association of the Czech Republic) 2012). Only 20% of the volume of water from surface water sources used by public systems is obtained from the mid or lower reaches of the rivers where wastewaters may substantially affect water quality. The data on water supplies are summarized in Table 1. We presume that groundwater sources are only under minimum influence of wastewater, because of their nature and their management. All water sources supplying more than 10,000 m^3 per year have obligatory protection zones with a special management regime to protect water quality; also many smaller sources have protection zones designated in the CR. Although all

surface water treatment plants (WTPs) use coagulation, sand filtration and chlorination, not all of them use advanced initial separation process (e.g. flotation), ozonation or granulated activated carbon. Because these water treatment processes may help reduce the concentrations of some pharmaceuticals and some surface water systems include groundwater sources, it is important to consider tap water concentrations when assessing health risks.

Due to the structure and protection of raw water sources for most of the population using public water systems, we hypothesized that exposure could be low; however, we lacked quantitative information about pharmaceuticals in water to estimate the risks.

In order to better inform the public about the possible risks in the CR, we conducted a systematic survey. The purpose of the study was (1) to detect the occurrence and concentrations of selected pharmaceuticals in both treated and tap water, especially in high-risk areas, and (2) to estimate human exposure to them and to assess average and maximum population health risks relating to such exposures.

METHODS

Selection of pharmaceuticals to be included in survey

Five pharmaceuticals were selected for the survey: naproxen, ibuprofen, diclofenac, carbamazepine, and 17α-ethinylestradiol. Their characteristics are given in Table 2. The selection and number of the pharmaceuticals was based on three factors:

(a) List of substances that are most commonly detected in drinking water above detection levels in other countries (data from available studies) (KNAPPE project 2008; Snyder *et al.* 2008).

(b) Drug consumption data from the CR (SUKL (State Institute for Drug Control) 2008), to verify whether selected substances found in other countries are used in important volumes in the CR.

(c) Analytical potential of the laboratory and the number of substances accepted for proper validation of the method.

No antibiotic was included because of the low detection rates reported to date in drinking water surveys from other

Table 1 | Overview of drinking water supply systems and sources in the Czech Republic in 2010 (MoA 2011)

Type of water supply	Population supplied (%)	Water source × population (%)		
		Groundwater	Surface water: upper reaches river	Surface water: mid-lower reaches river
Private supplies[a]	6.9	100	0	0
Public supplies	93.1	49.7	40.2[b]	10.1[b]

[a]Wells supplying single households.
[b]Expert estimate (SOVAK CR 2012) based on published total volume of surface water (50.3%) used for drinking water production (MoA 2011).

Table 2 | Characteristics of the substances monitored

Name (abbreviation)	Systematic name	CAS No.	Drug class
Ibuprofen (IBU)	(*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid	15687-27-1	NSAID[a]
Naproxen (NAP)	(+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid	22204-53-1	NSAID[a]
Carbamazepine (CARB)	5*H*-dibenzo[*b,f*]azepine-5-carboxamide	298-46-4	Anticonvulsant
Diclofenac (DICL)	{2-[(2,6-Dichlorophenyl)amino]phenyl}acetic acid	15307-86-5	NSAID[a]
17α-ethinylestradiol (EE2)	19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol	57-63-6	Hormonal contraceptive

[a]NSAID – non-steroidal anti-inflammatory drug.

countries (KNAPPE project 2008). On the other hand, despite its low detection rate in drinking water, we included 17α-ethinylestradiol because this hormonally active agent has been intensively discussed both by the mass media and the general public.

Selection of drinking water sampling sites

Drinking water samples were collected during three time periods. The objective of the first survey was a basic screening of tap water from all 14 administrative regions of the CR. Regional public health authorities were asked to suggest eight of the largest water supply zones based on the number of people supplied, five of them preferably supplying surface water or mixture of ground and surface water and three of them supplying ground water (if possible). Because surface water has a higher probability of wastewater discharges and occurrence of pharmaceuticals, we included a greater representation of surface water systems in the survey. During August 2010 to early November 2010, we collected a single tap sample of drinking water from 92 various water supply zones supplying altogether about 3.898 million people. The samples were taken at consumers' taps at different public buildings (schools, restaurants, municipal offices, etc.). Forty-eight tap water samples of surface water were from 48 water supply zones supplying altogether about 2.262 million people. Seventeen tap water samples of mixed surface and ground water were from 17 water supply zones supplying about 0.962 million people. These samples included bank filtration systems. Twenty-seven tap water samples of ground water were from 27 water supply zones supplying about 0.674 million people.

The second survey took place from May 2011 to July 2011 and focused on areas with the highest probability of the presence of the pharmaceuticals monitored. Twenty-four samples were collected from 23 WTPs after the drinking water was treated but before it was distributed to consumers – a single water sample was collected at 22 WTPs and two samples were collected at one riverbank filtration site that used two alternating wells without mixing. Eleven of the WTPs (supplying about 0.5 million people) obtained raw water through direct abstraction from the mid or lower reaches of rivers or from water supply reservoirs located in such areas. Nine WTPs (supplying about 1.7 million people) were located in upper reaches where the water was influenced by wastewater discharges and was of a lower raw water quality. The raw water quality of all 20 WTPs abstracting surface water directly met either the A2 or A3 categories of the former European Directive 75/440/EEC (EEC (European Economic Community) 1975). Finally, three WTPs (supplying more than 0.3 million people) obtained raw water from riverbank filtration or artificial infiltration in lower reaches of rivers. Finished water from all WTPs complied with current drinking water quality standards.

