Available online at www.sciencedirect.com
SCIENCE DIRECT®
Regulatory Toxicology and Pharmacology 42 (2005) 296–312
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Human pharmaceuticals in US surface waters: A human health risk assessment

Bradley W. Schwab [a], Eileen P. Hayes [b], Janice M. Fiori [c], Frank J. Mastrocco [d], Nicholas M. Roden [e], David Cragin [f], Roger D. Meyerhoff [c], Vincent J. D'Aco [g,*], Paul D. Anderson [a]

[a] *AMEC Earth and Environmental, 239 Littleton Road, Suite 1B, Westford, MA 01886, USA*
[b] *Bristol-Myers Squibb Company, P.O. Box 191, New Brunswick, NJ 08903, USA*
[c] *Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA*
[d] *Pfizer, 235 East 42nd Street, New York, NY 10017, USA*
[e] *Schering-Plough, 1095 Morris Avenue, Union, NJ 07083, USA*
[f] *Merck and Co., Two Merck Drive, Whitehouse Station, NJ 08889, USA*
[g] *Quantum Management Group, 1187 Main Avenue, Clifton, NJ 07011, USA*

Received 24 December 2004
Available online 23 June 2005

Abstract

The detection of low levels of pharmaceuticals in rivers and streams, drinking water, and groundwater has raised questions as to whether these levels may affect human health. This report presents human health risk assessments for 26 active pharmaceutical ingredients (APIs) and/or their metabolites, representing 14 different drug classes, for which environmental monitoring data are available for the United States. Acceptable daily intakes (ADIs) are derived using the considerable data that are available for APIs. The resulting ADIs are designed to protect potentially exposed populations, including sensitive sub-populations. The ADIs are then used to estimate predicted no effect concentrations (PNECs) for two sources of potential human exposure: drinking water and fish ingestion. The PNECs are compared to measured environmental concentrations (MECs) from the published literature and to maximum predicted environmental concentrations (PECs) generated using the P*h*ATE model. The P*h*ATE model predictions are made under conservative assumptions of low river flow and no depletion (i.e., no metabolism, no removal during wastewater or drinking water treatment, and no instream depletion). Ratios of MECs to PNECs are typically very low and consistent with PEC to PNEC ratios. For all 26 compounds, these low ratios indicate that no appreciable human health risk exists from the presence of trace concentrations of these APIs in surface water and drinking water.

Keywords: Risk assessment; P*h*ATE; Pharmaceutical; Medicine; Human health; Environment; Drinking water; Fish consumption

1. Introduction

Pharmaceuticals have contributed significantly to the rise in quality of life and life expectancy (McClung et al., 2001; Neer et al., 2001; Qureshi et al., 1998; SOLVD, 1991). Associated with use of pharmaceuticals (referred to here as active pharmaceutical ingredients or APIs) is a potential for either the APIs or their metabolites to enter the environment. The pharmaceutical industry ensures the safety of its products by collecting significant amounts of data from studies with animals and humans during the drug development process and subsequent post-marketing safety surveillance activities. Data to support environmental risk assessments are also

* Corresponding author. Fax: +1 973 340 9818.
E-mail address: vdaco@qmg-inc.com (V.J. D'Aco).

0273-2300/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2005.05.005

generated to support registration of products in the US, Europe, and other countries, as required by existing regulations. In the US, formal assessments are supplied to the FDA for any new drug with projected use that could result in a surface water concentration above one part-per-billion (U.S. FDA, 1997, 1998).

In recent years, a number of investigators employing increasingly sensitive analytical techniques have reported finding trace quantities of APIs and/or metabolites of APIs in wastewater treatment plant effluents, surface waters, drinking water, and groundwater (Halling-Sorensen, 1998; Heberer, 2002; Ternes, 2001; Williams, 2005). These studies have been conducted primarily in Europe and North America. The US Geological Survey (USGS) recently surveyed US surface waters for 95 analytes, including many APIs (Kolpin et al., 2002). Only a few reports address the potential effect to human health from the presence of trace levels of APIs in the environment. Christensen (1998); Mons et al. (2003); Schulman et al. (2002); and Webb et al. (2003) have all evaluated potential human health impact for several APIs found in surface and drinking water, and report no significant impact to human health.

The pharmaceutical industry in the US continues to investigate the potential effects on the environment of trace levels of APIs in surface waters. Through the Pharmaceutical Research and Manufacturers of America (P*h*RMA), the industry has developed an environmental fate and effects model (P*h*ATE) to predict concentrations of APIs in surface and drinking water to support risk assessment activities (Anderson et al., 2004).

This paper evaluates the potential for trace levels of APIs in US surface waters to affect human health, as represented by direct effects from exposure. This work relies upon measured concentrations of APIs from the USGS national reconnaissance (Kolpin et al., 2002) and other investigators, and predicted concentrations derived using P*h*ATE. Using P*h*ATE provides the advantage of evaluating the potential effect on human health associated with API concentrations below detection limits in US surface waters (Anderson et al., 2004).

2. Materials and methods

The evaluation of potential risk of APIs in surface water to humans presented in this paper is comprised of four general steps. First, the APIs to be evaluated were selected. Second, predicted no effect concentrations (PNECs) were developed for both drinking water and fish consumption exposures. Third, measured environmental concentrations (MECs) reported for US surface waters were identified from the peer-reviewed literature. In addition, P*h*ATE was used to develop predicted environmental concentrations (PECs) in US surface waters. Fourth, PNECs were compared to both MECs and PECs for US surface waters and drinking water intakes. Each of these steps is described in more detail below.

2.1. Selection of compounds for evaluation

The 26 compounds included in this risk assessment represent the APIs used for human therapy (and their metabolites) reported by Kolpin et al. (2002). All compounds identified as "prescription drugs" and "non-prescription drugs" by Kolpin et al. (2002) are included in this analysis, as well as the subset of the category "veterinary and human antibiotics" that are approved for human use (Table 1). Approximately 14 general pharmacological classes, exhibiting a broad spectrum of pharmacologic activities, are included in this evaluation. The natural and synthetic steroid hormones are not included in this analysis. They require evaluation of confounding contributions from sources (e.g., plants and animals) beyond those of prescription drugs used for human health and such an evaluation is beyond the scope of this assessment. Additionally, caffeine, nicotine, and their metabolites are not included because human therapeutic use is not the primary source for their occurrence in the environment. This evaluation does not attempt to address the potential for interactions among APIs because there is no accepted methodology for performing such an evaluation.

