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Human health risk assessment of pharmaceuticals in water: An uncertainty analysis for meprobamate, carbamazepine, and phenytoin

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ABSTRACT

This study presents a step-wise development of a quantitative pharmaceutical risk assessment (QPhRA, hereafter) framework, including Monte Carlo uncertainty analysis for meprobamate, carbamazepine, and phenytoin during (1) accidental exposures of stream water and fish consumption and (2) direct ingestion of finished drinking water for children and adults. Average hazard quotients of these pharmaceuticals (i.e., the ratio of values of chronic daily intake to acceptable daily intake) were found to lie between 1×10^{-10} and 3×10^{-5} and 99th percentile values of hazard quotients were found to be less than 1×10^{-4} for both sub-populations, indicating no potential risks of adverse effects due to pharmaceuticals exposures. In addition, pharmaceutical concentrations were also observed to be lower than their respective calculated acceptable daily intake-equivalent drinking water levels, indicating no potential human health risks. To the authors' knowledge, for the first time in QPhRA studies, this study has attempted to characterize and quantify effects of factors, such as considerations for sensitive sub-populations using subpopulation-specific toxic endpoints and use of pharmaceutical concentrations in stream and finished drinking waters on risk estimates. Acceptable daily intake was observed to be the primary contributor (>93% variance contribution) in the overall uncertainties of estimates of hazard quotients, followed by fish consumptions and pharmaceutical concentrations in water. Further research efforts are required to standardize use of acceptable daily intake values to reduce large variability in estimation of hazard quotients.

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1. Introduction

In recent years, pharmaceuticals have received growing attention from environmental and health agencies all over the world owing to recent studies showing occurrence of pharmaceutical compounds in environment, especially in water bodies and have become one of the emerging water pollutants (Jones et al., 2005; Xagoraraki and Kuo, 2008; Benotti et al., 2009; Kolpin et al., 2002; Sabourin et al., 2009; Schwab et al., 2005; Snyder, 2008; Snyder et al., 2007, 2008a,b; Stackelberg et al., 2007; Westerhoff et al., 2005).

Due to emerging health concerns, recent studies have attempted to address the issue of health risks associated with exposures of pharmaceuticals from water (Christensen, 1998; Schulman et al., 2002; Webb et al., 2003; Schwab et al., 2005; Bercu et al., 2008; Snyder, 2008; Cunningham et al., 2009; Cleuvers, 2004; Jones et al., 2005; Pomati et al., 2008; Sanderson et al., 2004). The results of almost all previous quantitative pharmaceuticals risk assessment (termed as QPhRA, hereafter) studies indicated no appreciable human health risks associated with exposure of pharmaceuticals in water (Christensen, 1998; Schulman et al., 2002; Webb et al., 2003; Schwab et al., 2005; Bercu et al., 2008; Snyder, 2008; Johnson et al., 2008; Cunningham et al., 2009; Rowney et al., 2009).

Very few studies have attempted to apply all stages of a quantitative risk assessment framework, consisting of (1) hazard identification, (2) exposure assessment, (3) dose–response, and (4) risk characterization (Haas et al., 1999; US EPA, 2009), for assessing health risks associated with pharmaceutical exposures from water (Christensen, 1998; Schulman et al., 2002; Webb et al., 2003; Schwab et al., 2005; Bercu et al., 2008; Johnson et al., 2008; Cunningham et al., 2009; Rowney et al., 2009). Review of all previous QPhRA studies indicated that uncertainties and particular concerns, associated with pharmaceuticals exposure still exist for factors such as critical endpoints; assumptions for worst-case scenario estimations; mixture effects (particularly at trace pharmaceutical concentrations); sensitive sub-populations (children, pregnant women, debilitated or immuno-suppressed populations); regional differences, and study durations on risk estimates (Johnson et al., 2008; Snyder et al., 2008a,b; Rowney et al., 2009).

The objective of this study was to present a step-wise development of a QPhRA framework, including a Monte Carlo uncertainty

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Nomenclature

Acronym	Description
ADI	acceptable daily intake
$ADI_{Therapeutic}$	acceptable daily intake value based on therapeutic dose
$ADI_{Toxicity}$	acceptable daily intake-based on toxicity studies
Age_{ch}	children's age (years)
BCF	bioconcentration factors
BW	body weight
CDI	chronic daily intake
CW	pharmaceutical concentration in water
$DWEL_{ADI}$	acceptable daily intake-equivalent drinking water level
$DWEL_{ADI_{therapeutic}}$	therapeutic-based acceptable daily intake-equivalent drinking water level
$DWEL_{ADI_{toxicity}}$	toxicity- daily intake-equivalent drinking water level
FR	daily fish intake rate
HQ	hazard quotient
HSDB	hazardous substance data bank
IR	daily water ingestion rate
K_{ow}	octanol–water partition coefficient
LOAEL	low-observed adverse effect level
N	total number of samples
NOAEL	no-observed adverse effect level
POD	point-of-departure
QPhRA	quantitative pharmaceutical risk assessment
TD	therapeutic dose
UF	uncertainty factor
$UF_{composite}$	composite uncertainty factor
USEPA	United States Environmental Protection Agency
Var	variance
f	ratio of variance contribution of an input variable to overall variance of the estimated hazard quotient value
μ	mean
σ	standard deviation
$\rho_{ADI_{therapeutic}}$	ration of pharmaceutical concentration in water and $DWEL_{ADI_{therapeutic}}$
$\rho_{ADI_{toxicity}}$	ration of pharmaceutical concentration in water and $DWEL_{ADI_{toxicity}}$

analysis for meprobamate, carbamazepine, and phenytoin (Fig. 1) for children and adults during accidental exposure of stream water and fish consumption during recreational activities and direct ingestion of finished drinking water. These three pharmaceuticals compounds were selected because they have been frequently detected in US waters and have toxic effects on pregnant women and children. Thus, it is important to assess risks associated to exposures of non-therapeutic dosages of these pharmaceuticals from water. Two different matrices: (1) Hazard quotients (i.e., ratio of chronic daily intake to acceptable daily intake values; *HQ*) and (2) acceptable daily intake-equivalent drinking water levels ($DWEL_{ADI}$) were calculated for all three pharmaceuticals for assessing their risks to humans. Uncertainty analysis for characterizing hazard quotients and variance attribution analysis of different parameters for hazard quotients were also performed. It is important to identify and separate effects of different factors influencing the extent of risk-associated with exposures of pharmaceuticals in water (i.e., during calculation of hazard quotients estimates) to focus resources and research efforts for improving the risk characterization process. This additional step in QPhRA is required to identify factors which are contributing significantly to the overall uncertainty in the estimation of hazard quotients. Literature review of QPhRA studies indicated that very few studies have attempted to identify and separate effects of different factors of risk estimates (Bercu et al., 2008). This study focuses on considerations for sensitive sub-populations using subpopulation-specific toxic endpoints, and on the use of finished drinking water pharmaceutical concentrations for assessing risks due to direct ingestion of water. Use of pharmaceutical concentrations in finished drinking water for assessing risks due to direct ingestion of water would provide accurate risk estimates compared to previous approaches, where pharmaceutical concentrations in stream water have been used for assessing risks associated with direct ingestion of water (Schwab et al., 2005; Bercu et al., 2008). Also, this study presents health risks estimates associated with pharmaceuticals exposure during accidental exposure of stream water and fish consumption during recreational activities. The QPhRA framework presented in this study is expected to provide a systematic step-wise approach for assessing risks associated with exposure of pharmaceuticals from water.