Survey 2 included 18 water supply zones fully or partially supplied from 12 WTPs previously sampled in survey 1 providing both tap and WTP samples at those sites. About 1.1 million people are served by these 12 WTPs with an additional 1.4 people served by the other WTPs sampled in survey 2. Survey 1 covered 3.9 million people, and with the overlap of the 1.1 million people in survey 2, the results of surveys 1 and 2 apply to 5.3 million people. The distribution of sampling sites in surveys 1 and 2 is shown in Figure 1. The third survey was conducted from September 2011 to October 2011 and focused on the eight WTPs with the highest concentrations found in survey 2. These eight WTPs supply a population of about 1.73
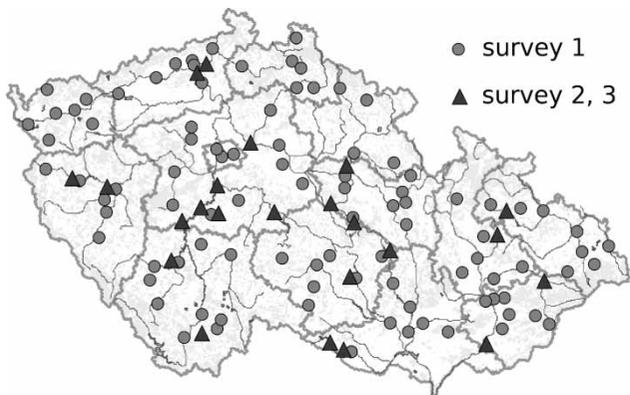
Figure 1 | Distribution of sampling sites in the Czech Republic. The dots indicate sites of survey 1, the triangles indicate sites of survey 2. Survey 3 was a follow-up of the eight water systems with the highest levels found in survey 2.

million people. Altogether 15 samples were collected to assess both the WTP outlet and tap water concentrations from the same supply system. We were not allowed to take repeated samples at one WTP, but two samples were collected at the riverbank filtration site using two alternating wells (both wells were sampled). Only seven tap samples from six supply systems are presented, because the samples from two systems were damaged during their processing. Relationships between sites and samples of survey 2 and 3 as well as short characteristics of the raw water sources are shown in Table 4.

The unit of monitoring in survey 1 was water supply zone as defined by the European Union (EU) Drinking Water Directive where a supply zone is a geographically defined area within which water intended for human consumption comes from one or more sources and within which water quality may be considered as being approximately uniform (EC (European Community) 1998). The reason was that water supply zone is the basic unit used for water quality control according to national regulation and as such is well defined in the national database of drinking water quality in terms of location, number of people supplied, operator, water quality, etc. In practice, smaller supply systems and some bigger ones are defined as one supply zone. However, many bigger water supply systems consisting of one distribution network are usually divided into several supply zones, because of administrative reasons (different operators manage different parts of the system), partial mixing with other source in some areas, or suspicion

that microbiological quality may differ within the system. That is why it is not always possible to simply put one water supply zone sampled in survey 1 on an equal footing with the distribution network of one of the WTPs sampled in survey 2 or 3.

Data on populations served by individual water supply zones were obtained from the national information system on drinking water quality run by the Ministry of Health. Data on populations served by individual WTPs included in survey 2 were obtained from its operators.

Sample collection and analysis

Drinking water samples were collected in 2 L silanized glass containers with 0.2 g of sodium azide added to stop biological activity in the sample. The chlorinated water samples were supplemented with several drops of 3% solution of sodium thiosulfate to deactivate free chlorine. Collected samples were transported to the laboratory in cool and dark conditions and were processed within 24 hours after collection. From each sampling site, 2 L samples were collected in duplicate and both were analyzed, but the result is presented as the average of the two values. Two samples (duplicates) of tap water in survey 3 were lost due to damage during manipulation before the concentration phase.

To detect the selected pharmaceuticals, the gas chromatography–mass spectrometry (GC/MS) method was used as previously described by Yu *et al.* (2007). In the analysis of survey 1 samples, the protocol of Yu *et al.* was followed. However, with the increasing number of analyses performed, the peak response and repeatability became worse and it was necessary to more frequently clean the ion source, liner and whole inlet, particularly due to the use of the derivatization agent injected directly into the GC/MS system. That is why, before analyzing survey 2 and 3 samples, minor modifications were made, primarily in the amount of the derivatization agent used (Kim *et al.* 1993; Kim & Yoon 1996).

Samples were acidified with concentrated HCl to pH 2–3 and were added with a mixture of surrogates (dihydrocarbamazepine and meclofenamic acid) to a final concentration of 100 ng/L of water. The analytes were

separated by solid phase extraction (SPE) on the Oasis HLB cartridges (3 mL, 60 mg).

