Environ Sci Pollut Res (2010) 17:486–496
DOI 10.1007/s11356-009-0195-4

AREA 7 • RISK ASSESSMENT AND MANAGEMENT, HEALTH • RESEARCH ARTICLE

Estimation of the cancer risk to humans resulting from the presence of cyclophosphamide and ifosfamide in surface water

Klaus Kümmerer · Ali Al-Ahmad

Received: 30 November 2008 / Accepted: 25 May 2009 / Published online: 24 June 2009

Abstract
Background, aim, and scope Anti-tumour agents and their metabolites are largely excreted into effluent, along with other pharmaceuticals. In the past, investigations have focused on the input and analysis of pharmaceuticals in surface and ground water. The two oxazaphosphorine compounds, cyclophosphamide and ifosfamide are important cytostatic drugs used in the chemotherapy of cancer and in the treatment of autoimmune diseases. Their mechanism of action, involving metabolic activation and unspecific alkylation of nucleophilic compounds, accounts for genotoxic and carcinogenic effects described in the literature and is reason for environmental concern. The anti-tumour agents cyclophosphamide (CP) and ifosfamide (IF) were not biodegraded in biodegradation tests. They were not eliminated in municipal sewage treatment plants. Degradation by photochemically formed HO radicals may be of some relevance only in shallow, clear, and nitrate-rich water bodies but could be further exploited for elimination of these compounds by advanced oxidation processes, i.e. in a treatment of hospital waste water. Therefore, CP and IF are assumed to persist in the aquatic environment and to enter drinking water via surface water. The risk to humans from input of CP and IF into surface water is not known.
Materials and methods The local and regional, i.e. nationwide predicted environmental concentration (PEC_{local}, $PEC_{regional}$) of CP and IF was calculated for German surface water. Both compounds were measured in hospital effluents, and in the influent and effluent of a municipal treatment plant. Additionally, published concentrations in the effluent of sewage treatment plants and surface water were used for risk assessment. Excretion rates were taken into account. For a worst-case scenario, maximum possible ingestion of CP or IF by drinking 2 L a day of unprocessed surface water over a life span of 70 years was calculated for adults. Elimination in drinking water processing was neglected, as no data is available. This intake was compared with intake during anti-cancer treatment.
Results and discussion Intake of CP and IF for anti-cancer treatment is typically 10 g within a few months. Under such conditions, a relative risk of 1.5 for the carcinogenic compounds CP and IF is reported in the literature. In the worst case, the maximum possible intake by drinking water is less than 10^{-3} (IF) and 10^{-5} (CP) of this amount, based on highest measured local concentrations. On a nationwide average, the factor is approx. 10^{-6} or less.
Conclusions The additional intake of CP and IF due to their emission into surface water and its use without further treatment as drinking water is low compared to intake within a therapy. This approach has shortcomings. It illustrates the current lack of methodology and knowledge for the specific risk assessment of carcinogenic pharmaceuticals in the aquatic environment. IF and CP are directly reacting with the DNA. Therefore, with respect to health effects a safe threshold concentration for these compounds cannot be given. The resulting risk is higher for newborns and children than for adults. Due to the lack of data the risk

K. Kümmerer (✉)
Department of Environmental Health Sciences,
University Medical Centre Freiburg,
Breisacherstraße 115b,
79106 Freiburg, Germany
e-mail: Klaus.Kuemmerer@uniklinik-freiburg.de

Present Address:
A. Al-Ahmad
Department of Preservative Dentistry and Periodontology,
University Medical Centre Freiburg,
Hugstetter Straße 55,
79106 Freiburg, Germany

for newborns and children cannot be assessed fully. The data presented here show that according to present knowledge the additional risk of cancer cannot be fully excluded, especially with respect to children. Due to the shortage of data for effects of CP and IF in low doses during a whole lifespan, possible effects were assessed using data of high doses of CP and IF within short-term ingestion, i.e. therapy. This remains an unresolved issue. Anyway, the risk assessment performed here could give a rough measure of the risks on the one hand and the methodological shortcomings on the other hand which are connected to the assessment of the input of genotoxic and carcinogenic pharmaceuticals such as CP and IF into the aquatic environment. Therefore, we recommend to take measures to reduce the input of CP and IF and other carcinogenic pharmaceuticals. We hope that our manuscript further stimulates the discussion about the human risk assessment for carcinogenic pharmaceuticals in the aquatic environment.

Recommendations and perspectives CP and IF are carcinogens. With respect to newborn and children, reduction of the emission of CP and IF into effluent and surface water is recommended at least as a precautionary measure. The collection of unused and outdated drugs is a suitable measure. Collection of patients' excreta as a measure of input reduction is not recommended. Data suitable for the assessment of the risk for newborn and children should be collected in order to perform a risk assessment for these groups. This can stimulate discussion and give new insights into risk assessment for pharmaceuticals in the environment. Our study showed that in the long term, effective risk management for the reduction of the input of CP and IF are recommendable.