2.2. Collection of substance-specific data

Table 1 lists the selected APIs together with background information, if available, about their therapeutic use, lowest therapeutic dose, and quantity sold in the US for human therapy in 2000. This is one of the years during which the USGS collected samples for their national reconnaissance. Data were obtained, if available, from FDA-approved labeling, FDA summary basis of approval documents, material safety data sheets, published information on the substance, standard drug information resources (e.g., Goodman and Gilman), subscription databases, or the manufacturers of the substances. These data are required for establishing acceptable daily intakes (ADIs), for calculating PNECs for drinking water and fish consumption, and for estimating PECs in water.

2.3. Development of ADIs

The ADI represents a level of daily intake that should not result in an adverse health effect from direct exposure in a population, including particularly sensitive individuals. Chemistry, pharmacokinetics, toxicity, and pharmacology are used to evaluate exposure and potential effects of each compound. Calculation of ADIs is based on the assumption that biological responses diminish to a threshold no effect level as the dose is reduced.

Table 1
Background information for APIs

Compound	Therapeutic use	Lowest therapeutic dose (mg)[a,c]	Kilograms of API used (2000)[b]
Acetaminophen	Analgesic/antipyretic	650	8,100,000
Albuterol	Antiasthmatic bronchodilator, β_2-adrenoceptor agonist; delivered either by inhalation or ingestion	2	4300
Cimetidine	Reduces gastric acid secretion in ulcer patients; histamine H2 receptor antagonist	200	160,300
Ciprofloxacin	Fluoroquinoline antibiotic (DNA gyrase inhibitor) for aerobic gram positive and some gram negative bacteria	100	132,200
Codeine	Opioid analgesic and cough suppressant	15	41,500
Dehydronifedipine	Inactive metabolite of nifedipine, an antianginal and antihypertensive drug	30 as nifedipine	40,100 as nifedipine
Digoxigenin	Digoxin metabolite; may have pharmacological activity but less active than digoxin	0.05 as digoxin	229 as digoxin
Digoxin	Cardiac glycoside used to treat congestive heart failure	0.05	229
Diltiazem	Antihypertensive, antianginal, anti arrhythmic, (calcium channel blocker)	30	213,700
Doxycycline	A tetracycline antibiotic	100	36,200
Enalaprilat	Antihypertensive ACE inhibitor; congestive heart failure; (active metabolite of enalapril)	1.25 (IV)	1087
Erythromycin-H_2O	Metabolite and degradant of a macrolide antibiotic for gram positive cocci and bacilli and some gram negative	250 as erythromycin	126,100 as erythromycin
Fluoxetine	Antidepressant, obsessive compulsive disorder, bipolar disorder	20	22,700
Gemfibrozil	Antihyperlipidemic	600	289,800
Ibuprofen	Antiinflammatory, analgesic	200	2,300,000
Lincomycin	Antibiotic	500	357
Metformin	Antidiabetic agent	500	1,700,000
Norfloxacin	Fluoroquinoline antibiotic	400	2700
Oxytetracycline	Tetracycline antibiotic	250	34
Paroxetine metabolite	Metabolite of paroxetine, an antidepressant (selective serotonin reuptake inhibitor)	20 as paroxetine	19,700 as paroxetine
Ranitidine	Reduces gastric acid secretion in ulcer patients; histamine H2 receptor antagonist	75	284,600
Sulfamethoxazole	Antibacterial sulfa drug	800	309,100
Sulfathiazole	Antibacterial sulfa drug	Variable–Topical	483
Tetracycline	Tetracycline antibiotic	250	112,800
Trimethoprim	Antibacterial drug	100	63,800
Warfarin	Anticoagulant	1	4300

[a] Lowest single dose resulting in a therapeutic effect. This dose is less than the total daily dose if the drug is given repeatedly over 24 h to maintain therapeutic blood levels.
[b] IMS (2003).
[c] Goodman & Gilman (2005).

Typically during the research and development of pharmaceuticals, a risk-benefit analysis is used by regulatory authorities to evaluate the safety of pharmaceuticals for the patient population (U.S. FDA, 1999). That process recognizes that a certain amount of risk, e.g., side effects, may be acceptable to receive the therapeutic benefits. This contrasts with the case of incidental exposure to pharmaceuticals through drinking water or fish consumption, where no benefit is presumed to be received by the exposed individual. In the present analysis, the potentially exposed population is presumed to include healthy adults as well as susceptible sub-populations (e.g., children, the elderly, and infirm) in which the pharmacologic effect is considered undesirable. Therefore, a conservative, regulatory, human health risk assessment approach is used in this analysis.

As noted by the U.S. EPA (2002), the database for a compound normally contains several toxic endpoints from which a point of departure should be determined to calculate the most restrictive reference value (or ADI). The point of departure for determining an ADI for chemicals is often either the highest dose resulting in no observed effects (no observed effect level or NOEL) or in no observed adverse effects (no observed adverse effect level or NOAEL) for a given toxic endpoint. For many APIs, however, a point of departure is the lowest dose resulting in an observable effect (lowest observed effect level or LOEL) or in an observable adverse effect (lowest observed adverse effect level or LOAEL). For an API, the therapeutic effect usually occurs at a dose considerably below those expected to result in toxicity.

Pharmacological effects are, however, assumed to be undesirable in the general population. So for the evaluations conducted here, the doses resulting in pharmacological effects in the extensive databases from human clinical trials are important to include as points of departure in calculating the most restrictive ADIs for APIs. The lowest therapeutic dose for an API, in many cases, is a LOEL for the therapeutic endpoint, in that a weak pharmacologic response occurs, sometimes in only a small percent of the population. An appropriate uncertainty factor is used to estimate a NOEL from a LOEL as part of the ADI calculation. Uncertainty factors (UFs) are applied, as shown in Eq. 1, to reduce the point of departure dose to a dose where there is reasonable certainty that no effect will occur (ATSDR, 1996; Dourson et al., 1996; IPCS, 1994)

$$\mathrm{ADI} = \frac{1000 \times \mathrm{POD}}{\mathrm{UF}_1 \times \mathrm{UF}_2 \times \mathrm{UF}_3 \times \mathrm{UF}_4 \times \mathrm{UF}_5}, \quad (1)$$

where ADI is in micrograms/kg-day (mcg/kg-day); POD is the point of departure in mg/kg-day; and UF are unitless uncertainty or modifying factors (described below) that reflect judgments on the required modification of observed toxicity data.