The analytes were eluted with 6 mL of a mixture of ethyl acetate and acetone (50/50 v/v) and the extracts were evaporated under a slight nitrogen flow at 45 °C. The dried extracts were derivatized by adding 10 μL of a mixture of MTBSTFA and TBDMCS (99% N-methyl-N-*tert*-butyl-dimethylsilyl-trifluoroacetamide + 1%   *tert*-butyl-dimethyl-chlorosilane) added with 190 μL of isooctane. The derivatization was performed at 60 °C for 90 min.

The derivatized analytes and surrogates were analyzed using an HP 6890 gas chromatography system interfaced with an HP 5973 mass selective detector and equipped with an HP 7683 autosampler. A non-polar HP-5 ms column (30 m × 0.25 mm, 0.25 μm) was utilized. A volume of 2 μL of each derivative was injected. The SCAN mode was selected for mass spectrometry peak detection and the SIM mode (electron ionization, 70 eV) was used for analyte quantification in samples.

Three replicates were performed using drinking water spiked with 20 ng/L for all compounds. The calculated amount was compared with the spiked concentration. The recovery rates for individual substance were: ibuprofen 87 (±17)%, naproxen 107 (±11)%, carbamazepine 63 (±18)%, diclofenac 62 (±10)%, 17α-ethinylestradiol 93 (±28)%. The standards show a linear range from 0.5 up to 20 ng/L, EE2 from 2 up to 20 ng/L. The concentrations of analytes in relation to an external calibration were measured and were compared to results from surrogates. When the concentration of surrogates was low, the measurement was not considered for this data analysis. More detailed information on the analytical method used and its verification was published elsewhere (Pomykacova *et al.* 2012).

The limit of quantification (LOQ) was 0.5 ng/L for naproxen, ibuprofen, diclofenac and carbamazepine in all three surveys. The LOQ for 17α-ethinylestradiol was 0.5 ng/L in survey 1, but increased to 2.0 ng/L in surveys 2 and 3, which is still lower than Yu *et al.* (2007) reported (4.8 ng/L). We would explain this improvement by using a new generation of laboratory equipment. While Yu *et al.* used a chromatograph HP 5890 interfaced with an MD 5791 mass selective detector, we did our analysis on a chromatograph Agilent 6890 with a mass selective detector MD 5973, which is thought to be much more sensitive. We used

the LOQ rather than the limit of detection to present the results because this proves to be a more accurate estimate of exposure for use in the risk assessment.

Health risk assessment

There is no generally accepted approach to health risk assessment of environmental exposure to drug residues but various approaches have been proposed. The approaches differ mainly in the way the safe or tolerable reference dose is derived (Schulman *et al.* 2002; Webb *et al.* 2003; Kroes *et al.* 2004; Schwab *et al.* 2005; Dieter & Mückter 2007; Snyder *et al.* 2008; Cunningham *et al.* 2009). For our study, we used the method recommended by the World Health Organization (WHO 2011a). This method utilizes the margin of exposure (MOE) as a safety factor level. MOE is the ratio between a defined point on the dose-response curve (benchmark dose) and the human intake (EFSA (European Food Safety Authority) 2005). As the point of departure or benchmark dose, the minimum (daily) therapeutic dose (MTD) has been used. The MTD is the lowest concentration that evokes a desired therapeutic effect among target populations that is usually equivalent to the lowest dose prescribed or recommended and takes into account the number of doses per day. Its value is derived from an assessment of the balance between efficacy and safety. All MTDs were derived from the drug databases of the State Institute for Drug Control (SUKL 2011). When a range of therapeutic doses is used in the treatment of a disease, the MOE was calculated from the lowest recommended MTD because this provides an additional safety factor.

Two levels of pharmaceutical exposure or daily dose from drinking water were considered: (1) the theoretical maximum intake based on the maximum concentration of the substance found in drinking water (as the worst case scenario); and (2) the average intake based on the median concentration found in drinking water for those samples that exceeded the LOQ. Because of the few positive findings in tap water samples, we used the maximum and median concentrations found at WTP outlets. The exposure is calculated on an individual scale. Daily water consumption of 2 L, as the default assumption considered by the World Health Organization (WHO 2011b), was used for exposure

calculation. The MOE was calculated as the MTD divided by the daily dose.

RESULTS

Detection of pharmaceuticals in drinking water

All of the 92 tap water samples collected in survey 1 were below the LOQ, i.e. <0.5 ng/L for naproxen, ibuprofen, diclofenac, carbamazepine, and 17α-ethinylestradiol.

In survey 2, which focused on potentially high-risk areas and samples at the WTP rather than the tap, all samples from four of 23 WTPs were below the LOQ. In the remaining 19 WTPs, one to three substances were detected above the LOQ: two substances were detected simultaneously in six WTPs (co-occurrence were ibuprofen-carbamazepine, diclofenac-carbamazepine and four times ibuprofen-naproxen) and three substances in one WTP (ibuprofen-naproxen-carbamazepine). The most often detected pharmaceuticals were ibuprofen and carbamazepine. Ibuprofen was found in 12 samples in concentrations from 0.7 to 20.7 ng/L, with a median of 2.0 ng/L. Carbamazepine was found in nine samples in concentrations from 2.2 to 18.5 ng/L, with a median of 5.5 ng/L. Naproxen was present in five samples in concentrations from 0.5 to 3.0 ng/L, and diclofenac was present in two samples (0.6 and 3.9 ng/L). The results of survey 1 and 2 are summarized in Table 3.