Keywords Cancer · Cyclophosphamide · Drinking water · Excretion · Hospital effluent · Ifosfamide · Intake · Life span · Risk · Surface water

1 Background, aim and scope

Data on the occurrence of pharmaceuticals in natural surface waters and the effluent from sewage treatment plants have been reported since the 1980s (Richardson and Bowron 1985). More recently, pharmaceuticals have been detected in ground and drinking water (Heberer 2002). However, little is known about the risk to humans from pharmaceuticals and their metabolites in surface and drinking water (Kümmerer 2008). There is currently no specific regulatory guidance as to how the significance of the potential presence of pharmaceuticals at trace level in drinking water supplies may be assessed. Cyclophosphamide (CP) and ifosfamide (IF) are among the most widely used cytotoxic compounds in anti-cancer therapy (Momerency et al. 1994a). Both are structural isomers (Fig. 1). CP and IF are pro-drugs which generate the same active metabolite in the human body. CP and IF are known to be mutagenic, genotoxic and teratogenic, and are known to be fetotoxic (International Agency for Research on Cancer 1975, 1981; Matney et al. 1985; Clever and Omenn 1988; ASTA Medica 1992; Allwood and Wright 1993) and a human carcinogen (Greene et al. 1986). Knight et al. reported that therapeutic treatment duration with CP longer than 1 year was associated with an eightfold increased risk (Knight et al. 2004). The absolute risk for bladder cancer in the cohort reached 10% 16 years after diagnosis of Wegener's granulomatosis. The authors concluded that the results indicate a dose–response relationship between CP and the risk of bladder cancer (Knight et al. 2004).

About 20% of the parent compounds is excreted unchanged into effluent. CP and IF were poorly eliminated in biodegradability laboratory tests OECD 301 D (closed-bottle test) as well as in a municipal sewage treatment plant (STP; Steger-Hartmann et al. 1996; Kümmerer et al. 1996, 1997; Schecker et al. 1998; Buerge et al. 2006). CP and IF are released unchanged into surface water (Steger-Hartmann et al. 1996, 1997; Kümmerer et al. 1997; Zuccato et al. 2000; Buerge et al. 2006). IF was eliminated by 50% in a tests simulating anaerobic landfill conditions (Schecker et al. 1998). CP and IF have been detected in the effluent of landfills in the range of 97–192 ng/L (CP) and 42–32 ng/L (IF) (Jjemba 2008). Furthermore, no elimination was observed in activated sludge incubation experiments within 24 h at concentrations of approximately 100 ng/L (Buerge et al. 2006). A slow dark-chemical degradation (half-lives on the order of years) is the most important transformation process (Buerge et al. 2006). In surface waters, concentrations ranged from below 50 pg/L up to 10.1 ng/L (Zuccato et al. 2000; Buerge et al. 2006; Jjemba 2008). Degradation by photochemically formed HO radicals may be of some relevance only in shallow, clear and nitrate-rich water bodies but could be further exploited for elimination of these compounds by advanced oxidation processes, i.e. in a treatment of hospital waste water (Buerge et al. 2006). These results suggest a high persistence in the aquatic environment. In most countries, surface water is used as drinking water after some processing. Physical–chemical

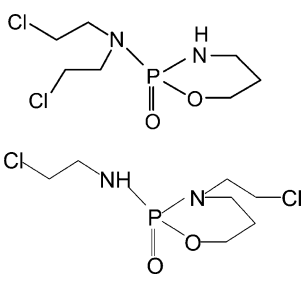

Fig. 1 Structural formula of cyclophosphamide (*top*) and ifosfamide (*bottom*)