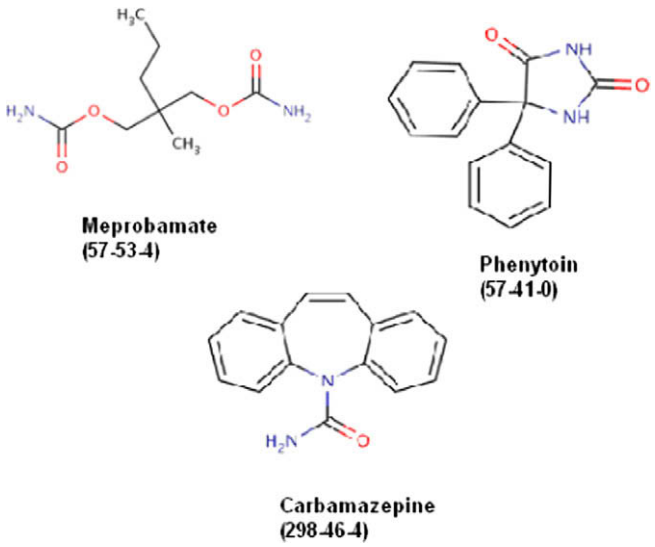

Fig. 1. Pharmaceuticals-of-interest (chemical name is followed by chemical abstract service registry number) (*Source*: www.DrugBank.com; accessed July 25, 2009).

2. Methodology

2.1. Hazard identification

Meprobamate, carbamazepine, and phenytoin pharmaceuticals (Fig. 1) were considered as model compounds in this study as these compounds have been routinely found in US stream water (Snyder et al., 2007; Benotti et al., 2009) (Table 1) and are considered to be toxic to pregnant women and unborn fetus (Snyder et al., 2008b; HSDB, 2009). Based on toxicity studies, acceptable daily intake values of these pharmaceuticals were found to be 0.0075, 0.058, and 0.010 mg kg^{-1} d^{-1} for meprobamate, phenytoin, and carbamazepine, respectively (Snyder et al., 2008a). Among these three pharmaceuticals, meprobamate is highly soluble (water solubility: 4700 mg L^{-1}) compared to other pharmaceuticals (water solubility: 32 mg L^{-1} for phenytoin and 112 mg L^{-1} for carbamazepine)

Table 1
Concentrations of selected pharmaceuticals in US stream water and finished drinking water (ng L^{-1}).

Pharmaceutical	Reference	Minimum (ng L^{-1})	Median (ng L^{-1})	Average (ng L^{-1})	Maximum (ng L^{-1})	Calculated normal median (ng L^{-1})	Calculated normal standard deviation (ng L^{-1})
Stream water and fish							
Meprobamate	Snyder et al. (2007)*	1.4	5.9	7	16	1.774952	0.874534
Phenytoin	Benotti et al. (2009)**	NA	5.1	NA	29	1.629241	1.056663
Carbamazepine	Snyder et al. (2007)	1.2	3.1	6.2	39	1.131402	1.539444
Finished drinking water							
Meprobamate	Snyder et al. (2007)	1.6	3.8	6.1	13	1.335	0.747755
Phenytoin	Benotti et al. (2009)	NA	6.2	NA	19	1.824549	0.680845
Carbamazepine	Snyder et al. (2007)	1.1	2.8	2.8	5.7	1.029619	0.56802

NA, not available.
* Total number of samples = 20.
** Total number of samples = 19.

(SCR, 2009), suggesting the possibility of frequent occurrence in stream water. Concentrations of these pharmaceuticals in US stream water and finished drinking water were obtained from literature reports (Snyder et al., 2007; Benotti et al., 2009; Kolpin et al., 2002) and are presented in Table 1. Kolpin et al. (2002) studied occurrence of different pharmaceuticals in US streams (number of samples (N) = 84) and both Snyder et al. (2007) and Benotti et al. (2009) studied occurrences of these pharmaceuticals in raw and finished drinking waters (N = 19). In US stream water, these compounds were observed to vary between 1.2 and 39 ng L^{-1} and in finished drinking water, these concentrations were observed to vary between 1.1 and 19 ng L^{-1} (Table 1), indicating the effectiveness of drinking water treatment plants in reducing concentrations of these compounds in water.

2.2. Exposure assessment

2.2.1. Exposure routes

Two different exposure routes: (1) Accidental ingestion of stream water during recreational activity and consumption of fish and (2) Direct ingestion of finished drinking water were assumed to be the primary sources of non-therapeutic exposures of meprobamate, phenytoin, and carbamazepine from water. Exposure of these pharmaceuticals from water through other possible exposure routes, such as dermal exposure and inhalation were assumed to contribute negligibly to risk estimates, however, the assumption needs to be verified.

2.2.2. Pharmaceuticals

Occurrence data of selected pharmaceuticals in US stream water and finished drinking water are presented in Table 1. Concentrations of occurrences of selected pharmaceutical compounds in fish were calculated using their concentration values in US stream water and respective bioconcentration factors (BCF) for fish. BCF values are calculated using Eqs. (1) and (2) (Meylan et al., 1999; Schwab et al., 2005) where K_{ow} represents octanol–water partition coefficient (K_{ow}), presented in Table 2.

Table 2
Calculated bioconcentration factors for selected pharmaceuticals.