In survey 3, concentrations at all WTP outlets were lower than survey 2 samples from corresponding sites; only three tap water samples from two supply zones were positive for any of the pharmaceuticals monitored, but at relatively low concentrations. Ibuprofen was detected in three tap samples (0.5–1.2 ng/L) and carbamazepine (4.0 ng/L) was present in a single tap sample (co-occurrence ibuprofen-carbamazepine). Interestingly, both of these supply zones were included in survey 1, where all tap water samples were less than the LOQ. All individual results from survey 3 together with results from the same WTPs in survey 2 are presented in Table 4.

In all samples, the concentration of 17α-ethinylestradiol was below the LOQ, i.e. 0.5 ng/L in survey 1 and 2 ng/L in surveys 2 and 3.

Health risk from drinking water exposure

For all substances except 17α-ethinylestradiol, the MOEs ranged from 10^6 to 10^7 when the exposure estimate considered the maximum concentration in drinking water and all variables were derived from the worst-case deterministic modeling. When median concentrations found in drinking water were considered, the MOEs for the four pharmaceuticals ranged from 10^7 to 10^8. The data for both exposure scenarios are summarized in Table 5. Because the health risk expressed as the MOE was computed only for the positive water samples, the above-mentioned individual exposures

Table 3 | Detection of pharmaceuticals in drinking water by concentration in surveys 1 and 2. Czech Republic, 2010 (survey 1) and 2011 (survey 2)

	Survey 1 Major Water Supply Zones ($n = 92$) Tap Water Samples ($n = 92$)					Survey 2 Possible Risky Water Systems ($n = 23$) Water Treatment Plant (WTP) Samples ($n = 24$)				
	IBU	NAP	CARB	DICL	EE2	IBU	NAP	CARB	DICL	EE2
<0.5[a] ng/L	92	92	92	92	92	12	19	15	22	24
0.5–3 ng/L	0	0	0	0	0	8	4	2	1	0
3–10 ng/L	0	0	0	0	0	2	1	6	1	0
>10 ng/L	0	0	0	0	0	2	0	1	0	0
Minimum[b]	<0.5	<0.5	<0.5	<0.5	<0.5	0.7	0.5	2.2	0.6	<2.0
Maximum[b]	<0.5	<0.5	<0.5	<0.5	<0.5	20.7	3.0	18.5	3.9	<2.0
Median[b]	<0.5	<0.5	<0.5	<0.5	<0.5	2.0	2.2	5.5	2.25	<2.0

[a]The limit of quantification for EE2 is 2.0 ng/L in survey 2.
[b]Of the values above the limit of quantification.
IBU – ibuprofen, NAP – naproxen, CARB – carbamazepine, DICL – diclofenac, EE2 – 17α-ethinylestradiol.

Table 4 | Detection of pharmaceuticals in drinking water by concentration in surveys 2 and 3 (Czech Republic, 2011)

No. of water supply	Survey 2 Water Treatment Plant (WTP) treated water ng/L					Survey 3 WTP treated water ng/L					Tap water ng/L				
	IBU	NAP	CARB	DICL	EE2	IBU	NAP	CARB	DICL	EE2	IBU	NAP	CARB	DICL	EE2
1	<0.5	<0.5	4.6	<0.5	<2.0	<0.5	1.2	<0.5	1.9	<2.0	<0.5	<0.5	<0.5	<0.5	<2.0
2	11.1	<0.5	<0.5	<0.5	<2.0	–	–	–	–	–	<0.5	<0.5	<0.5	<0.5	<2.0
3	9.3	0.9	<0.5	<0.5	<2.0	1.1	0.8	1.4	<0.5	<2.0	1.2	<0.5	4.0	<0.5	<2.0
4	2.3	2.2	<0.5	3.9	<2.0	0.6	<0.5	<0.5	<0.5	<2.0	<0.5	<0.5	<0.5	<0.5	<2.0
5	20.7	3.0	<0.5	<0.5	<2.0	3.6	3.0	<0.5	<0.5	<2.0	–	–	–	–	–
6	2.6	<0.5	<0.5	<0.5	<2.0	<0.5	<0.5	<0.5	<0.5	<2.0	–	–	–	–	–
7	<0.5	<0.5	<0.5	<0.5	<2.0	2.5	<0.5	<0.5	<0.5	<2.0	<0.5	<0.5	< 0.5	<0.5	<2.0
8a	<0.5	<0.5	9.4	<0.5	<2.0	<0.5	<0.5	<0.5	<0.5	<2.0	0.8	<0.5	< 0.5	<0.5	<2.0
8b	<0.5	<0.5	18.5	0.6	<2.0	<0.5	<0.5	13.6	<0.5	<2.0	0.5	<0.5	< 0.5	<0.5	<2.0