Originally, Lehman and Fitzhugh (1954) suggested that an uncertainty factor of 100 be applied to account for both animal-to-human extrapolation and potential variability within the sensitivity of a human population (i.e., interspecies and intraspecies variability). Since that time, uncertainty factors have evolved into five general categories (Table 2): interspecies variability, intraspecies variability, extrapolation from a low effect to no-effect level, accounting for the duration of exposure in toxicological studies, and a general "data quality" factor (Dourson et al., 1996). Historically, the "default" value of an uncertainty factor has been 10. However, in recognition of the additional information that is frequently being obtained by current toxicological practices, some are advocating the derivation and use of "non-default" assumptions. For instance, the U.S. EPA (2002) recommends using "half log" (i.e., $10^{0.5}$ or approximately 3) factors where uncertainty is reduced by the availability of multispecies pharmacokinetic or pharmacodynamic data. Others have advocated uncertainty factors that are derived on a compound-specific basis from supporting data ("data-derived factors"; Naumann and Weideman, 1995; Renwick, 1993; Silverman et al., 1999 or "chemical-specific adjustment factors"; IPCS, 2001). Table 2 describes our implementation of these concepts, incorporating the considerable amount of human and laboratory data available for APIs. The UFs described in Table 2 were recommended to develop ADIs in this paper. However, it should be noted that determination of an ADI requires much scientific judgment and there is no single default approach for assessing UFs.

2.4. Development of predicted no effect concentrations

ADIs were combined with standard assumptions about potential exposure, via drinking water and fish consumption, to derive a PNEC for each API. A PNEC represents the concentration in surface water at or below which no adverse human health effects are expected. Three categories of PNECs were estimated. One was for APIs in water used only as a drinking water source ($\mathrm{PNEC_{DW}}$); a second for water from which the only potential exposure to APIs is through consumption of fish ($\mathrm{PNEC_F}$); and the third, for water used both as a drinking water source and as a source of fish for human consumption ($\mathrm{PNEC_{DW+F}}$). PNECs were estimated for both adults and children using Eqs. (2)–(4). These general exposure equations are consistent with those used by the US Environmental Protection Agency (U.S. EPA) for developing concentration limits to protect against threshold-type effects, such as the Ambient Water Quality Criteria (AWQC) for the protection of human health or maximum contaminant levels. The equations were applied using human exposure parameters recommended by U.S. EPA guidance to derive AWQC (U.S. EPA, 2000), as shown in Table 3

$$\mathrm{PNEC_{DW}} = \frac{1000 \times \mathrm{ADI} \times \mathrm{BW} \times \mathrm{AT}}{\mathrm{IngR_{DW}} \times \mathrm{EF} \times \mathrm{ED}}, \quad (2)$$

$$\mathrm{PNEC_F} = \frac{1000 \times \mathrm{ADI} \times \mathrm{BW} \times \mathrm{AT}}{\mathrm{BCF} \times \mathrm{IngR_F} \times \mathrm{EF} \times \mathrm{ED}}, \quad (3)$$

$$\mathrm{PNEC_{DW+F}} = \frac{1000 \times \mathrm{ADI} \times \mathrm{BW} \times \mathrm{AT}}{(\mathrm{IngR_{DW}} + \mathrm{BCF} \times \mathrm{IngR_F}) \times \mathrm{EF} \times \mathrm{ED}}, \quad (4)$$

where PNEC is in ng/L; ADI is acceptable daily intake (mcg/kg-day); 1000 is a conversion factor (ng/mcg); BW is the child or adult body weight (kg/person); $\mathrm{IngR_{DW}}$ is the child or adult drinking water ingestion rate (L/person-day); $\mathrm{IngR_F}$ is the child or adult fish consumption rate (kg/person-day); BCF is the bioconcentration factor for fish (L/kg); AT is the averaging time (days); EF is the exposure frequency (days/year); ED is the exposure duration (years).

Bioconcentration of APIs in fish tissue was estimated using a bioconcentration factor (BCF). The BCF for each API was estimated using the approach developed by Meylan et al. (1999). For non-ionic compounds, Meylan et al. (1999) recommend using a series of regression equations and a compound's K_{ow} to estimate its BCF. For most, but not all, ionic compounds, Meylan et al. (1999) recommend using a fixed BCF within a specific range of K_{ow}. Note that when the BCF is less than 115

Table 2
Extrapolation uncertainities and considerations for selection of uncertainty factors

Extrapolation uncertainties	Considerations for uncertainty factor selection
LOAEL to NOAEL (UF_1)	• 10 recommended when a NOAEL is not available • 3 recommended when the LOAEL is a therapeutic response, operative only in a disease state • 1 recommended when the LOEL is associated with a homeostatic response or an equivocal effect (i.e., the LOEL is a NOAEL)
Duration of exposure (UF_2)	• 10 recommended when no relevant chronic data available • 3 recommended when no chronic data are available, but PK or PD analyses suggest little persistence of compound or effect • 1 recommended when no chronic data are available, but PK and PD analysis suggest little persistence of compound and effect • 1 recommended when adequate chronic data are available
Interspecies (UF_3)	• 10 recommended when no human data are available unless considerations below apply • 3 recommended when ADME data are similar for multiple species, including humans or non-human primates • 1 used when derivation is based on human data
Intra individual susceptibility (UF_4)	• 10 recommended if NOAEL is from a general adult population and/or animal study, with no multigenerational study of toxicity • 3 recommended when effect is therapeutic and there is little difference between the median and minimally effective dose • 3 recommended when using an adjusted LOEL, NOEL or therapeutic dose specific to a sensitive sub-population • 1 recommended when sufficient post-marketing data indicate the absence of specific and particularly sensitive individuals or when using a LOEL or NOEL for a specifically identified sensitive human population based on a large post-marketing study
Data Quality (UF_5)	10, 3 or 1, or a number smaller than 1, are recommended for the professional judgement on the quality of data available on a compound: • Critical studies used small number of animals or groups (UF>1) • Results are poorly described or analyzed (UF>1) • Data require route-to-route extrapolation to be relevant to the exposure condition (UF< or >1 depending on the relevance and relative sensitivity to the effect by alternate dosing routes) • Important specialized studies not conducted (e.g., reproductive, teratogenicity, carcinogenicity) when positive genetic toxicity data is available, (UF>1) • The absence of data is mitigated (UF<1) or exacerbated (UF>1) by results on a compound of similar structure and responses • Non-standard study designs (UF> or < 1 depending on the nature of the study) • Esoteric or extreme effects (UF greater or less than 1 depending on the nature of the study) • NOEL is the highest dose tested (possibly a UF<1)

PK, pharmacokinetic; PD, pharmacodynamic.

for adults (150 for children) the drinking water PNEC is more stringent than the fish consumption PNEC; and when the BCF is greater than 115 (150 for children) the fish consumption PNEC is more stringent.

The APIs included in this assessment are non-volatile substances. Consequently, the inhalation exposure pathway is considered to be of little significance. Likewise, exposure via the dermal pathway is considered insignificant compared to the drinking water and fish consumption pathways.