data such as log K_{ow} and findings on elimination of CP and IF in sewage treatment suggest that elimination by sorption in bank filtration and onto charcoal in processing drinking water will be low. Due to analytical limitations, concentrations of CP and IF in drinking water are below detection limits. Therefore, data for a risk assessment based on such concentrations are missing and data for surface waters have to be used. However, IF and CP are directly reacting with the DNA. However, therapeutic efficacy of anti-neoplastic chemotherapy is more determined by the total administered dose than by the actual concentrations of a given drug (Jjemba 2008). For alkylating compounds such as CP and IF a safe threshold concentration with no effects cannot be given (Umweltbundesamt 2003). Furthermore, therapeutic efficacy of anti-neoplastic chemotherapy is more determined by the total administered dose than by the actual concentrations of a given drug (Jjemba 2008). Therefore, only acceptable levels based on a risk assessment can be established. For highly active genotoxic compounds, a limit of 10 ng/L was recommended (Umweltbundesamt 2003; Dieter and Mückter 2007) based on an addition lifetime risk of $<10^{-6}$ (Umweltbundesamt 2003). However, it was emphasised by the German Drinking Water Commission and the Environmental Federal Agency that the presence of such strongly genotoxic compounds in drinking water would be tolerable only within exposition periods that are shorter than a lifetime of 70 years according to the ration of the concentration level and the threshold level of 10 ng/L (Umweltbundesamt 2003). Up to now, only a few studies have been published addressing more detailed the significance of pharmaceuticals in water for humans (Christensen 1998; Schulman et al. 2002; Webb et al. 2003; Kim and Aga 2007; Schwab et al. 2005). Some authors conclude that the presence of pharmaceuticals in surface water and drinking water is a concern for humans only for hygienic reasons (Schulman et al. 2002; Webb et al. 2003; Schwab et al. 2005). One concern with genotoxic and carcinogenic compounds, however, is that a cancer risk may exist, at any level of exposure, i.e. that there is no threshold dose below which no carcinogenic effect may occur (Umweltbundesamt 2003; Dieter and Mückter 2007). The risk assessments by Schulman et al. (2002) and Webb et al. (2003) were based only on a few published concentrations measured for CP in water on a local scale. Organic trace compounds that lack an adequate toxicological database, and their mixtures, in drinking water can be safely regulated and provisionally assessed by combining the "similar joint action" addition rule (Umweltbundesamt 2003; Dieter and Mückter 2007). However, IF was not included in the risk assessments of Schulman et al. (2002) and Webb et al. (2003) despite the common active metabolite and therefore the some mode of action of CP. Possible effects on children have not been addressed by these authors.

In our study, we report a rough risk assessment for both CP and IF. We employed measured as well as predicted concentrations both on a local and a national scale for this purpose. We calculated expected concentrations (predicted environmental concentration: PEC) and measured concentrations (MEC) of CP and IF in STP effluent on a local basis. Furthermore, published data on the consumption of CP and IF in Western countries were used to calculate the predicted environmental concentration (PEC) for surface waters in Germany. The intake of CP and IF with surface water was calculated. For this purpose, the PEC of surface water was used. For humans, data of adverse effects of CP and IF at low doses and long-term ingestion are not available. In a conservative approach, we compared the expected life-long intake with drinking water with the lowest dose administered within a chemotherapy.

2 Materials and methods

2.1 Hazard assessment: usage, environmental occurrence, fate and effects

The degree of CP and IF excretion depends on several factors, such as the constitution of the patient or the time of administration (Boos et al. 1991). For CP and IF, 10% to 40% excretion of non-metabolised substance was reported; most authors report 10–30% (Bagley et al. 1973; Saul et al. 1979; Wagner and Ehinger 1987; Sorsa et al. 1988; Goren 1991; Boos et al. 1991, 1992; Martino et al. 1992; Gilard et al. 1993; Ensslin et al. 1994). An excretion rate of 20% for non-metabolised drugs is a reliable average value. This has been shown by comparing calculated and measured concentrations of CP and IF in hospital effluents (Steger-Hartmann et al. 1996). Based on consumption data for CP and IF, this rate was therefore used to calculate the PECs. For reasons of data quality and differences between the nationwide and local situation, data from different sources were used in the calculation, as illustrated in Fig. 2. The two approaches were (1) the calculation of a nationwide predicted environmental concentration ($PEC_{regional}$) in surface water from the total annual amounts of CP and IF used in Germany and (2) PEC_{local} using (a) expected and (b) measured CP and IF concentrations in the effluent of a municipal sewage treatment plant. This plant receives hospital effluents amongst others from a big university hospital and a hospital specialised in anti-cancer treatment.

2.2 Annual CP and IF used in Germany: $PEC_{regional}$

The overall use of CP in Germany was estimated on the basis of the per capita amount of CP used in Western countries. Data on the manufacture of CP were used in as