Chemical	Octanol–water partition coefficient ($\log K_{ow}$)	Bio-concentration factor (BCF, L kg^{-1})*
Meprobamate	0.7 (Westerhoff et al., 2005; SCR, 2009)	3.16
Phenytoin	2.47 (SCR, 2009)	3.16
Carbamazepine	2.48 (Westerhoff et al., 2005); 2.45 (Sabourin et al., 2009) (average = 2.47)	15.92

BCF, bioconcentration factor; K_{ow}, octanol–water partition coefficient.
* As per Eqs. (1) and (2).

$$\text{Ionic compound}: \log K_{ow} < 5 : \log BCF = 0.50 \quad (1)$$

$$\text{Non-ionic compound}: \log K_{ow} < 1 : \log BCF = 0.50 \quad (2a)$$

$$\log K_{ow} = 1 - 7 : \log BCF = 0.77 \times \log K_{ow} - 0.70 \quad (2b)$$

Whenever full occurrence data of concentrations of selected pharmaceuticals were available (i.e., minimum, median, mean (μ), standard deviation (σ), and maximum values), occurrence data were used to determine distributions of concentrations of selected pharmaceuticals; otherwise, median and maximum values were used. This study assumes that aqueous concentrations of selected pharmaceuticals follow lognormal distributions, which has been observed to describe concentrations of environmental contaminants (Ott, 1995; Gurian et al., 2004; Kumar et al., 2009). Briefly, concentration statistics of selected pharmaceutical compounds were first log-transformed and subsequently, log-transformed minimum, median, and maximum values of concentrations were assumed to be values of 5th percentile, 50th percentile, and 95th percentile statistics of normal distributions. Log-transformed values of concentrations are generally normally distributed and log-transformation of concentration values does not change order or percentiles of concentration values (Ott, 1995). Assumptions of equality of minimum and maximum values of concentrations to respective 5th and 95th percentiles values of normal distributions of different pharmaceuticals represent a conservative estimate of the range of pharmaceutical concentrations to error on the safer side. Among different data sources, study with lowest σ and high number of samples (N) were used to calculate parameters of normal distributions of selected pharmaceuticals (i.e., μ and σ).

2.2.3. Exposed population

To calculate risks of exposure of selected pharmaceuticals from water, two different types of sub-populations were considered: (1) Children (1–10 years) and (2) Adults (18–75 years). Distributions of different exposure parameters are presented in Table 3. Distribution of body weights of children was determined by first calculating weights using the relationship given by Argall et al. (2003) (i.e., $BW_{ch} = 2 \times (4 + Age_{ch})$ where BW_{ch} is children's body weight in kilograms and Age_{ch} is children's age in years) and subsequently, fitting normal distribution to the calculated body weight data (N = 1000, μ = 16.67 kg, and σ = 5.987 kg; minimized residual error of cumulative distribution function = 0.0176). Distributions of body weights of adult's subgroup, daily drinking water intakes, and daily fish consumptions for both sub-populations were obtained from the US EPA exposure factors handbook (US EPA, 1997) (Table 3). For both sub-populations, accidental daily ingestion rate of stream water was assumed to be 100 mL (Dufour et al., 2006; Donovan et al., 2008; Wong et al., 2009) (Table 3).

Table 3
Model distributions of different exposure parameters.

Parameter	Sensitive subpopulation	Distribution[#]	Reference
Body weight (kg)	Children (1–10 years) Adults (18–75 years)	Normal (16.67, 5.987^2) Normal (70.00, 14.00^2)	Argall et al. (2003) US EPA (1997)
Drinking water intake (mL d^{-1})	Children (1–10 years) Adults (18–75 years)	Log-normal (6.429,0.498^2) Normal (7.170, 0.442^2)	US EPA (1997) US EPA (1997)
Accidental water ingestion (mL d^{-1})	Both sub-populations	Constant (100 mL over 2 h of daily activity, i.e., 100 mL d^{-1})	Dufour et al. (2006), Donovan et al. (2008), Wong et al. (2009)
Fish consumption (g d^{-1})	Both sub-populations	Normal (3.00, 0.695^2) (Mean = 20.1 g d^{-1}; 95th percentile: 63 g d^{-1})	US EPA (1997)

[#] Distribution (mean, variance).

2.3. Dose response

2.3.1. Chronic daily intake (CDI)

Chronic daily intake of a pharmaceutical compound during recreational activity and direct ingestion of finished drinking water was calculated using Eq. (3), where *IR* represents daily water intake (equal to daily drinking water intake for direct ingestion of finished drinking water and equal to daily accidental ingestion of stream water), *CW* represents pharmaceutical concentration in water, *FR* represents daily consumption of fish, *BCF* represents bioconcentration factor of pharmaceutical in fish, and *BW* represents body weight of the selected subpopulation.

$$CDI = \frac{(IR + BCF \times FR) \times CW}{BW} \quad (3)$$

2.3.2. Acceptable daily intake (ADI)

Acceptable daily intake of a pharmaceutical compound (*ADI*) is that value of the daily intake which does not result in any adverse health effects from direct exposure in a population, including all sensitive sub-populations (Schwab et al., 2005). *ADI* values were calculated using Eq. (4), where *POD* represents point-of-departure (i.e., the lowest observed dose which may result in an effect in humans or no observable effects; Bercu et al., 2008) and $UF_{composite}$ represents composite uncertainty factor. $UF_{composite}$, consists of (1) inter-species variability (i.e., among species; UF_1), (2) intra-species variability (i.e., within humans; UF_2), (3) extrapolation from a low-observable-adverse-effect-level (*LOAEL*) to no-observable-adverse-effect level (*NOAEL*) (UF_3), (4) duration of exposure in toxicological studies (i.e., sub-chronic to chronic; UF_4), and (5) quality of data (UF_5) (Schwab et al., 2005; Snyder et al., 2008a), and is calculated using Eq. (5). Values of individual uncertainty factors and their justifications are presented in Table 4.

$$ADI = \frac{POD}{BW \times UF_{composite}} \quad (4)$$

$$UF_{composite} = \prod_{i=1}^{5} UF_i \quad (5)$$

Different risk assessment studies have used different *POD* values based on animal or human toxicity studies. Some studies have also used minimum therapeutic dose (*TD*) as *POD* to calculate *ADI* value. For example, Schwab et al. (2005) used minimum therapeutic dose of acetaminophen (i.e., 650 mg d^{-1}) as *POD* to calculate *ADI* value for children and adult's sub-populations. In this study, two types of *POD* values, first based on animal or human toxicity data and second based on minimum *TD*, were used for calculating *ADI* and termed as $ADI_{toxicity}$ and $ADI_{therapeutic}$, respectively. $ADI_{toxicity}$ values shown in Table 5 were adapted from Snyder et al. (2008a), where values of *NOAEL* and *LOAEL* were obtained based on previous toxicity studies (NTP, 2000; Ohmori et al., 1997; Samren et al., 1997, 1999; Hernandez-Diaz et al., 2000, 2001). For meprobamate and phenytoin, data from toxicity studies on mouse (systemic and development toxic effects, respectively) were used to calculate $ADI_{toxicity}$ values for both sub-populations (Table 5). For carbamazepine, data from toxicity studies on human (i.e., developmental toxic effect) was used to calculate values of $ADI_{toxicity}$ (Table 5).