2.5. Estimating exposure to APIs from drinking water and fish consumption

Concentrations of APIs reported by Kolpin et al. (2002) for US surface waters were compiled. The concentrations of APIs present in surface water are used as a conservative estimate of API concentrations that might be present in drinking water (i.e., this assessment assumes no degradation or removal of an API during drinking water purification processes). Kolpin et al. (2002) used more than one analytical method to measure the concentrations of some APIs. For those instances, this assessment conservatively assumes the highest concentration is present in surface waters. For the seven (of 26) APIs included in this paper that were not detected by Kolpin et al. (2002), one-half of the reporting levels (RLs, defined as the lowest concentration standard that could be reliably quantitated) are conservatively assumed to represent concentrations in US surface waters (U.S. EPA, 1989).

To supplement the data presented by Kolpin et al. (2002), the peer-reviewed literature was also searched for other instances where these APIs were identified in

Table 3
Parameters relating to adult and child receptors

Parameter	Units	Symbol	Receptor	
			Adult	Child
Body weight	kg	BW	70	14
Water consumption	L/day	$IngR_{DW}$	2	1
Fish consumption	kg/day	$IngR_F$	0.0175	0.0065
Exposure frequency	days/year	EF	350	350
Exposure duration	years	ED	30	6
ADI averaging time	days	AT	10,950	2190

surface water. In addition, to further enhance this assessment, PECs were estimated using P*h*ATE (Anderson et al., 2004), run in a conservative screening mode. This is a useful approach to provide supplemental information for substances that were not detected by Kolpin et al. (2002). P*h*ATE was run using 7Q10 low flows (i.e., the lowest consecutive 7-day flow that occurs on average once every 10 years) with no adjustment for mass removal by POTW treatment or in-stream removal mechanisms (i.e., screening mode). The annual estimate of total API sold in the US for the year 2000 was obtained from IMS Health Inc. (IMS) and used in the model runs (IMS, 2003). Additionally, the annual mass was not adjusted either for metabolism of the API to inactive and/or less active metabolites or for drug product that was sold but not used. The P*h*ATE model estimates concentrations at drinking water withdrawal points (i.e., PEC_{DW}) and in stream segments (i.e., PEC_{SW}) throughout 11 watersheds in the US, yielding distributions of both PEC_{DW} and PEC_{SW} values for each API. The maximum concentration for all of the drinking water intake points included in P*h*ATE (maximum PEC_{DW}) is used in this analysis to represent a conservative estimate of drinking water exposure. The maximum concentration for all of the stream segments included in P*h*ATE (maximum PEC_{SW}) is used to represent a conservative estimate of fish consumption exposure. For the combined drinking water and fish consumption exposure, the maximum PEC_{SW} is used to represent the most conservative estimate of exposure.

2.6. Risk characterization

The ratios of either the maximum measured concentration or 1/2 RL and of the maximum PEC (from P*h*ATE) to the drinking water PNEC, fish consumption PNEC, and combined drinking water and fish consumption PNEC for each API were calculated. APIs with ratios less than 1 are presumed to present no appreciable risk to human health from the consumption of drinking water and fish. APIs with ratios greater than 1 may warrant additional assessments taking into consideration depletion mechanisms or other appropriate factors to assess potential risk.

3. Results

3.1. Acceptable daily intakes

As summarized in Table 4, ADIs were derived by dividing the point of departure by five uncertainty factors. The points of departure range from 0.0007 (for digoxin and digoxigenin) to 100 mg/kg/day (for dehydronifedipine) (Table 4) and the combined uncertainty factors range from 1 (for ciprofloxacin, doxycycline, oxytetracycline, tetracycline, and trimethoprim) to 1000 (for dehydronifedipine) (Table 4). The ADIs derived for the APIs and/or their metabolites range from 0.07 (for digoxin and digoxigenin) to 340 mcg/kg/day (for acetaminophen) (Table 4). For many APIs, the dose used for the point of departure was established from the lowest therapeutic dose in humans. In some cases, the human population to which the point of departure applies represents a very sensitive or susceptible population compared to a healthy adult population. While children are often considered a sensitive sub-population, the doses approved for use in adults are lower on a per kilogram basis than those approved for children for all of the APIs included in this assessment where the therapeutic effect is the critical effect for establishing the point of departure. In some cases, the dose used for the point of departure was established based on specific toxicological effects such as thyroid effects and sensitivity of specific microbes.

3.2. Bioconcentration factors

Log BCFs range from 0.15 (for digoxigenin) to 1.64 L/kg (for dehydronifedipine) (Table 5). Twenty-three of 26 APIs were assigned a log BCF of 0.5 L/kg either because the API is ionic with a log K_{ow} of less than 5 (22 of 23) or because the API is non-ionic but has a log K_{ow} of less than 1.0 (1 of 23, Table 5). Only one API has a log BCF of greater than 1.0 L/kg (Table 5).

3.3. Predicted no effect concentrations

Three different types of PNECs were derived for both children and adults: a PNEC protective of drinking water exposures only ($PNEC_{DW}$); a PNEC protective of fish consumption exposures only ($PNEC_F$); and, a PNEC protective of combined drinking water and fish consumption exposures ($PNEC_{DW+F}$) (Table 6). PNECs for children are always lower than adult PNECs (by a factor of about 2.5, 1.9, and 2.3–2.5, respectively, for drinking water, fish consumption, and drinking water and fish consumption combined) because children are assumed to drink more water and eat more fish on a body weight basis than adults. Only the PNECs calculated for children are discussed here because they are lower than PNECs for adults and are therefore more