IBU – ibuprofen, NAP – naproxen, CARB – carbamazepine, DICL – diclofenac, EE2 – 17α-ethinylestradiol.
Limit of quantification: 0.5 ng/L for IBU, NAP, CARB, and DICL; 2 ng/L for EE2.
WTPs of supplies 2, 5, and 6 abstract raw water from reservoirs situated in mid or lower reaches of the rivers. WTPs of supplies 1 and 3 abstract raw water from reservoirs situated in upper to mid reaches of the rivers, but have lower water quality. WTPs of supplies 7 and 8 abstract raw water from riverbank filtration situated in the lower reach of the river. WTP 8 uses two alternating wells without mixing and both options were sampled (8a, 8b). WTPs 1, 3, 4, 5 and 6 supply water into 10 water supply zones sampled in survey 1, but in at least three zones water is mixed with another source.

Table 5 | Margins of exposure (MOEs) for the pharmaceuticals monitored and their detection. Czech Republic, 2010–2011

	MTD (mg)	Maximum concentration in water (ng/L)	Daily exposure dose (ng)	MOE (for the maximum)	Median concentration in water[a] (ng/L)	Daily exposure dose (ng)	MOE (for the median)
IBU	400	20.7	41.4	9.66×10^6	2.0	4.0	1.00×10^8
DICL	50	3.9	7.8	6.41×10^6	2.25	4.5	1.11×10^7
NAP	440	3.0	6.0	7.33×10^7	2.2	4.4	1.00×10^8
CARB	200	18.5	37.0	5.41×10^6	5.05	10.1	1.98×10^7
EE2	0.015[b]	2.0[c]	4.0	3.75×10^3	1.0[c]	2.0	7.50×10^3

[a]From the values above the limit of quantification.
[b]The expression 'therapeutic' dose is somewhat misleading, since this pharmaceutical is used on a preventive basis for contraception.
[c]Since EE2 was always under the limit of quantification, the limit of quantification was used as the theoretical maximum possible concentration for the calculation of MOE and half the limit of quantification was used as the median.
MTD – minimum (daily) therapeutic dose, IBU – ibuprofen, NAP – naproxen, CARB – carbamazepine, DICL – diclofenac, EE2 – 17α-ethinylestradiol.

and risk are relevant only to persons supplied with drinking water from systems with a positive sample. Public water systems with a positive sample provide water for a minor part of the Czech population. Considering theoretical maximum concentrations in drinking water (based on figures from WTPs, not confirmed at taps), the risk is relevant for only about 1% of the CR population (104,000 people). Using median or higher concentrations including maximums, the risk applies to less than 6% of the CR population (608,000 people).

If we consider the movement of people who may consume water at work or school, additional people may be partially exposed to supplies with a positive sample. Of the possible 2.3 million people in the CR who commute to work or school (CSO (Czech Statistical Office) 2005), 1.4 million commute within a district, 0.43 million commute outside a district, but within a region, and 0.48 million commute between the regions; most are people from suburbs of Prague commuting to Prague. One regional capital and eight district towns are the largest cities supplied by a water system

with a positive sample, and in these areas there are about 260,000 people exposed. We assess that not more than 100,000 commuters or an additional 1% is the maximum population that may be partially exposed to the above-mentioned levels of pharmaceuticals in drinking water.

For 17α-ethinylestradiol, a hormone that has an extremely low 'therapeutic' dose, the MOE was much lower in the order of 10^3 (3,750 for maximum exposure and 7,500 for median exposure). Because 17α-ethinylestradiol was not detected in a concentration above the LOQ, the higher LOQ (2 ng/L) was used as the theoretical maximum possible concentration in drinking water and one-half of this value was used as the median concentration for computing the MOE. An MOE of 3,750 suggests there is a large difference between the tolerable dose and drinking water exposure, i.e. the assumed safe dose of the hormone is more than 3,750 times greater than the hypothetical maximum daily exposure from drinking water.

DISCUSSION

Pharmaceuticals in drinking water

The results of the large-scale sampling of tap water from the major water supply systems in the CR supported our initial hypothesis about the likely low levels of pharmaceuticals in drinking water. The concentrations of the five pharmaceuticals were less than the LOQ in all of the tap water samples of survey 1, even though most samples were collected from systems using, in part or in whole, surface water sources. The most likely explanation is that most surface water sources are protected water supply reservoirs located at the upper reaches of the rivers.

Survey 2 focused on the drinking water produced from lower-quality surface water, and samples were collected directly from WTPs. Pharmaceuticals were rarely detected and when found were quantified in relatively low concentrations (medians <5.5 ng/L). In survey 3, we resampled the WTPs with the highest concentrations, collecting both WTP and tap water samples and found lower concentrations at all sites compared with survey 2, with the exception of ibuprofen in tap water at one site with a concentration slightly above the LOQ. The most often detected

pharmaceuticals were ibuprofen and carbamazepine. This can be explained by the low efficacy of carbamazepine removal during wastewater treatment (KNAPPE project 2008) and the high consumption of ibuprofen in CR reported to be about 15.6 g/person/year in 2007 (SUKL 2008). This consumption is more than three times as high as in Germany (Alder *et al.* 2006) and results in a relatively high introduction of this drug into wastewater and subsequently into surface water.