Values of $ADI_{therapeutic}$ for different sub-populations were calculated by dividing minimum *TD* to $UF_{composite}$ (Table 5). Values of minimum *TD* for children were obtained from the RxList internet drug index (www.rxlist.com) and ranged between 1.25 and 7 mg kg^{-1} d^{-1}. For adults, minimum *TD* values of different pharmaceuticals were found by dividing daily dosages of different pharmaceuticals, also found from the RxList internet drug index (www.rxlist.com), with average adult body weight (i.e., 70 kg). Daily dosages of meprobamate, phenytoin, and carbamazepine for adults were found to be 1200, 300, and 200 mg d^{-1}, respectively. Calculated minimum *TD* values of pharmaceuticals for children (Table 5) were observed to be comparable with that reported by Snyder et al. (2008a).

To calculate parameters of distributions for *ADI*, values of $ADI_{toxicity}$ and $ADI_{therapeutic}$ were assumed as average and maximum values of the acceptable daily intake parameter for a pharmaceutical compound, respectively (Table 6). *ADI* was assumed to follow a normal distribution based on assumptions of use of $ADI_{toxicity}$ values for 50% of the times (i.e., 50th percentile value) and $ADI_{therapeutic}$ values for 95% of the times (i.e., 95th percentile value) in QPhRA studies for assessing risks associated with exposure of pharmaceuticals from water.

2.3.3. Hazard quotient (HQ)

The risk of exposure of a pharmaceutical compound for a particular sensitive population type was calculated by estimating *HQ* (Eq. (6)), which is a ratio of *CDI* value to *ADI* value. A hazard quotient of value greater than 1 indicates higher chronic daily intake than acceptable daily intake, suggesting possibility of risk of exposure and warrants remedial actions. Margin-of-safety for every pharmaceutical was also calculated by dividing *ADI* to *CDI* (i.e., $1/HQ$).

$$HQ = \frac{CDI}{ADI} \quad (6)$$

Hazard quotients of mixture of selected three pharmaceutical compounds could not be estimated due to lack of quantitative toxicity information about their interactions in water at trace-level concentrations and thus pharmaceutical compounds are assumed to act independently in water for calculation purposes.

2.4. Risk characterization

Hazard quotient, calculated using Eq. (6), indicates the point estimate of the extent of possible risk due to ingestion of chemical. Values of *HQ* are expected to vary around point estimate depending on variability of *CDI* and *ADI* and thus it becomes important

Table 4
Uncertainty factors used for calculating *ADI* values.

Uncertainty type	ADI_{toxic}		$ADI_{therapeutic}$	
	Values adapted from Snyder et al. (2008a)	Justification	Values assigned by authors (This study)	Justification
Meprobamate				
Inter-species variability (UF_1)	10	Animal data	1	Human therapeutic values were used, so no inter-species consideration is required
Intra-species variability (UF_2)	10	For accounting variation among human beings	3	As studies are only conducted on adults and toxicity information comparing meprobamate use in children compared to other age-groups are not available (Snyder et al., 2008a)
LOAEL to *NOAEL* (UF_3)	1	*NOAEL* value is given	3	As *LOAEL* represents minimum therapeutic dose, an uncertainty value of 3 is required for extrapolating *NOAEL* values from *LOAEL* values
Exposure duration (UF_4)	10	13 weeks study	10	Because toxicity studies are generally conducted for short study durations
Database quality (UF_5)	10	Animal toxicity studies	1	As therapeutic values associated with pharmaceuticals are used from the referred database
Phenytoin				
Inter-species variability (UF_1)	10	Animal data	1	Human therapeutic values were used, so no inter-species consideration is required.
Intra-species variability (UF_2)	3	For accounting variation among human beings	1	Sub-population specific therapeutic dose is used
LOAEL to *NOAEL* (UF_3)	1	*NOAEL* value is given	3	As *LOAEL* represents minimum therapeutic dose, an uncertainty value of 3 is required for extrapolating *NOAEL* values from *LOAEL* values
Exposure duration (UF_4)	3	PND2-4	10	Because toxicity studies are generally conducted for short study durations.
Database quality (UF_5)	3	Animal toxicity studies	1	As therapeutic values associated with pharmaceuticals are used from the referred database
Carbamazepine				
Inter-species variability (UF_1)	1	Human data	1	Human therapeutic values were used, so no inter-species consideration is required.
Intra-species variability (UF_2)	3	For accounting variation among human beings	1	Sub-population specific therapeutic dose is used
LOAEL to *NOAEL* (UF_3)	10	*LOAEL* value is given	3	As *LOAEL* represents minimum therapeutic dose, an uncertainty value of 3 is required for extrapolating *NOAEL* values from *LOAEL* values
Exposure duration (UF_4)	3	Gestation	10	Because toxicity studies are generally conducted for short study durations
Database quality (UF_5)	3	Human toxicity studies	1	As therapeutic values associated with pharmaceuticals are used from the referred database

LOAEL, low-observed adverse effect level; NA, not applicable; *NOAEL*, no-observed adverse effect level; *UF*, uncertainty factor.

to provide uncertainty bounds to point estimate values of *HQ* for different chemicals. In addition, it is equally important to identify those parameters which contribute high variability in estimation of *HQ* as this information could be useful in selecting important parameters and focusing efforts for reducing their variability.

The following sections present brief descriptions of uncertainty analysis and variance attribution used in this study.

2.4.1. Uncertainty analysis

To characterize risk of pharmaceutical exposure through ingesting finished drinking water, the Monte Carlo uncertainty analysis was conducted on *HQ* estimates (Chowdhury et al., 2009; Kumar et al., 2009). Briefly, 10,000 random values of different parameters, such as pharmaceutical concentration, acceptable daily intake, daily direct water ingestion rate, daily fish intake rate, and body weight were sampled from their respective distributions (Tables 3 and 6) using a Random Number Generation function of Microsoft Excel (Random seed = 1) and were used to calculate 10,000 values of *HQ* for each pharmaceutical for each subpopulation type. Further, *HQ* values were characterized using summary statistics.

2.4.2. Variance attribution

To determine relative contributions of variances of different input variables to the overall variance in *HQ* for each pharmaceutical for every subpopulation type ($Var(HQ)$), a first-order linear approximation was used to conduct a variance attribution analysis at mean values of variables using Eqs. (7) and (8) (assuming negligible higher order terms; Morgan and Henrion, 1995; Kumar et al., 2009).

$$Var(HQ) = \sum_{i=1}^{k} \left[Var(A) \left(\frac{dHQ}{dA} \right)^2 \right] \tag{7}$$

$$f_A = \frac{\left[Var(A) \left(\frac{dHQ}{dA} \right)^2 \right]}{\sum_{i=1}^{k} \left[Var(A) \left(\frac{dHQ}{dA} \right)^2 \right]} \tag{8}$$

In Eq. (7), k represents number of input variables and A represents one of the input variables with variance ($Var(A)$). f_A represents ratio of variance contribution of A (i.e., $Var(A)$) to overall variance of the estimated hazard quotient value (i.e., $Var(HQ)$) (Eq. (8)). Values of $\frac{dHQ}{dA}$ for different parameters are given by $\frac{HQ}{CW}$ for *CW*; by $\frac{HQ}{(IR+BCF\times FR)}$ for accidental ingestion of stream water; by $\frac{HQ}{IR}$ for direct ingestion of finished water; by $\frac{HQ\times BCF}{(IR+BCF\times FR)}$ for *FR*; by $(-)\frac{HQ}{ADI}$ for *ADI*, and by $(-)\frac{HQ}{BW}$ for *BW*.