Table 4
Parameters for estimation of acceptable daily intakes

Substance	POD (mg/kg/day)	UF_1	UF_2	UF_3	UF_4	UF_5	ADI (mcg/kg/day)	Critical effect and basis for POD
Acetaminophen	9.3	3	3	1	3	1	340	Therapeutic effect. POD is the lowest single effective therapeutic dose in adults of 650 mg, or 9.3 mg/kg in a 70-kg adult, when taken once in a day (Goodman & Gilman, 2001)
Albuterol	0.029	3.2	1	1	3.2	1	2.8	Therapeutic effect. POD is the lowest single therapeutic oral dose in adults of 2 mg/day or 0.029 mg/kg/day taken three to four times per day (HSDB, 2005; PDR, 2005b)
Cimetidine	2.9	10	1	1	10	1	29	Therapeutic effect. POD is the lowest single therapeutic dose for over-the-counter use for reducing gastric acid secretion in adults of 200 mg/day or 2.9 mg/kg/day taken once or twice daily (GSK, 2002; Martindale, 2005)
Ciprofloxacin	NA	NA	NA	NA	NA	NA	1.6	Sensitivity of human intestinal microflora. ADI of 1.6 mcg/kg/day is based on minimum inhibitory concentration (MIC) values for ciprofloxacin (lowest $MIC_{50} = 0.0016$ mcg/ml) against human intestinal flora following EMEA methodology (EMEA, 1998)
Codeine	0.21	10	1	1	10	1	2	Therapeutic effect. POD is the lowest single therapeutic dose for pain relief in adults of 15 mg/day or 0.21 mg/kg/day taken four to six times per day (PDR, 2005c)
Dehydronifedipine	100	1	10	10	10	1	100	Animal study NOEL. POD is the NOEL in the longest term data available for the metabolite which is 100 mg/kg/day in rodent studies of up to four weeks in duration (Bayer HealthCare, private communication, 28-Mar-05)
Digoxigenin	0.0007	10	1	1	1	1	0.07	Therapeutic effect of parent compound. Digoxigenin is a metabolite of digoxin and has similar properties but reduced activity when compared to the parent compound (ASHP, 2003; Hoffman and Bigger, 1990). Digoxigenin is assumed to be pharmacologically equipotent with digoxin for purposes of this ADI
Digoxin	0.0007	10	1	1	1	1	0.07	Therapeutic effect. POD is the lowest maintenance dose to regulate heart rate and increase cardiac output in a very sensitive population (i.e., persons with congestive heart failure and renal impairment) of 0.05 mg/day or 0.0007 mg/kg/day taken once daily (PDR, 2005a)
Diltiazem	0.43	3	1	1	10	1	14	Therapeutic effect. POD is the lowest single therapeutic dose to lower blood pressure in adults of 30 mg or 0.43 mg/kg taken four times per day (Hoechst et al., 1999)
Doxycycline	NA	NA	NA	NA	NA	NA	30	Sensitivity of human intestinal microflora. ADI of 30 mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal microflora (JECFA, 1998)
Enalaprilat	0.6	3	1	1	3	1	70	Therapeutic effect. POD is based on an initial dose to lower blood pressure in adults of 1.25 mg given intravenously every 6 h (Goodman & Gilman, 2001). POD calculated using a bodyweight of 70 kg and 3% oral bioavailability (Merck, 2005)
Erythromycin-H_2O	3.6	3	10	1	3	1	40	Therapeutic effect of parent compound. POD is the lowest single therapeutic dose in adults of 250 mg/day or 3.6 mg/kg/day taken four times per day (Goodman & Gilman, 2001). ADI established by EMEA based on antimicrobial activity of the parent is not applicable since the erythromycin-H_2O metabolite is not active as an antibiotic (Roth and Fenner, 1994)
Fluoxetine	0.29	10	1	1	10	1	2.9	Therapeutic effect. POD is the lowest therapeutic dose for depression in adults of 20 mg/day or 0.29 mg/kg/day taken once daily (PDR, 2005c)
Gemfibrozil	8.6	3	1	1	5	10	55	Therapeutic effect. POD is the lowest single therapeutic dose for reducing cholesterol in adults of 600 mg/day or 8.6 mg/kg/day taken twice daily (Pfizer, 2003)
Ibuprofen	2.9	3	1	1	3	3	110	Therapeutic effect. POD is the lowest single therapeutic dose for pain relief in adults of 200 mg/day or 2.9 mg/kg/day taken four to six times per day (PDR, 2005b)
Lincomycin	2.5	1	1	1	10	10	25	Sensitivity of human intestinal microflora. POD was established by WHO based on correlation to clindamycin which had a human intestinal microflora NOEL of 2.5 mg/kg/day (JECFA, 2000)
Metformin	5.6	3	1	1	10	3	62	Therapeutic effect. POD is the lowest effective dose on blood glucose in adults of 500 mg/day of metformin HCl (390 mg/day or 5.6 mg/kg/day of metformin free base) taken once daily (Goodman & Gilman, 2001)
Norfloxacin	5.7	3	1	1	10	1	190	Gastrointestinal upset. POD is the GI effect associated with the lowest clinical dose, 400 mg/day or 5.7 mg/kg/day (Merck, 2004)

Oxytetracycline	NA	NA	NA	NA	NA	NA	30	Sensitivity of human intestinal microflora. ADI of 30 mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal microflora (JECFA, 1998)
Paroxetine metabolite	0.29	10	1	1	10	1	2.9	Therapeutic effect of parent compound. POD is the lowest therapeutic dose of the parent compound relative to antidepressant effects in adults of 20 mg/day or 0.29 mg/kg/day taken once daily (PDR, 2005c)
Ranitidine	1.1	10	1	1	10	1	11	Therapeutic effect. POD is the lowest therapeutic dose for over-the-counter use to reduce gastric acid secretion in adults of 75 mg/day or 1.1 mg/kg/day taken once daily (PDR, 2005b)
Sulfamethoxazole	25	1	1	10	10	2	130	Animal study NOEL. POD is based on NOEL for thyroid tumors in rats that may have no relevance for humans. POD is the 25 mg/kg/day dose of the rat studies (Swarm et al., 1973)
Sulfathiazole	5	1	1	10	10	1	50	Changes in thyroid tissue. Established by reference to the WHO assessment of sulfamethazine which had a NOEL of 5 mg/kg for thyroid effects in animal studies. POD is the thyroid tissue NOEL of 5 mg/kg/day (JECFA, 1994)
Tetracycline	NA	NA	NA	NA	NA	NA	30	Sensitivity of human intestinal microflora. ADI of 30 mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal microflora (JECFA, 1998)
Trimethoprim	NA	NA	NA	NA	NA	NA	4.2	Sensitivity of human intestinal microflora. ADI of 4.2 mcg/kg/day was established by EMEA (1997) based on the in vitro minimum inhibitory concentration (MIC) of the most sensitive species in a study of trimethoprim activity against human gut flora
Warfarin sodium	0.014	3	1	1	3	10	0.16	Therapeutic effect. POD is a low fixed therapeutic dose (converted to free acid) that is sometimes effective in selected patients and is also sometimes used in more susceptible populations (e.g., Asians) of 1 mg/day or 0.014 mg/kg/day (Bern et al., 1997; Yu et al., 1996)

NA, not applicable.

conservative for screening purposes. Drinking water PNECs for children range from 1.0×10^3 (for digoxin and digoxigenin) to 5.0×10^6 ng/L (for acetaminophen). Fish consumption PNECs for children range from 8.4×10^4 (for digoxin) to 2.4×10^8 ng/L (for acetaminophen). Combined drinking water and fish consumption PNECs for children range from 1.0×10^3 (for digoxin and digoxigenin) to 4.9×10^6 ng/L (for acetaminophen).