When considering the results from the point of view of the impact on the consumer, the emphasis should be on the detection of pharmaceuticals within the water supply system rather than at the outlet of the WTP. We expected to find lower concentrations of the pharmaceuticals within the distribution system, and this was confirmed by the results from both surveys 1 and 3. The primary rationale for lower concentrations in tap water is that, in some water supply systems, the treated surface water is mixed with ground water. Another factor is the chemical oxidation taking place in the water supply system, since drinking water produced from surface sources in the CR is disinfected with chlorine or chlorine dioxide before entering the distribution network. The removal rates associated with chlorination for various pharmaceuticals range widely from 0 to 100% but are usually more than 20% (WHO 2011a). A smaller role in reduction may be due to possible biological degradation as a result of the activity of bacteria and biofilms in the distribution system.

In summary, the pharmaceuticals monitored were detected above the LOQ in only three of 99 tap water samples. Ibuprofen was present in only three samples at two sites in survey 3 at concentrations of 0.5, 0.8, and 1.2 ng/L and carbamazepine was also found in one of these samples at a concentration of 4.0 ng/L. Moreover, one of these sites comes from a large water supply that was already sampled in survey 1 with no positive findings. All other samples were found to be below quantification levels. Given the low number of positive samples observed, the positive samples from the outlet of WTPs were also used for the calculation of health risk.

The absence or very limited presence of the five pharmaceuticals in this study is not necessarily a reason to imply that other pharmaceuticals were not present. Nevertheless, the pharmaceuticals in our surveys were expected to be

detected with the highest probability and may serve as an indicator for other pharmaceuticals. For example, carbamazepine, because of its characteristics, is considered as a suitable indicator of the presence of an important class of pharmaceuticals, as reported in studies from Romania (Moldavan *et al.* 2007), the Netherlands (Wuijts *et al.* 2008), and France (Anonymous 2011). Carbamazepine was detected in only 12 of all samples collected in the three surveys. Based on our results and experience from other countries (KNAPPE project 2008) as well as drug consumption data from the CR (SUKL 2008), it is reasonable to assume that the occurrence of other pharmaceuticals in drinking water in the CR is either very low (less than the quantification limits of the available analytical methods) or highly unlikely. This assumption is supported by the tap water results from surveys 1 and 3 that were above the limit of detection, but below the LOQ. We found only ibuprofen in three samples (0.2, 0.3 and 0.4 ng/L), no other substances were found in any sample above limits of detection, that were 0.2 ng/L for ibuprofen, 0.2 ng/L for naproxen, 0.3 ng/L carbamazepine, 0.3 ng/L for diclofenac, and 0.3 ng/L (survey 1) or 1.4 ng/L (survey 3) for 17α-ethinylestradiol.

It should also be noted that the sampling was performed during months of low precipitation with low mean flow rates in the watercourses and with wastewater discharges being less diluted. Consequently, the pharmaceuticals were more likely to be detected in raw water. On the other hand, our surveys did not include metabolites of the pharmaceuticals monitored. If they had been taken into account, a greater number of positive samples above the LOQ would likely have been detected. Nevertheless, only limited data are available on the toxicity of these metabolites and it is generally known that the daughter metabolites are less toxic than the parent compounds (NRMMC, EPHC & NHMRC (Natural Resource Management Ministerial Council, Environment Protection and Heritage Council, and National Health and Medical Research Council) 2008).

Concentrations of 17α-ethinylestradiol were below the LOQ in all samples. For the 92 tap water samples in survey 1, the LOQ was 0.5 ng/L. In surveys 2 and 3 that focused on high risk water systems, samples were primarily collected from the WTP, and the LOQ was 2.0 ng/L. Based on modeling by Hannah *et al.* (2009), 17α-ethinylestradiol

concentrations below 0.5 ng/L can be expected in surface and drinking water if the presence of a given pharmaceutical is not a result of the point-source pollution from the production of this drug. There are no discharges to water sources in the CR from the production of 17α-ethinylestradiol. Although survey 3 included relatively few tap water samples, we feel confident that drinking water concentrations are not only less than 2.0 ng/L, but also less than 0.5 ng/L because the concentrations in the tap water samples in survey 1 were less than the LOQ.

The key question regarding the interpretation of our results is whether the concentrations of pharmaceuticals found in our survey are representative of the levels in all public water supplies in the CR. The selection of sampling sites in survey 1 was designed to cover the most important water supply zones from all administrative regions due to the population supplied. A greater focus was on surface water sources because of the increased concern about contamination by pharmaceuticals. The selection of sampling sites in surveys 2 and 3 was designed to reveal maximum concentrations and risk.