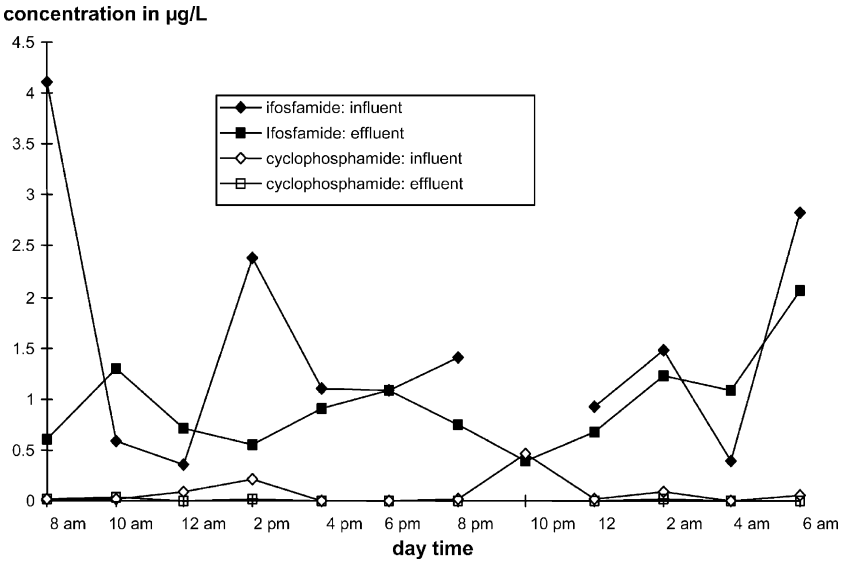

Fig. 2 Typical influent and effluent profile of cyclophosphamide and ifosfamide concentrations of the sewage treatment plant

far as they were available (International Agency for Research on Cancer 1975, 1981; Boos et al. 1991; Schwab et al. 2005). No such data were available for IF, but according to the manufacturer the amount of IF used in Germany is approximately the same as for CP. Therefore, the same consumption data were used for CP and IF. An average, consumption of 2.8–3.3 mg CP per capita has been estimated for Western countries based on population and amounts used (International Agency for Research on Cancer 1975; Statistisches Bundesamt, German Federal Statistical Agency 1990). Germany has a population of approximately 80,000,000. We calculated annual CP and IF consumption for Germany. Total consumption of CP and IF in three hospitals (Freiburg University Hospital, about 1,800 beds, large oncology department; The Offenburg communal hospital, about 450 beds; and a hospital specialised in anti-cancer treatment, 200 beds) at the time of data collection. Annual consumption data where retrieved from the electronic data system by the hospital pharmacies. Annual use of CP and IF in Germany was calculated by using national-wide data on medical service offered, number of hospitals and number of beds (Statistisches Bundesamt, German Federal Statistical Agency 1990). For $PEC_{regional}$, the formula proposed by the EU in the risk-assessment guidelines was applied (European and Direction General 1995).

$$PEC[g/l] = A \times (100 - R)/(365 \times P \times V \times D \times 100)$$

where

A [kg]	amount used per year in the country
R [%]	removal rate due to loss by adsorption, volatilization, hydrolysis, biodegradation or other processes (80% for CP and IF due to metabolism)
P	population (80,000,000 for Germany)
V [m^3]	volume of waste water per capita per day (generally 0.15 to 0.30 m^3)
D	factor for dilution of waste water through surface water flow (average factor: 10 (European and Direction General 1995)

2.3 STP effluent concentrations: PEC_{local}

Concentrations of CP and IF were measured in the influent and the effluent of a sewage treatment plant (STP; see Fig. 2). Expected concentrations of CP and IF were calculated in hospital effluent, municipal sewage and the influent and effluent of this municipal STP (Forchheim, AZV Breisgauer Bucht). These concentrations served (Kümmerer et al. 1997; Steger-Hartmann et al. 1997) as a basis for calculation of PEC_{local}. The effluents of six hospitals of different sizes and structures are purified together with municipal sewage in the investigated STP. The different ways for the calculation of $PEC_{regional}$ and PEC_{local} are shown in Fig. 3.

2.4 IF and CP intake during therapy vs. intake with surface water used as drinking water

The amount of CP and IF administered during anti-cancer treatment was compared with that resulting from intake with surface water. A single dose for anti-cancer treatment with CP and IF is 0.7–2.8 g/m^2 body surface; and up to 60 g/m^2 body surface is common for whole treatment (Bier et al. 1987; Fichtner and Nowak 1987; Allwood and Wright 1993). This corresponds to approx. 150 mg/kg body weight or 10.5 g for a patient weighing 70 kg. In interval therapy, up to 500–1,000 mg/kg of IF