Because BCFs are relatively low for most APIs, the $PNEC_F$ is substantially higher than the matched $PNEC_{DW}$ and $PNEC_{DW+F}$ for most APIs. This suggests that fish consumption is unlikely to be a major pathway of exposure for most APIs.

3.4. API concentrations in surface water

The maximum concentrations of APIs or their metabolites reported by Kolpin et al. (2002) are summarized in Table 7. Table 7 also summarizes concentrations of APIs reported in surface water by other investigators. For five of the 26 APIs, measured surface water concentration data were only available from Kolpin et al. (2002) (Table 7). For the remaining 21 APIs, Kolpin et al. (2002) as well as other papers, report results of surface water analyses. For nine APIs, the maximum MEC is reported by Kolpin et al. (2002); for 10 APIs, the maximum MEC is reported by others; and for one API (ciprofloxacin), the same maximum MEC was reported by Kolpin et al. (2002) and others (Table 7). One API (digoxigenin) was not detected by Kolpin et al. (2002) or by others. Except for tetracycline, the maximum MECs reported by others are never greater than four times those reported by Kolpin et al. (2002) (Table 7). Because Kolpin et al. (2002) represents a comprehensive and systematic survey of MECs for all APIs included in this assessment and the results of Kolpin et al. (2002) are generally consistent with other researchers, this assessment develops MEC/PNEC ratios based upon the findings of Kolpin et al. (2002).

Table 7 also summarizes the maximum PECs for drinking water (PEC_{DW}) and surface water (PEC_{SW}) under 7Q10 low flow conditions derived using P*h*ATE for all the APIs. As discussed above, these PECs were developed using the annual mass (kg) of drug sold in the US for human therapy, without accounting for reductions due to human metabolism or depletion mechanisms at POTWs or in surface waters or the amount of drug product not used. Fig. 1 illustrates the distribution of surface water and drinking water PECs over 11 watersheds for cimetidine. The 95th percentile, 99th percentile, and maximum surface water concentrations predicted by P*h*ATE are approximately 35, 47, and 79 times higher, respectively, than the median surface water PEC. Because P*h*ATE was run without accounting for any API-specific loss mechanisms, the relative differences between the median and maximum PECs (and between any other percentiles of the PEC distribution) observed

Table 5
Chemical structure, log K_{ow}, and log BCF data

Compound	Chemical structure	log K_{ow}	log BCF (L/kg)	BCF (L/kg)
Acetaminophen	Non-ionic	0.46[1]	0.50[12]	3.2
Albuterol	Ionic, amine protonated at pH 7	−2.80[2]	0.50[11]	3.2
Cimetidine	Ionic, amine protonated at pH 7	0.20[2]	0.50[11]	3.2
Ciprofloxacin	Ionic, amine protonated at pH 7	0.28[3]	0.50[11]	3.2
Codeine	Ionic, amine protonated at pH 7	1.19[4]	0.50[11]	3.2
Dehydronifedipine	Non-ionic	3.04[5]	1.64[13]	44
Digoxigenin	Non-ionic	1.10[6]	0.15[13]	1.4
Digoxin	Non-ionic	1.26[1]	0.27[13]	1.9
Diltiazem	Ionic, amine protonated at pH 7	2.70[6]	0.50[11]	3.2
Doxycycline	Ionic, amine protonated at pH 7	−0.02[1]	0.50[11]	3.2
Enalaprilat	Ionic, amine protonated, carboxylic acid anion at pH 7	−0.74[6]	0.50[11]	3.2
Erythromycin-H_2O	Ionic, amine protonated at pH 7	3.06[7]	0.50[11]	3.2
Fluoxetine	Ionic, amine protonated at pH 7	2.60[8]	0.50[11]	3.2
Gemfibrozil	Ionic, carboxylic acid	2.14[5]	0.50[11]	3.2
Ibuprofen	Ionic, carboxylic acid	3.97[9]	0.50[11]	3.2
Lincomycin	Ionic, amine protonated at pH 7	0.56[6]	0.50[11]	3.2
Metformin	Ionic, amine protonated at pH 7	−1.43[6]	0.50[11]	3.2
Norfloxacin	Ionic, amine protonated, carboxylic acid anion at pH 7	−1.03[6]	0.50[11]	3.2
Oxytetracycline	Ionic, amine protonated at pH 7	−0.90[1]	0.50[11]	3.2
Paroxetine metabolite	Ionic, amine protonated at pH 7	1.32[10]	0.50[11]	3.2
Ranitidine	Ionic, amine protonated at pH 7	0.27[1]	0.50[11]	3.2
Sulfamethoxazole	Ionic, acidic H in SO_2NH	0.89[6]	0.50[11]	3.2
Sulfathiazole	Ionic, acidic H in SO_2NH	0.05[6]	0.50[11]	3.2
Tetracycline	Ionic, amine protonated at pH 7	−1.37[6]	0.50[11]	3.2
Trimethoprim	Ionic, basic pyrimidine	0.91[6]	0.50[11]	3.2
Warfarin	Ionic, acidic enol	2.70[6]	0.50[11]	3.2

Note. [1] Sangster (1994); [2] log D @ pH 7.0, Glaxo-SmithKline (personnal communication, May 7 2004); [3] Takacs-Novak et al. (1992); [4] Avdeef et al. (1996); [5] log D @ pH 7.0 calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67; [6] Hansch et al. (1995); [7] McFarland et al. (1997) (for Erythromycin); [8] Eli Lilly and Company (2000); [9] Avdeef (1993); [10] Cunningham et al. (2004).
[11] Ionic compound with log $K_{ow} < 5$; log BCF = 0.50 (Meylan et al., 1999).
[12] Non-ionic compound with log $K_{ow} < 1$; log BCF = 0.50 (Meylan et al., 1999).
[13] Non-ionic compound with log K_{ow} 1–7; log BCF = 0.77 log K_{ow} − 0.70 (Meylan et al., 1999).

for cimetidine will be the same for all other APIs included in this assessment.

Consistent with the use of P*h*ATE in a conservative screening mode (i.e., the assumption of no metabolism and no other depletion), the maximum surface water PECs generated by P*h*ATE are higher than the maximum MECs for 17 of the 19 APIs included in this assessment that were detected by Kolpin et al. (2002). The exceptions are lincomycin and oxytetracycline. These antibiotics have veterinary uses in addition to human therapy and, therefore, have sources and pathways into the environment that are not included in the P*h*ATE model. Nevertheless, it is notable that no appreciable human health risk is found for these two APIs even when MECs that likely reflect both human and veterinary use are compared to PNECs.