2.5. Acceptable daily intake-equivalent drinking water levels ($DWEL_{ADI}$)

In addition to using *HQ* assessing pharmaceuticals risks to humans as described above, therapeutic- and toxicity-based accept-

Table 5
Calculated acceptable daily intake values of selected pharmaceuticals for non-cancer end points.

Chemical	Toxicological information				Therapeutic information		
	Study conditions	Effect dose ($mg\ kg^{-1}\ d^{-1}$/ Effect condition)	Composite uncertainty factor (adapted from Snyder et al., 2008a) ($mg\ kg^{-1}\ d^{-1}$)	Acceptable daily intake-based on toxicity studies ($mg\ kg^{-1}\ d^{-1}$) (adapted from Snyder et al., 2008a)*	Calculated minimum therapeutic dose ($mg\ kg^{-1}\ d^{-1}$)	Calculated composite uncertainty factor ($UF_{composite}$)*,**	Calculated acceptable daily intake-based on therapeutic usages ($mg\ kg^{-1}\ d^{-1}$)
Meprobamate	13 weeks; systemic (mouse) (NTP, 2000)	75 (*NOAEL*)[1]	10000	0.0075	7 (children); 17.142857 (adults)	90	0.077778 (children); 0.190476 (adults)
Phenytoin	PND2-4, developmental (mouse) (Ohmori et al., 1997)	17.5 (*NOAEL*)[2]	300	0.058	4 (children); 4.285714 (adults)	30	0.13333 (children); 0.142857 (adults)
Carbamazepine	Gestation; developmental (human) (Samren et al., 1997, 1999; Hernandez-Diaz et al., 2000, 2001)	3 (*LOAEL*)[3]	300	0.010	1.25 (children); 2.857143 (adults)	30	0.041667 (children); 0.095238 (adults)

$UF_{composite}$, composite uncertainty factor.
* For both sub-populations.
** Values are shown in Table 4.
[1] Value adapted from Snyder et al. (2008a), determined from NTP (2000) study.
[2] Value adapted from Snyder et al. (2008a), determined from Ohmori et al. (1997) study.
[3] Value adapted from Snyder et al. (2008a), calculated assuming 200 mg d^{-1} as therapeutic dose and 70 kg women body weight (Hernandez-Diaz et al., 2000, 2001).

Table 6
Calculated distributions of acceptable daily intakes ($mg\ kg^{-1}\ d^{-1}$).#

Chemical	Children	Adults
Meprobamate	Normal (0.0075, 0.0427^2)	Normal (0.0075, 0.1112^2)
Phenytoin	Normal (0.058, 0.0458^2)	Normal (0.058,0.0516^2)
Carbamazepine	Normal (0.01, 0.0193^2)	Normal (0.01, 0.0518^2)

Note: Distributions were calculated using toxicity- and therapeutic-acceptable daily intake values shown in Table 5.
Distribution (mean, variance).

able daily intake-equivalent drinking water levels of pharmaceuticals were also calculated (termed as $DWEL_{ADI_{therapeutic}}$ and $DWEL_{ADI_{toxicity}}$, respectively) using Eq. (9) as per the US EPA (2006) approach and used to assess exposure risks.

$$DWEL_{ADI} = \frac{ADI \times BW}{IR} \tag{9}$$

The Eq. (9) is obtained by re-organizing Eq. (3) for calculating *CW* values corresponding to *ADI* values (assumption: $BW = 70$ kg for adults and 16.67 kg for children, $IR = 2\ L\ d^{-1}$, and no fish consumption for stream water case).

$$\rho_{ADI} = \frac{CW}{DWEL_{ADI}} \tag{10}$$

Further, using $DWEL_{ADI}$ and pharmaceutical concentration (*CW*) values, ratio of concentrations was calculated for each pharmaceutical corresponding to $ADI_{therapeutic}$ and $ADI_{toxicity}$ (termed as $\rho_{ADI_{therapeutic}}$ and $\rho_{ADI_{toxicity}}$, respectively) for both stream water and finished drinking water (Eq. (10)) and compared with 1. Pharmaceuticals with ratio greater than 1 represents pharmaceuticals-of-concern (US EPA, 2006; Snyder et al., 2008a).

3. Results

Average hazard quotients of meprobamate, carbamazepine, and phenytoin for children and adults for two exposure scenario: (1) exposure through accidental ingestion of stream water and fish consumption and (2) exposure through direct ingestion of finished drinking water were found to be comparable and lie between 1×10^{-10} and 3×10^{-5} (i.e., margin-of-safety > 10^5) (Table 7), indicating no potential risks of adverse effects due to exposures of these pharmaceuticals from water. Meprobamate appears to pose relatively higher risk (average *HQ* range: 4.74×10^{-7}–2.48×10^{-5}) compared to carbamazepine (average *HQ* range: 3.59×10^{-9}–1.32×10^{-5}) and phenytoin (average *HQ* range: 1.06×10^{-9}–1.84×10^{-5}) for both exposure scenarios (Table 7).

Table 7 also shows statistical characterization of hazard quotients, in terms of 90% confidence interval values and 99th percentile values of different hazard quotients. 99th percentile values of hazard quotients were found to be less than 1×10^{-4} (i.e., margin-of-safety: 10^4) for both sub-populations, indicating no potential risks of adverse effects due to individual exposures of these pharmaceuticals from water. Also, 99th percentile values of hazard quotients were observed to be higher for finished drinking water scenario compared to stream water ingestion and fish consumption scenario for both sub-populations. 90% confidence interval values of different hazard quotients were observed to vary between 1.74×10^{-9} and 7.17×10^{-6} for stream water ingestion and fish consumption scenario (i.e., margin-of-safety > 10^6) and vary between 8.00×10^{-6} and 3.99×10^{-5} for direct ingestion of finished drinking water scenario (i.e., margin-of-safety > 10^5), indicating that more uncertainties exist in estimation of risks associated with finished drinking water scenario compared to stream water ingestion and fish consumption scenario (Table 7).

Fig. 2 shows variance contributions of different input variables towards total variance in hazard quotients for meprobamate for both exposure scenarios for both sub-populations. In both exposure scenarios, acceptable daily intake was observed to be the primary contributor (>93% variance contribution) in the overall uncertainties of estimates of hazard quotients for both sub-populations. Fish consumption was observed to be the second most contributing input parameters, followed by pharmaceutical concentration (Fig. 2). For carbamazepine and phenytoin, pharmaceutical concentrations were observed to be primary contributors in overall uncertainties of hazard quotients for exposure to stream water and fish (>89% variance contributions) (Table 8). However, during exposures of these pharmaceuticals from ingesting finished drinking water, acceptable daily intake was observed to be the primary (>38% variance contributions) in the overall uncertainties of estimates of hazard quotients for both sub-populations, followed by pharmaceutical concentration (Table 8).