In 2010, 30.75% of the population (3.000 million people) were supplied with drinking water produced from surface sources in 272 water supply zones, 41.28% (4.027 million people) were supplied with groundwater in 3,610 zones, and 27.97% (2.729 million people) were supplied with drinking water produced from mixed (ground and surface) sources in 156 zones (NIPH 2011). In survey 1, we sampled a total of 92 zones. Although it represents only 2% of Czech supply zones, these zones supply 3.898 million people (37% of the state population). There were 48 (52%) zones supplied with surface water (2.262 million people or 58% of the population surveyed), 27 (29%) zones supplied with ground water (0.674 million people or 17% of population surveyed), and 17 (19%) supplied with mixed surface and ground water (0.962 million people or 25% of the population surveyed). This shows the relatively high population from which water samples were collected and the over-representation of surface water supplies among the samples in survey 1. Thus, results of the risks assessment would represent an over-estimate of the population risk. Our sampling in survey 2 was focused specifically on the most risky treatment plants, abstracting raw water of the worst

quality with the highest probability of pharmaceutical occurrence (we included all WTPs which used A3 raw category or were located in lower reaches of rivers) to map supplies representing probable highest exposure. These WTPs supplies about 2.5 million people. If we consider the population living in the zones sampled in survey 1 and supplied by the WTPs sampled in survey 2 (about 1.1 million) we get a total population of about 5.3 million covered by the survey (50.5% of state population).

Although our calculation of exposure was based on a worst case scenario approach (using results from WTPs), the risk estimate was very low. People who use either private wells (7% of the population), or are supplied from public supplies not covered by the survey (about 42.5%) use in most cases either groundwater or surface water from protected reservoirs not influenced by wastewater, and we would presume their exposure and risk is even lower. However, as most analyses from these supplies would probably provide concentrations below the LOQ as we have seen in survey 1, it is not possible to quantify the exposure and risk for a more detailed population stratification.

That is why we consider exposure relating to our positive findings in 19 WTPs as relevant for less than 10% of the population of the CR. We can confidently say that more than 50% of the population receives drinking water with pharmaceuticals that are below the LOQ (if any).

Health risk

For our health risk assessment, we calculated the MOE for each pharmaceutical by dividing the MTD by the theoretical maximum or median intake from drinking-water. Theoretical maximum and median intake or daily exposure was calculated for each pharmaceutical from maximum and median concentrations found, and an assumed daily water consumption of 2 L. This method was also used by the Drinking Water Inspectorate for England and Wales (DWI), which commissioned a comprehensive desk-based review of current knowledge on and estimation of potential levels of 396 pharmaceuticals and 11 illegal drugs in drinking water in the United Kingdom (DWI 2007). For the DWI evaluation, an uncertainty factor of 1,000 was applied as a precautionary value. MOEs greater than 1,000 were considered to provide a substantial margin of safety against

potential adverse health impacts from exposure to trace concentrations of pharmaceuticals in drinking water.

All MOEs in our evaluation were greater than 1,000: 3,750 and 7,500 for 17α-ethinylestradiol and even 3–5 orders of magnitude greater for other pharmaceuticals monitored. The consumer may consider the margin of safety of 1,000 arbitrary and determined in an unclear way and might also object that MTD as a benchmark dose may not be adequate for estimating health safety. This is because the MTD is not determined from the toxicological point of view, does not exclude side (adverse) effects of the pharmaceutical and, as a rule, does not expect continual consumption (Webb *et al.* 2003). Therefore, to better explain this risk to the general public, risk comparisons, in which an unfamiliar risk is contrasted with a more common one, might be more appropriate (Fischhoff 1995). This relative exposure approach is based on the comparison of the concentration or activity of a given pharmaceutical (detected by a bioassay) in drinking water with that in food, or possibly with another exposure that is not considered as high-risk (Snyder *et al.* 2008).

Although the relative exposure approach is used primarily for hormonally active substances, such as estrogen hormones, it might also be usable for the illustrative assessment of the difference between exposures with reference to the MTD. For instance, when considering an ibuprofen tablet (400 mg) as the MTD and assuming a daily consumption of 2 L of drinking water, a person would have had to drink water containing the maximum concentration of 20.7 ng/L detected in our study for about 26,000 years (!) to ingest a dose of ibuprofen corresponding to a tablet, commonly taken by several hundred thousand population in the CR.

The relative exposure approach to hormonally active pharmaceuticals is illustrated in the study of Caldwell *et al.* (2010). They compared the estrogen exposure from drinking water with dietary estrogen exposure (our diet naturally contains some estrogens of both vegetal and animal origin – e.g. milk). Based on the US data, the authors calculated, according to the worst scenario, model concentrations of estrone, 17-beta-estradiol (E2), estriol, and ethinyl estradiol in drinking water to compare the respective drug exposure doses from drinking water and the diet (standard diet in adults and 0.42 L of milk in children).

They concluded that in children, total estrogen exposure (expressed as E2 equivalent quantity) from drinking water is about 150 times lower in comparison with a half liter of milk as recommended for daily consumption by children. Estrogen exposure of adults from drinking water was estimated to be 82 times lower in comparison with the standard diet. Similar data were reported by Stanford *et al.* (2010) who compared estrogen exposure from drinking water in 17 large US cities and from 40 common types of drinks and food.