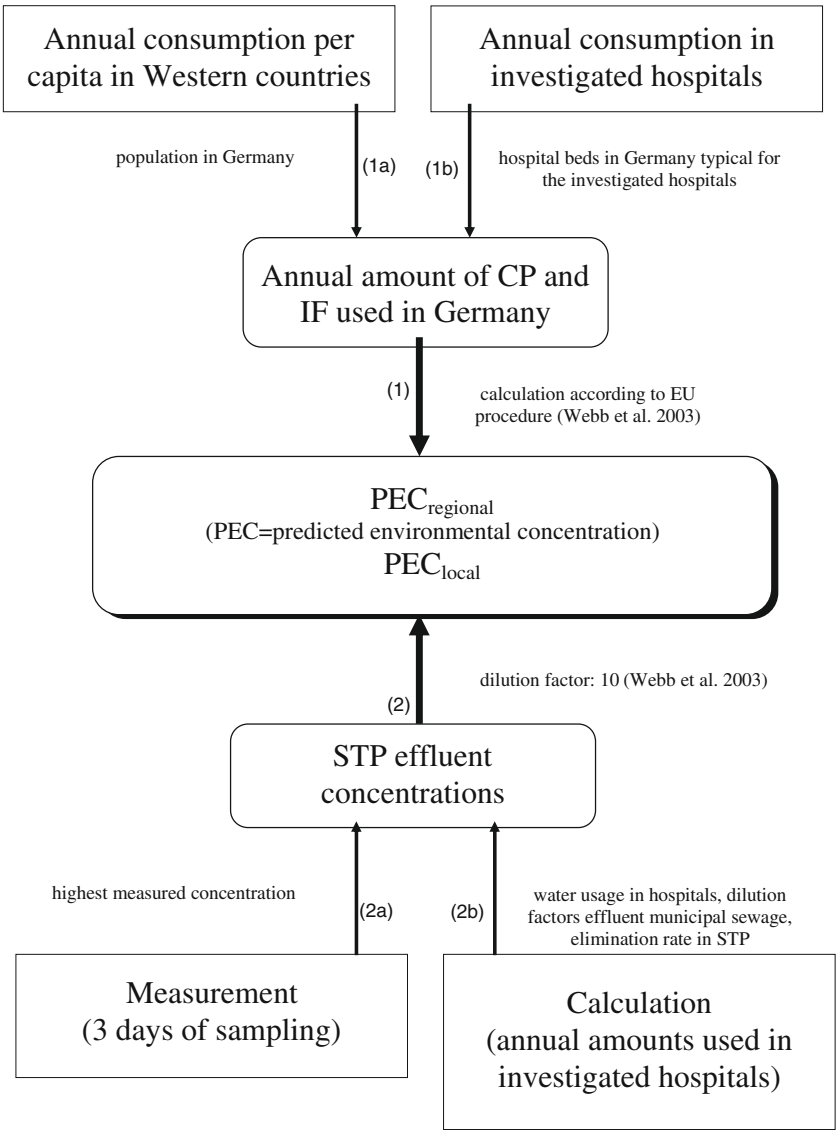

Fig. 3 Scheme of the different ways for the PEC calculation. *Numbers in brackets* indicate the different routes and origins of data used for the calculation of PEC (*STP* sewage treatment plant)

i.e. 14–70 g are administered within a few months (Fichtner and Nowak 1987; ASTA Medica 1992; Steger-Hartmann 1995). Adsorption onto granular activated carbon or oxidative treatment is a widespread method used to eliminate pollutants during drinking water processing. Degradation by photochemically formed HO radicals may be of some relevance only in shallow, clear, and nitrate-rich water bodies but could be further exploited for elimination of these compounds by advanced oxidation processes, i.e., in a treatment of hospital waste water (Buerge et al. 2006). A conservative approach was made: (a) as no data were available for CP and IF oxidation in drinking water processing, and as CP and IF were not adsorbed onto sewage sludge, elimination of CP and IF during drinking water processing was neglected. Therefore, the PECs for surface water were used to calculate the resulting intake with water, assuming 2 L of water daily over a life span of 70 years.

(b) The lowest dose of CP/ IF given within anti-cancer therapy was compared with the highest dose calculated from PEC, i.e. the highest possible intake with drinking water. For the risk assessment, the following restrictive assumptions were made as established in the literature:

- There is a dose–effect relationship for secondary cancer induction by CP (Kinlen 1985; Clewell et al. 1995; Knight et al. 2004) and IF.
- The dose–effect relationship is linear in the low-dose area and the whole (Brock and Pohl 1987).

- The effects of long-term low doses are similar to those of short-term high doses.
- The frequency of primary tumours in immune deficient patients and the frequency of secondary tumours in patients who are not undergoing chemotherapy are comparable to the frequency of tumours in a disease-free control group.
- The age dependency, incidence of secondary tumours and survival times in the control groups is the same as in the general public.
- We assumed that protecting against cancer should protect against all other adverse effects (Schulman et al. 2002; Umweltbundesamt 2003) such as neurotoxicity that is also reported for CP (Jjemba 2008).