Table 7
Statistical characterization of hazard quotients.

Pharmaceutical	Average value		90% confidence interval		99th percentile	
	Stream water and fish	Finished drinking water	Stream water and fish	Finished drinking water	Stream water and fish	Finished drinking water
Adults						
Meprobamate	4.74×10^{-7}	2.48×10^{-5}	7.15×10^{-7}	6.35×10^{-5}	3.71×10^{-6}	1.17×10^{-4}
Carbamazepine	3.59×10^{-9}	1.32×10^{-5}	2.52×10^{-9}	9.14×10^{-6}	1.37×10^{-8}	1.23×10^{-4}
Phenytoin	1.06×10^{-9}	1.84×10^{-5}	1.74×10^{-9}	8.00×10^{-6}	7.93×10^{-9}	1.83×10^{-4}
Children						
Meprobamate	6.77×10^{-6}	2.48×10^{-5}	7.17×10^{-6}	2.63×10^{-5}	3.35×10^{-5}	1.17×10^{-4}
Carbamazepine	1.36×10^{-8}	1.32×10^{-5}	3.03×10^{-8}	2.96×10^{-5}	1.39×10^{-7}	1.23×10^{-4}
Phenytoin	5.27×10^{-9}	1.84×10^{-5}	1.06×10^{-8}	3.99×10^{-5}	5.81×10^{-8}	1.83×10^{-4}

Table 9 presents values of $DWEL_{ADI_{therapeutic}}$ and $DWEL_{ADI_{toxicity}}$ and ratio of pharmaceutical concentration in water and $DWEL_{ADI}$ for all three pharmaceuticals for both stream water and finished drinking water. None of the pharmaceuticals investigated had ratio greater than 1, indicating none of them represent any risk to human beings and are not pharmaceutical-of-concern. $DWEL_{ADI_{therapeutic}}$ values were observed to be higher than $DWEL_{ADI_{toxicity}}$ due to higher values of $ADI_{Therapeutic}$ compared to $ADI_{Toxicity}$.

4. Discussion

In general, exposure of pharmaceuticals through accidental ingestion of stream water and fish consumption resulted in smaller hazard quotients compared to that through ingesting finished drinking water. The observed difference in hazard quotients for two exposure scenarios is primarily attributed to the fact that very small volume of water is assumed to be accidentally ingested during accidental exposure of stream water (i.e., 0.1 liter) compared to large volume of finished drinking water (~1.5–2 liters), which is assumed to be directly ingested. Some pharmaceuticals risk assessment studies (Schwab et al., 2005; Bercu et al., 2008) have used stream water as a source of drinking water in assessing pharmaceutical risks with application of removal factors for reducing pharmaceutical concentrations as drinking water treatment plants remove pharmaceutical compounds (Stackelberg et al., 2004, 2007). However, this study presented separate risk estimates for exposures of pharmaceutical during accidental ingestion of stream water (using stream water concentration) and direct ingestion of finished drinking water (using finished drinking water concentration), presenting a more representative exposure scenario. In the absence of occurrence data of a pharmaceutical compound in finished drinking water, use of stream water concentration of pharmaceutical with removal factors could be useful in getting estimates of hazard quotients.

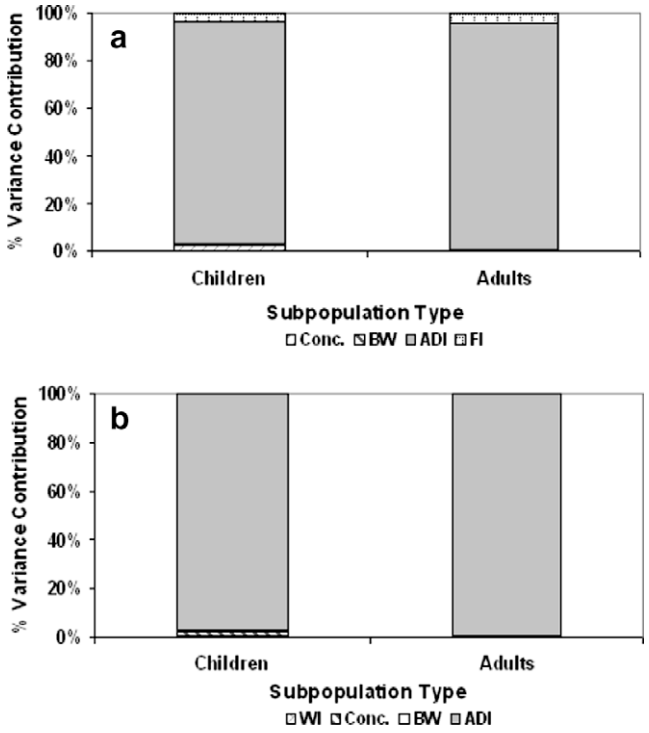

Fig. 2. Variance contributions of different parameters for total variance of hazard quotient for meprobamate for two exposure scenario: (a) Accidental ingestion of stream water and fish consumption and (b) Direct ingestion of finished drinking water.

In present case, the hazard quotient depends on different factors, such acceptable daily intake, body weight, pharmaceutical

Table 8
Variance contributions of different input variables towards overall variance of hazard quotients of different pharmaceutical compounds calculated using Eq. (8).

Parameters	Meprobamate		Carbamazepine		Phenytoin	
	Children (%)	Adults (%)	Children (%)	Adults (%)	Children (%)	Adults (%)
Stream water and fish						
Pharmaceutical concentration	2.5	0.5	*98.16*[*]	*88.54*	*94.91*	*92.42*
Body weight	0.3	0.0	0.03	0.01	0.03	0.01
Acceptable daily intake	*93.8*	*95.2*	0.82	4.97	0.15	0.19
Fish intake	3.4	4.3	0.99	6.48	5.91	7.39
Finished drinking water						
Pharmaceutical concentration	1.7	0.3	8.83	1.56	36.83	36.77
Body weight	0.3	0.0	2.95	0.16	7.90	2.43
Acceptable daily intake	*97.4*	*99.6*	*81.71*	*97.42*	*37.81*	*47.78*
Water intake	0.6	0.1	6.51	0.86	17.46	13.03

[*] Italicized values indicate the highest variance contribution towards overall variance of hazard quotient for different pharmaceuticals.

Table 9
Acceptable daily intake-equivalent drinking water levels and decision for identifying pharmaceutical-of-concern (Pharmaceuticals with concentration ratio greater than 1 are of concern and shown as shaded texts).