Again consistent with the use of P*h*ATE in a screening mode, the maximum surface water PECs generated by P*h*ATE are higher than 1/2 RL for all but one (i.e., digoxin) of the seven APIs included in this assessment that were not detected by Kolpin et al. (2002). For digoxin, 1/2 RL (130 ng/L) is a factor of 10 greater than the maximum PEC_{SW} (13 ng/L) calculated using very conservative assumptions of low flow and no depletion. Because 1/2 RL (130 ng/L) is not considered to be representative of actual surface water concentrations of digoxin in the US, it is not compared to its PNEC in the following analysis.

3.5. Comparison of MECs to PNECs

For all APIs and metabolites detected by the USGS, the ratios of maximum MEC to $PNEC_{DW}$, to $PNEC_F$, and to $PNEC_{DW+F}$ are considerably less than 1 (Table 8). Only ratios for children are shown in Table 8 since these are higher than the ratios for adults by an amount equal to the difference between child and adult PNECs (see above). The drinking water ratios for children range from 2.1×10^{-5} (for dehydronifedipine) to a maximum of 0.034 (for codeine). For six of the seven compounds not detected in the USGS reconnaissance, PNECs are compared to 1/2 RL. The resulting 1/2 RL/$PNEC_{DW}$ ratios for children range from 3.4×10^{-5} (for sulfathiazole) to a maximum of 3.9×10^{-3} (for digoxigenin) (Table 8). As discussed earlier, a 1/2 RL/$PNEC_{DW}$ ratio is not presented for digoxin.

The maximum MEC to $PNEC_F$ ratios are also markedly less than 1, ranging from 8.9×10^{-7} (for norfloxa-

Table 6
Predicted no effect concentrations (PNEC) for children for three exposure scenarios: drinking water, fish consumption, and combined drinking water/fish consumption

Compound	ADI (μg/kg/day)	$PNEC_{DW}$ (ng/L)	$PNEC_{F}$ (ng/L)	$PNEC_{DW+F}$ (ng/L)
Acetaminophen	340	5.0E + 06	2.4E + 08	4.9E + 06
Albuterol	2.8	4.1E + 04	2.0E + 06	4.0E + 04
Cimetidine	29	4.2E + 05	2.1E + 07	4.1E + 05
Ciprofloxacin	1.6	2.3E + 04	1.1E + 06	2.3E + 04
Codeine	2	2.9E + 04	1.4E + 06	2.9E + 04
Dehydronifedipine	100	1.5E + 06	5.1E + 06	1.1E + 06
Digoxigenin	0.07	1.0E + 03	1.1E + 05	1.0E + 03
Digoxin	0.07	1.0E + 03	8.4E + 04	1.0E + 03
Diltiazem	14	2.0E + 05	9.9E + 06	2.0E + 05
Doxycycline	30	4.4E + 05	2.1E + 07	4.3E + 05
Enalaprilat	70	1.0E + 06	5.0E + 07	1.0E + 06
Erythromycin-H_2O	40	5.8E + 05	2.8E + 07	5.7E + 05
Fluoxetine	2.9	4.2E + 04	2.1E + 06	4.1E + 04
Gemfibrozil	55	8.0E + 05	3.9E + 07	7.9E + 05
Ibuprofen	110	1.6E + 06	7.8E + 07	1.6E + 06
Lincomycin	25	3.7E + 05	1.8E + 07	3.6E + 05
Metformin	62	9.1E + 05	4.4E + 07	8.9E + 05
Norfloxacin	190	2.8E + 06	1.3E + 08	2.7E + 06
Oxytetracycline	30	4.4E + 05	2.1E + 07	4.3E + 05
Paroxetine metabolite	2.9	4.2E + 04	2.1E + 06	4.1E + 04
Ranitidine	11	1.6E + 05	7.8E + 06	1.6E + 05
Sulfame thoxazole	130	1.9E + 06	9.2E + 07	1.9E + 06
Sulfathiazole	50	7.3E + 05	3.6E + 07	7.2E + 05
Tetracycline	30	4.4E + 05	2.1E + 07	4.3E + 05
Trimethoprim	4.2	6.1E + 04	3.0E + 06	6.0E + 04
Warfarin	0.16	2.3E + 03	1.1E + 05	2.3E + 03

cin) to a maximum of 7.0×10^{-4} (for codeine) (Table 8). The ratio of 1/2 RL to $PNEC_F$ for six of the seven APIs (excluding digoxin as discussed earlier) that were not detected range from 7.0×10^{-7} (for sulfathiazole) to a maximum of 6.3×10^{-5} (for paroxetine metabolite) (Table 8).

Because $PNEC_{DW}$ is similar to $PNEC_{DW+F}$ for any given API, the MEC (or 1/2 RL) to $PNEC_{DW}$ or $PNEC_{DW+F}$ ratios are also similar. The maximum MEC to $PNEC_{DW+F}$ ratios range from 2.6×10^{-5} (for dehydronifedipine) to a maximum of 0.035 (for codeine) (Table 8). The ratio of 1/2 RL to $PNEC_{DW+F}$ for six of the seven APIs (excluding digoxin as discussed earlier) that were not detected range from 3.5×10^{-5} (for sulfathiazole) to a maximum of 3.9×10^{-3} (for digoxigenin) (Table 8).

3.6. Comparison of PECs (from PhATE) to PNECs

Review of the ratios of maximum drinking water PECs from P*h*ATE (generated assuming low flow conditions and no depletion) to $PNEC_{DW}$ for children indicates drinking water PECs are at least sixfold lower than $PNEC_{DW}$ for all APIs (Table 8). For children, the $PEC_{DW}/PNEC_{DW}$ ratios range from 2.1×10^{-6} (for oxytetracyline) to a maximum of 0.15 (for ciprofloxacin) (Table 8). $PEC_{SW}/PNEC_F$ ratios are generally lower than the ratios for drinking water because, as discussed above, potential exposure from fish consumption is less than exposure from drinking water for most APIs. For fish consumption, all PECs are at least 150-fold lower than $PNEC_F$ for children. For children, the $PEC_{SW}/PNEC_F$ ratios range from 9.1×10^{-8} (for oxytetracyline) to a maximum of 6.7×10^{-3} (for ciprofloxacin) (Table 8).

For drinking water and fish consumption combined, all surface water PECs are at least threefold lower than $PNEC_{DW+F}$ for all APIs (Table 8). For children, the $PEC_{SW}/PNEC_{DW+F}$ ratios range from 4.5×10^{-6} (for oxytetracycline) to a maximum of 0.33 (for ciprofloxacin) (Table 8). The APIs with the four highest $PEC_{SW}/PNEC_{DW+F}$ ratios are ciprofloxacin (0.33), warfarin (0.11), metformin (0.11), and ranitidine (0.10). These ratios are based on maximum surface water PECs generated with conservative assumptions of low flow and no depletion. By comparison, the maximum $MEC/PNEC_{DW+F}$ ratios for these same four APIs are significantly lower (0.0013, 0.00022, 0.00017, and 0.000064 for ciprofloxacin, warfarin, metformin, and ranitidine, respectively), indicating a greater margin of safety.