The structural isomeric oxazaphosphorines CP and IF are inactive per se and require metabolic activation, predominantly by mixed-function hydroxylase of the liver, to acquire their alkylating properties. For both substances, the 4-hydroxy-oxazaphosphorine is the basic compound of cytotoxic specificity and carcinogenic selectivity (Momerency et al. 1994b). The related mustards (phosphoramide mustard and isophosphoramide mustard) are the alkylating agents for both compounds (Saul et al. 1979; Haas et al. 1987; Goren 1991; Martino et al. 1992; Boos et al. 1992; Gilard et al. 1993; Kümmerer 2008). Organic trace compounds that lack an adequate toxicological database, and their mixtures, in drinking water can be safely regulated and provisionally assessed by combining the "similar joint action" addition rule (Dieter and Mückter 2007). Thus, the data for risk of secondary bladder tumour reported for CP was assumed to be the same for IF. Several studies on secondary tumour growth after a cumulative given CP dose of between <10 g and 51 g reported a relative risk for leukaemia or bladder cancer of between 1.5 (10 g) and 100 (51 g; Plotz et al. 1979; Kinlen et al. 1979, 1981; Grochow and Calvin 1983; Pedersen-Bjergaard et al. 1985; Travis et al. 1994; Knight et al. 2004).

3 Results

3.1 Occurrence: annual amounts of CP and IF used in Germany

The results of the calculations are summarised in Table 1. CP and IF consumption was 230–260 kg per year in Germany applying data on the average use per capita consumption in Western countries. If the communal hospital (450 beds) is taken as a representative for the amount of CP and IF used per hospital bed in Germany (approx. 600,000 beds), total consumption amounts to 248 kg for CP and 343 kg for IF per year (=0.42 g CP and 0.57 g IF per bed and year). About 40 kg of CP and 90 kg of IF per year (1 g CP, 2.05 g IF per bed and year) were calculated for university and comparable hospitals (approx. 40,000 beds). The amounts used in the hospital specialised in anti-cancer treatment were 1.26 g per bed and year for CP and 1.65 g per bed and year for IF. Based on these data, total consumption in Germany amounted to 288 kg of CP and 433 kg of IF per year. These results were used to calculate the PEC.

3.2 Environmental concentrations

Based on consumption data (see section 3.1), the $PEC_{regional}$ in surface water in Germany was 0.6–0.7 ng/L for CP and 0.6–1.0 ng/L for IF. PEC_{local} was calculated from the measured and expected concentrations in the effluent from the communal STP. The concentration was 5.6 ng/L for CP and 10.9 ng/L for IF based on the calculated consumption. Using the highest STP effluent concentrations measured, the result was 4 ng/L for CP and 206 ng/L for IF (see Table 1).

3.3 Risk ratio: intake of CP and IF in surface water vs. administration in anti-cancer treatment

In Germany, the resulting intake of CP and IF by an adult through use of unprocessed surface water as drinking water over a life span of 70 years (consuming 2 L water daily) is, in average, between 30.7 µg and 35.8 µg for CP and between 30.7 µg and 51.2 µg for IF. Local intake is much higher, 205–286 µg for CP and 558–10,530 µg for IF. Nationwide intake of IF and CP with unprocessed surface water used as drinking water is $<1\times10^{-6}$, in relation to intake by therapy taking the lowest and the highest intake dose with surface water on the one hand and a dose of 10 g (relative risk 1.5) and 51 g (relative risk 100) during anti-cancer treatment on the other.

4 Discussion

The nationwide PEC ($PEC_{regional}$) calculated in different ways using the different available data (see Fig. 2) was almost identical for both compounds, which indicates sufficient quality of data. The local concentrations were one to two orders of magnitude higher, which is due to the fact that not every influent of an STP receives cytotoxic or mutagenic drugs, i.e., concentrations in the effluent of some STPs are higher, while in others they are lower than the nationwide average. The concentrations for IF measured locally were lower, and were in the same range as those for CP (Kümmerer et al. 1997; Steger-Hartmann et al. 1997). Two of these (Freiburg University Hospital and the hospital specialised in cancer treatment) run, by far, the biggest

Table 1 Use and assessed possible risk of CP and IF in surface water ingested as drinking water (adults)

	Annual amounts used in Germany				Local STP effluent concentration			
	Based on per capita use in Western countries (International Agency for Research on Cancer 1975, 1981; Goren 1991; Boos et al. 1992)		Based on consumption in investigated hospitals (Kümmerer et al. 1997; this study)		Expected annual average concentration based on use in local hospitals (Kümmerer et al. 1997; this study)		Maximum measured on three days of sampling (Kümmerer et al. 1997; Steger-Hartmann et al. 1997)	
	CP	IF	CP	IF	CP	IF	CP	
1. Input	260 kg	260 kg	288 kg	433 kg	56 ng/L	109 ng/L	n.d. −40 ng/L	n.d. −2060 ng/L
2. Resulting PEC (ng/L)								
•$PEC_{regional}$ [a]	0.6	0.6	0.7	1.0				
•PEC_{local} [b]					5.6	10.9	4	206
3. Intake by surface water[c]								
•Per day (ng)	1.2	1.2	1.4	2.0	11.2	21.8	8	412
•Life-time 70 years (μg)	30.7	30.7	35.8	51.2	286	558	205	10,530
4. Intake surface water vs. therapy[d]								
• Relative risk 1.5[e]	3.1×10^{-6}	3.1×10^{-6}	3.6×10^{-6}	5.1×10^{-6}	2.9×10^{-5}	5.6×10^{-5}	2.1×10^{-5}	1.1×10^{-3}
• Relative risk 100[e]	6.1×10^{-7}	6.1×10^{-7}	7.1×10^{-7}	1.0×10^{-6}	5.7×10^{-6}	1.1×10^{-6}	4.1×10^{-7}	2.2×10^{-4}