Pharmaceutical	*ADI* type	Calculated normal median concentration * (ng L^{-1})	*ADI*-equivalent drinking water level ($DWEL_{ADI}$)** (ng L^{-1})	Conc. ratio (Normal median conc./$DWEL_{ADI}$)***	Decision ("No" if ratio < 1 and "Yes" if ratio > 1)
Stream water					
Meprobamate	Therapeutic	1.774952	6.666×10^6	2.662×10^{-7}	No
	Toxic		0.263×10^6	6.762×10^{-6}	No
Phenytoin	Therapeutic	1.629241	4.999×10^6	3.259×10^{-7}	No
	Toxic		2.030×10^6	8.026×10^{-7}	No
Carbamazepine	Therapeutic	1.131402	3.333×10^6	3.394×10^{-7}	No
	Toxic		0.350×10^6	3.233×10^{-6}	No
Finished drinking water					
Meprobamate	Therapeutic	1.335	6.666×10^6	2.003×10^{-7}	No
	Toxic		0.263×10^6	5.086×10^{-6}	No
Phenytoin	Therapeutic	1.824549	4.999×10^6	3.649×10^{-7}	No
	Toxic		2.030×10^6	8.988×10^{-7}	No
Carbamazepine	Therapeutic	1.029619	3.333×10^6	3.089×10^{-7}	No
	Toxic		0.350×10^6	2.942×10^{-6}	No

* Values obtained from Table 1.
** Calculated using Eq. (9) assuming $BW = 70$ kg for adults and 16.67 kg for children, $IR = 2$ L d^{-1}, and no fish consumption for stream water case.
*** Calculated using Eq. (10).

concentration, water intake, and fish intake. Among these variables, acceptable daily intake and pharmaceutical concentration appear to be the two important parameters influencing variability in estimation of hazard quotients. In this study, distributions of *ADI* values, derived using $ADI_{toxicity}$ and $ADI_{therapeutic}$ values, were observed to differ significantly between sub-populations and amongst different pharmaceuticals (Table 5). $ADI_{therapeutic}$ values were observed to be almost 7–9 times higher than $ADI_{toxicity}$ values which could be attributed to observed differences in *UF*, *LOAEL*, *NOAEL*, and minimum *TD* values used (Tables 4 and 5). For example, for meprobamate, *NOAEL* value was observed to be ~4.4 times higher than its minimum *TD* value and $UF_{composite}$ for toxicity studies was observed to be ~111 times higher than that for therapeutic studies, resulting in higher $ADI_{therapeutic}$ values than $ADI_{toxicity}$ values (Table 5). Similar effects of differences of these factors on *ADI* values of phenytoin and carbamazepine were also observed (Table 5). Among different uncertainty factors (Table 4), UF_1 was observed to decrease $UF_{composite}$ value by a factor of 10, indicating the importance of uncertainty due to inter-species variation. Use of minimum *TD* as an estimate of *LOAEL* for calculating $ADI_{therapeutic}$ values appears to reduce overall uncertainty in estimation of *ADI* values.

To study the effect of choice of acceptable daily intake values on variance contributions of different pharmaceuticals, coefficients of variation of acceptable daily intake values for children and adults (i.e., ratio of values of standard deviation to median) were calculated using their normal median and standard deviations values (Table 6) and compared (Fig. 3a). Coefficients of variation of acceptable daily intake values of all pharmaceuticals were observed to be higher than 100% indicating large variability in distributions of acceptable daily intake values. Higher values of coefficients of variation were observed for adults compared to children, indicating larger contributions of variances from acceptable daily intake values of adults compared to that from acceptable daily intake values of children (Fig. 3a). For example, for hazard quotients of carbamazepine in finished drinking water, acceptable daily intake values of adults contributed 97% variability compared to acceptable daily intake values of children which contributed 82% variability in estimation of hazard quotient (Table 8).

Pharmaceuticals, found in stream water, appear to contribute more uncertainty associated with estimation of hazard quotients compared to that found in finished drinking water (Table 8), which could be attributed to observed differences in their concentration values (Table 1). Coefficient of variations of pharmaceutical concentrations in stream water and finished drinking water were calculated using their normal median concentration and normal standard deviations values (Table 1) and compared (Fig. 3b). Coefficient of variations of meprobamate concentrations in surface water and finished drinking water were observed to be comparable (i.e., 49% for surface water and 56% for finished drinking water) (Fig. 3b), explaining the observed comparable variance contributions in estimation of hazard quotients (i.e., variance contributions of 0.5–2.5% for stream water and fish consumption scenario and 0.3–1.7% for finished drinking water scenario; Table 8). Pharmaceutical concentrations in finished drinking water were observed to be less variable (range of coefficient of variation: 37–55%) compared to that in stream water (range of coefficient of variation:

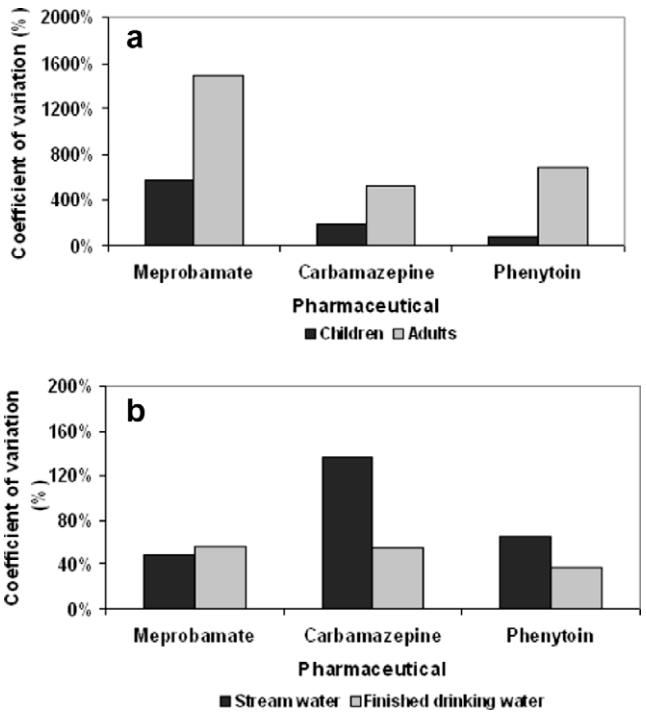

Fig. 3. Coefficients of variation: (a) Acceptable daily intakes of different pharmaceuticals for children and adults and (b) Pharmaceutical concentrations in stream water and finished drinking water.

Table 10
Interactions of different pharmaceutical compounds.

Primary pharmaceutical compound	Other co-occurring pharmaceutical compounds		
	Meprobamate	Carbamazepine	Phenytoin
Meprobamate	–	No interaction reported	No interaction reported
Carbamazepine (for tegretol)	No interaction reported	–	Plasma concentration decreases in presence of phenytoin as CYP 3A4 inducers increase rate of tegretol metabolism
Phenytoin (for dilantin)	No interaction reported	Plasma concentrations decreases in presence of carbamazepine	–

Source: http://www.rxlist.com/, accessed August 16, 2009.