The very high MOEs associated with the concentrations of the five pharmaceuticals measured in this study suggest a very low health risk and provide a large factor of safety compared to MOEs of more frequently detected chemical contaminants in drinking water. For comparison, we used the example of chloroform, which is the main component of the trihalomethanes produced when water is disinfected with chlorine. Considering a tolerable daily intake of 15 µg/kd/day, common concentration in chlorinated water of 30 µg/L, daily water consumption of 2 L (adult) or 1 L (child), and body weight of 60 kg (adult) or 10 kg (child), the MOE for chloroform is 15 (for adult) or 5 (for child). This suggests that the safe dose for chloroform is only five to 15 times greater than the routine exposures from chlorinated drinking water. The MOE for any of the five pharmaceuticals is much larger and suggests that the safe dose is at least 1,000 times greater than the infrequent exposure from only a few water systems.

No pharmaceutical (e.g. from the chemotherapy group) with genotoxic (carcinogenic) properties and no threshold effect that at any, even negligible, concentration implies a certain, even if very low, cancer risk, was included in our study. The available data on drinking water health risk assessment indicate that the individual lifetime cancer risk from such pharmaceuticals is lower than 10^{-6}, thus reaching a socially acceptable level, as reported by Kümmerer & Al-Ahmad (2010).

Risk assessments are subject to uncertainty. One important source of uncertainty is that the contaminants are considered separately and not in interaction with the other contaminants. Pharmaceuticals may be present in drinking water in various mixtures. Recent laboratory experiments focused on the effects of 13 pharmaceuticals at low concentrations in various mixtures of environmental relevance have revealed toxic effects on test microorganisms and human cells (Pomati *et al.* 2008). Various drug–drug interactions may take place within such mixtures to produce antagonistic, additive or synergistic effects (potentiation). Such interactions in relation to environmental exposure to pharmaceuticals are presented in more detail by Dieter & Mückter (2007). We are unable to evaluate whether the mixture of the five substances may increase or decrease the risk that we computed by considering each substance separately. However, based on the high levels of safety observed in our risk assessment for individual substances, we suspect that this may not be a significant factor in interpreting our risk assessment.

There is still no universally accepted method for health risk assessment for environmental exposure to traces of pharmaceuticals, although several approaches have been proposed. Nevertheless, no matter which approach is used, our results indicate very little or no risk to the consumer from the five pharmaceuticals at the concentrations detected in this study (WHO 2011a).

CONCLUSIONS

Our study was motivated by the misleading information disseminated by some mass media on the presence of pharmaceuticals in drinking water in the CR. Because the media reports raised public concern about the accidental and undesirable 'medication' associated with pharmaceuticals in drinking water, we conducted a systematic survey and health risk assessment of selected representative pharmaceuticals to estimate average and maximum population risk.

The results of this survey confirmed our assumption that the occurrence of pharmaceuticals in drinking water in the CR is rare or very low. Our assumption was based on the nature and sources of public drinking water supplies in the CR where almost half of the population receives drinking water obtained from ground water that receives no or very little wastewater discharges. As for the remaining population that receives drinking water from surface sources, the majority (more than 80%) of this population drinks surface water from protected water supply reservoirs located at the upper reaches of the rivers. In the water supply systems that use raw water from the mid or lower

reaches of the rivers, traces of pharmaceuticals were detected in treated water before delivery to the distribution system (one to three substances were quantified in 19 of 23 WTPs in the range of 0.5–20.7 ng/L). However, as a result of mixing with ground water sources and probably also of chemical oxidation due to disinfection, few pharmaceuticals were detected in tap water samples. Of the 98 water supply zones where tap water samples were collected, two of the five pharmaceuticals were detected slightly above the LOQ in three consumer tap samples from two water systems in survey 3. As shown above, this exposure does not pose a health risk.

From the consumer's point of view, there is another important aspect – psychological or aesthetic concerns. These concerns underlie one of the goals of modern drinking water management in the Bonn Charter: to provide good safe drinking water that has the trust of consumers (IWA (International Water Association) 2004). Consumers may find it unpleasant if the drinking water contains some contaminants, such as pharmaceuticals and hormones released from the human body. However, given the water cycle, it must be realized that most H_2O molecules in our drinking water are likely to have entered and left both human and animal bodies many times. This message was part of our discussion with consumers about the relevance of water contaminants and their possible risks.

These results serve to better inform consumers about the rare occurrence and the low concentrations of pharmaceuticals found in public water systems in the CR. Outputs of our study included the following:

- A brief press release and a more detailed web report for the general public explaining the issue and its health and environmental importance.
- A public announcement through media and website about the consumer's role in helping to maintain high quality water, e.g. responsible drug use, especially disposal of unwanted drugs (by law, all pharmacies in the CR must take back expired, unwanted, or unused drugs, and consumers should return these pharmaceutics for incineration rather than placing them in the garbage or flushing them into the sewers).
- Detailed information for water producers, in particular for those operating in high-risk areas, on how to

approach this issue (monitoring of selected pharmaceuticals in risky supplies, treatment options) and on how to openly and truthfully communicate it with consumers (publishing of occurrence if found, levels and relevant health risk using relative exposure approach, recommendation as to what can be done by consumers to decrease environmental load by pharmaceuticals) in a similar way to the information brochure issued by the American Water Work Association (Hoffbuhr 2009).

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