[a] According to EU formula (European and Direction General, 1995)

[b] Measured in STP effluent, dilution factor 10 (European and Direction General 1995) for surface water; Zuccato et al. measured up to 10.1 ng/L in surface water (Zuccato et al. 2000)

[c] 2 L per day, life span 70 years

[d] On the basis of a dose of 10 g within anti-cancer treatment, relative risk for secondary tumours: 1.5; on basis of a dose of 51 g within anti-cancer treatment, relative risk for secondary tumours: 100 (see text)

[e] (Plotz et al. 1979; Kinlen et al. 1979, 1981; Grochow and Calvin 1983; Pedersen-Bjergaard et al. 1985; Travis et al. 1994, 1995)

oncology departments in Freiburg. We therefore neglected the emissions from the other hospitals in the calculations. This is justified by the fact that the concentrations measured in the STP influent were in the same range for CP and IF as those calculated using the consumption data for CP and IF in these two hospitals. Elimination during sewage treatment was neglected for the calculation of CP and IF effluent concentrations, because neither CP nor IF was biodegraded. The compounds were detected in untreated and treated waste water at concentrations of <0.3–11 ng/L in a Swiss study, which corresponded well with concentrations predicted from consumption data and typical renal excretion rates (Buerge et al. 2006). CP and IF were not eliminated by adsorption onto sewage sludge or glass in laboratory testing (Steger-Hartmann et al. 1996, 1997; Kümmerer et al. 1997; Buerge et al. 2006). This is in accordance with a log K_{ow} of 0.63 for CP and of 0.86 for IF (Hansch et al. 1995).

In the worst case of highest local IF concentration measured in STP effluent, i.e. highest possible PEC_{local}, the ratio of intake with drinking water to that during therapy is approx. 1/1.000–1/10.000.

Schulman et al. employed a non-significant risk-level of 1 µg/d (1×10^{-3} cancer risk) for CP as this is the level of risk recommended by the State of California for drinking water. This value corresponds with a concentration of 500 ng/l (2 L daily intake). We found up to 400 ng/L in our study, which is quite close to this value. A risk-specific dose of 14 ng/kg and day for adults was derived using this no-significant-risk-level of 1 µg/day. The risk associated is within the range of the risk levels of 10^{-4} to 10^{-6} recommended by the US EPA for drinking water. Protecting against cancer should protect against all other adverse effects (Schulman et al. 2002; Dieter and Mückter 2007). However, Schulman et al. (2002) and Webb et al. (2003) did not take into account the different situation for children, babies (European Environment and WHO Regional Office for Europe 2002; US EPA 2003; Umweltbundesamt 2004), and unborn life.

The recommendation of the German Federal Environmental Agency and the German Commission for Drinking Water (Umweltbundesamt 2003) is a concentration below 100 ng/L as a limit for weak genotoxic compounds in drinking water and 10 ng/L for strong genotoxic compounds (additional 1×10^{-6} cancer risk). The corresponding data are: 200 ng/day and 20 ng/day. These are close to the nationwide expected average concentrations (see Table 1). Considering that organic trace compounds that lack an adequate toxicological database in drinking water can be safely regulated and provisionally assessed by combining the "similar joint action" addition rule (Dieter and Mückter 2007) results in a total concentration of IF and CP above the threshold of 20 ng/d.