64–136%) for carbamazepine and phenytoin (Fig. 3b), explaining observed differences in variance contributions in estimation of hazard quotients (i.e., variance contributions of 88–98% for stream water and fish consumption scenario versus 1–37% for finished drinking water scenario; Table 8). These observations suggest that extensive spatial and temporal monitoring of pharmaceuticals is required at local-to-regional scale to reduce variability in pharmaceuticals concentration values for QPhRA. Given that not all pharmaceuticals pose human health risks and considering high costs of monitoring for large number of pharmaceuticals, a judicious approach would be to first screen and prioritize pharmaceuticals, based on criteria, such as aquatic and human toxicity, occurrence, and removal of pharmaceuticals in drinking water treatment plants (Mitchell et al., 2002; Sanderson et al., 2004; Munoz et al., 2008; Voigt and Bruggemann, 2008; Johnson et al., 2008; Rowney et al., 2009). Monitoring of pharmaceuticals based on the priority list would reduce monitoring and treatment costs for utilities.

Water intake and fish intake rates variables were also observed to contribute uncertainties to overall uncertainties in estimations of hazard quotients of different pharmaceuticals for both populations for both exposure scenarios (Table 8). For exposure scenario of accidental exposure of stream water and fish, contributions of fish intake towards uncertainty was observed to vary between 1% and 7.4% (Table 8), which could be attributed to uncertainties associated with fish intake rate. Accidental ingestion of stream water was assumed to be constant and thus this parameter did not contribute any variability in estimations of hazard quotients. However, for exposure scenario of direct ingestion of finished drinking water, contributions of water intake towards uncertainty in estimates of hazard quotients was observed to be variable (from 0.1% to 17.46%; Table 8).

As occurrence studies of pharmaceuticals in water sources have indicated the co-occurrence of different pharmaceuticals in stream water (Kolpin et al., 2002; Stackelberg et al., 2004) and finished drinking water (Stackelberg et al., 2004, 2007), it becomes imperative to assess risks of exposure of all pharmaceuticals in mixture (i.e., considering mixture effect on exposure), instead of assuming them to act independently. Thus, estimations of overall hazard quotients of exposures of different pharmaceuticals, present in stream water and finished drinking water, are required. Depending on pharmaceuticals end points and intended usages, they may act independently or synergistically (i.e., worsening the individual toxic effect) or antagonistically (i.e., compensating toxic effects of each others) (Pomati et al., 2008; Cleuvers, 2004; Silva et al., 2002; Schwab et al., 2005) in influencing their overall toxic effects on human health.

To understand the interactive effects of meprobamate, carbamazepine on human health, possible interactions of these pharmaceuticals in water were qualitatively assessed using interactions information, reported in the RxList internet drug index (www.rxlist.com) and HSDB (2009) for individual pharmaceutical compound (Table 10). No interaction was reported for use of meprobamate with carbamazepine and phenytoin, suggesting that co-occurrence of meprobamate with carbamazepine or co-occurrence of meprobamate with phenytoin in water does not change their individual toxic effects on human health. Carbamazepine and phenytoin appear to interact with each other and are not suggested to be used simultaneously; indicating that co-occurrence of these two pharmaceuticals in water may alter their individual toxic effects on human health and consideration of mixture effects in QPhRA of these pharmaceuticals are required. However, these interactions among drugs have been reported at their therapeutic doses, which may or may not be true at non-therapeutic doses, commonly found in water supplies. It is important to study interactions of these pharmaceuticals at trace concentrations commonly found in stream water and especially in finished drinking water.

5. Conclusions

This study presented a step-wise development of a quantitative pharmaceutical risk assessment (QPhRA) framework, including a Monte Carlo uncertainty analysis for meprobamate, carbamazepine, and phenytoin during accidental exposures of stream water and fish consumption (i.e., first exposure scenario), and direct ingestion of finished drinking water (i.e., second exposure scenario) for children and adults. Summary of important findings are given below:

1. Average hazard quotients for meprobamate, carbamazepine, and phenytoin were found to lie between 1×10^{-10} and 3×10^{-5} and 99th percentile values of hazard quotients were found to be less than 1×10^{-4} (i.e., margin-of-safety: 10,000) for both sub-populations, indicating no potential risks of adverse effects due to individual exposures of these pharmaceuticals from water. In addition, pharmaceutical concentrations were also observed to be lower than their respective calculated acceptable daily intake-equivalent drinking water levels, indicating no potential human health risks.
2. In general, exposure of pharmaceuticals through accidental ingestion of stream water and fish consumption resulted in smaller hazard quotients compared to that through ingesting finished drinking water.
3. In both exposure scenarios, acceptable daily intake was observed to be the primary contributor (>93% variance contribution) in the overall uncertainties of estimates of hazard quotients for both sub-populations, followed by fish consumption and pharmaceutical concentrations.

Further research efforts are required to standardize use of acceptable daily intake values to reduce large variability in estimation of hazard quotients. To capture local-scale spatial and temporal variability in pharmaceutical concentrations, continuous monitoring of surface water bodies and finished drinking water supplies for pharmaceuticals is required using a judicious and cost-effective prioritization approach, consisting of first selecting

and prioritizing pharmaceuticals, based on criteria, such as aquatic and human toxicity, occurrence, and removal of pharmaceuticals in drinking water treatment plants (Mitchell et al., 2002; Sanderson et al., 2004; Munoz et al., 2008; Voigt and Bruggemann, 2008; Johnson et al., 2008; Rowney et al., 2009; Cooper et al., 2008). A development of a system for prioritizing emerging organic compounds (i.e., pharmaceuticals, personal care products, and endocrine-disrupting chemicals) in water for monitoring and treatment efforts using these criteria are underway, which is expected to help drinking water utilities selecting important emerging organic compounds for monitoring and removal efforts in drinking water treatment plants.

The QPhRA framework presented in this study provides a systematic step-wise approach for assessing risks associated with exposure of pharmaceuticals from water. This study focused on issues, such as considerations for sensitive sub-populations using subpopulation-specific toxic endpoints and use of pharmaceutical concentrations in stream and finished drinking waters for assessing risks associated with exposures of pharmaceuticals in water. Other issues, such as mixture effects, study duration, and regional consideration need to be included in the proposed QPhRA framework to obtain more accurate estimates of risks due to pharmaceuticals exposure from water (Johnson et al., 2008; Snyder et al., 2008a, 2008b; Rowney et al., 2009).

Conflict of interest statement

The authors declare that there are no conflicts of interest. Signed copies of the *Regulatory Toxicology and Pharmacology* Conflict of Interest policy form are submitted with this manuscript submission.

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