The PEC_{local} of IF during a life span of 70 years for adults is considerably lower than that for CP in our study. On a nationwide average ($PEC_{regional}$), the ratio for intake with drinking water vs. intake within an anti-cancer therapy is $<10^{-6}$. A ratio of $<10^{-5}$ is quite typical for local situations. Considering that CP and IF are present at the same time and that they share the same active metabolite the concentrations and therefore the risk can be twice as high as compared to the single compounds. Regarding peak concentration on a local basis, a ratio of 10^{-3} is possible for short periods of time. However, for short-term peak concentration, a limit of 100 ng/L, i.e. a tolerable uptake of 200 ng/day is regarded as safe (Umweltbundesamt 2003). Furthermore, a fivefold increase in intake during therapy results in a 67-fold increase of the relative risk for secondary cancer (Plotz et al. 1979; Kinlen et al. 1979, 1981; Grochow and Calvin 1983; Pedersen-Bjergaard et al. 1985; Travis et al. 1994) in adults. In another study (Knight et al. 2004), it was found that under therapeutical conditions, i.e. much higher concentration than that considered here, the risk of bladder cancer caused by CP doubled every 10 g increment in CP. Authorities recommend for children an additional assessment factor of 10 for children (European Environment and WHO Regional Office for Europe 2002; US EPA 2003; Umweltbundesamt 2004). Therefore, the relevant ratios for children found in our study will be approx. 10^{-4} and could reach 10^{-2} if the additional assessment factor of 10 is taken into account. These data here show that according to present knowledge the additional risk of cancer cannot be fully excluded, especially with respect to children.

Drug remains are collected in the hospitals that were investigated here. If this is not the case with other hospitals, the risk ratios will be higher. The method used to assess the risk due to CP and IF has some shortcomings. The assumption, that there is a dose–effect relationship for secondary cancer induction by CP (Kinlen et al. 1981; Haas et al. 1987) and IF is only established for high and short-term doses as applied in therapy. Additionally, the risk perception within the wanted therapy is probably different from the one in case of not wanted and not avoidable limitations in case of intake with drinking water. CP and IF are pro-drugs; their toxicity and the stability of their metabolites such as the 4-hydroxy derivatives, acrolein and others (Saul et al. 1979; Wagner and Ehinger 1987; Goren 1991; Boos et al. 1991, 1992; Martino et al. 1992; Gilard et al. 1993) were not considered in our study. Aside from these limitations, our study shows the present limitations of risk assessment for carcinogenic compounds in the environment and especially for cytotoxics and mutagens where necessary data are missing.

We recommend to reduce the emission of CP and IF into waste water and surface water at least from a precautionary

view despite the fact that there is additional treatment within drinking water processing because of the special susceptibility of children and unborn life. A reduction can be achieved by short-term measures such as collection of drug remains. Collection of patients' excretions is not recommended. For personnel exposed to CP in hospitals or in CP production, a daily intake of 40–100 μg or less was reported (Matney et al. 1985), which corresponds to 100–10,000-fold the maximum possible daily intake with drinking water. Epidemiological studies of health professionals handling anti-cancer agents have also described higher mutagen excretion levels, and have not concluded that there are increased cancer risks (Bagley et al. 1973; Sorsa et al. 1988; Clever and Omenn 1988; Cooke et al. 1991; Sessink et al. 1995). The risk to hospital staff assigned to collecting the excreta or vomit of patients receiving CP and IF is much higher than that of the general public from excreta disposal with other sewage. Improvements in sewage treatment such as prolongation of residence time can improve the elimination of pharmaceuticals in sewage treatment. However, it has been found for CP and IF that longer contact times, even in static testing that necessitates much longer contact times both, CP and IF were not biodegraded and only after several years can some biodegradation be expected (Steger-Hartmann et al. 1996, 1997; Kümmerer et al. 1996, 1997; Schecker et al. 1998; Buerge et al. 2006). Other opportunities are advanced treatment technologies if they are affordable. However, data for CP and IF are scarce in this respect.

Compliance with the value of 10 or 100 ng/L in the long term will only be possible if the chemical and biological degradation of pharmaceuticals and their metabolites in waste water and waste-water-treatment plants is effectively improved. Therefore, in the long run, the biodegradability of pharmaceuticals should be included as a desirable property in the development of active compounds (Kümmerer et al. 2000; Kümmerer 2007). For IF, such an alternative is under clinical trial (http://www.thresholdpharm.com/sec/glufosfamide). Alternatively, there is the risk of drinking water degenerating into a sink for highly mobile, polar and persistent compounds. Their elimination at a stage as late as technical drinking water treatment would be neither close to the initial cause nor justifiable in terms of technical effectiveness (Umweltbundesamt 2003). The risk assessment of sometimes mutagenic or carcinogenic by-products, e.g. resulting from ozonation, chlorination or UV disinfection would give rise to further uncertainties.

Acknowledgements The authors wish to thank E. Strehl (Freiburg University Hospital Pharmacy) for providing the data on local use of cyclophosphamide and ifosfamide. Also, B. Dries (Abwasserzweckverband Breisgauer Bucht) for sampling the influent and effluent of the sewage treatment plant and A. Eitel for GC/MS-analysis. The work presented was supported by the "Projekt Wasser-Abfall-Boden (PWAB)" of the Ministry of Environment of Baden-Württemberg (Grant PA 94 154).

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