4. Discussion

The results of this assessment indicate that the presence of low levels of APIs in surface waters and drinking water pose no appreciable risk to human health. The 26 APIs included in this risk assessment represent a broad range of classes of pharmaceuticals (including analgesics, antidepressants, anticoagulants, antihistaminics, antihypertensives, and several classes of antibiotics) for which surface water concentrations are available for the US from Kolpin et al. (2002) or can be predicted using P*h*ATE (Anderson et al., 2004). A comparison of maximum MECs reported by Kolpin et al. (2002) to PNECs protective of children both drinking water and eating fish from surface waters indicates that the approximate margins of safety for these potential exposures range from factors of 30 to 38,000. A similar comparison of maximum surface water PECs from the P*h*ATE model (generated assuming conservative conditions of low flow and no depletion) to PNECs protective of children for combined drinking water and fish consumption exposure indicates that the approximate margins of safety range from factors of 3 to 220,000. These findings are supported by Mons et al. (2003) who found even larger margins of safety.

The extensive dataset available from Kolpin et al. (2002) has been supplemented by reviewing the results of 39 additional studies worldwide reporting on environmental measurements of these 26 APIs in surface waters. These studies report higher maximum MECs than the USGS for 10 of the 26 APIs included in this assessment

Table 7
Measured concentrations in surface water and predicted concentrations in surface water and drinking water

Compound	Kolpin et al., 2002	Other investigators	Maximum P*h*ATE model PECs at low flow	
	Maximum concentration or 1/2 RL	Maximum concentration	Drinking water	Surface water
Acetaminophen	10,000	1,950[9,13,27,29,33]	220,000	470,000
Albuterol	15[a]	35[2,4,10,13,27,39]	120	250
Cimetidine	580	338[13]	4400	9300
Ciprofloxacin	30	30[4,13]	3600	7600
Codeine	1000	123[13,23]	1100	2400
Dehydronifedipine	30	2.0[13]	1100	2300
Digoxigenin	4.0[a]	ND[13]	6.3	13.0
Digoxin	130[a]	*	6.3	13.0
Diltiazem	49	106[13]	5900	12,000
Doxycycline	50[a]	100[13,15,36,37]	990	2100
Enalaprilat	46	*	30	63
Erythromycin-H_2O	1700	220[13,29,38]	3500	7300
Fluoxetine	12	46[1,2,13,18,19,29]	620	1300
Gemfibrozil	790	1550[5,8,12,13,14,16,19,22,24,25,27,29,33]	8000	17,000
Ibuprofen	1000	2700[3,4,5,8,9,12,13,14,16,17,19,21,22,24,25,26,27,28,29,31,32,33,34,35,39]	63,000	130,000
Lincomycin	730	249[4,13,39]	9.8	21.0
Metformin	150	*	47,000	98,000
Norfloxacin	120	30[13]	74	160
Oxytetracycline	340	1340[4,11,13,15,36,37]	0.92	1.94
Paroxetine metabolite	130[a]	*	540	1100
Ranitidine	10	39[4,13,39]	7800	16,000
Sulfamethoxazole	1900	1020[2,6,7,9,11,13,15,29,30,33,36,37]	8500	18,000
Sulfathiazole	25[a]	80[15]	13.0	28
Tetracycline	110	1000[11,13,15,20,30,36,37]	3100	6500
Trimethoprim	710	200[9,11,13,19,29,33]	1800	3700
Warfarin	0.50[a]	*	120	250

All concentrations in ng/L.
[*] This API has not been analyzed in surface water by other investigators.
[a] Indicates that the API was not detected by Kolpin et al. Value shown is 1/2 the RL.
Note. [1]Boyd et al. (2003); [2]Bratton et al. (2003); [3]Buser et al. (1999); [4]Calamari et al. (2003); [5]Gross et al. (2004); [6]Hartig and Jekel (2001); [7]Hartig et al. (1999); [8]Heberer et al. (2002); [9]Hilton and Thomas (2003); [10]Hirsch et al. (1996); [11]Hirsch et al. (1999); [12]Jux et al. (2002); [13]Kolpin et al. (2004); [14]Farre et al. (2001); [15]Lindsey et al. (2001); [16]Loos et al. (2003); [17]Marchese et al. (2003); [18]McQuillan et al. (2001); [19]Metcalfe et al. (2003); [20]Mulroy (2001); [21]Ollers et al. (2001); [22]Sacher et al. (1998); [23]Snyder et al. (2001); [24]Stan and Heberer (1997); [25]Stumpf et al. (1996); [26]Stumpf et al. (1999); [27]Ternes (1998); [28]Tixier et al. (2002); [29]Vanderford et al. (2003); [30]Watts et al. (1983); [31]Weigel et al. (2002); [32]Weigel et al. (2004a); [33]Weigel et al. (2004b); [34]Weigel et al. (2004c); [35]Winkler et al. (2001); [36]Yang and Carlson (2003); [37]Yang and Carlson (2004a); [38]Yang and Carlson (2004b); [39]Zuccato et al. (2000).

(Table 7). Use of these other maximum MECs in the MEC/PNEC comparisons does not affect the conclusion that a considerable margin of safety exists for each of the ten APIs. The range in the margin of safety for these 10 compounds for combined drinking water and fish consumption exposure changes from approximately 1000–29,000 using USGS maximum MECs to 320–8900 using maximum MECs reported by other researchers.

The finding of no adverse effect to human health from exposure to trace quantities of pharmaceuticals is supported by other results reported in the literature for drinking water and/or surface water. Christensen (1998) evaluated potential health effects for three APIs using the EUSES model to predict worst case concentrations in Denmark and determined that environmental exposure for these substances pose a negligible human risk. Schulman et al. (2002), who reviewed published information on reported concentrations in surface waters of four APIs and compared these to acceptable drinking water intakes, concluded there was no appreciable risk at the reported concentrations. Webb et al. (2003) arrived at a similar conclusion after evaluating human health effects associated with potential drinking water exposure for 64 APIs.

Several of the assumptions used in this evaluation are very conservative (i.e., are more likely to overestimate than underestimate the potential for adverse effects to human health). Some of the more important of these are discussed below.

This assessment compares PNECs to maximum MECs reported by Kolpin et al. (2002) and maximum drinking water and surface water PECs generated by P*h*ATE. Typical exposures are expected to be significantly lower. As discussed above, maximum PECs are 79 times higher than median concentrations. Likewise for the measured data, only eight of 26 APIs sampled

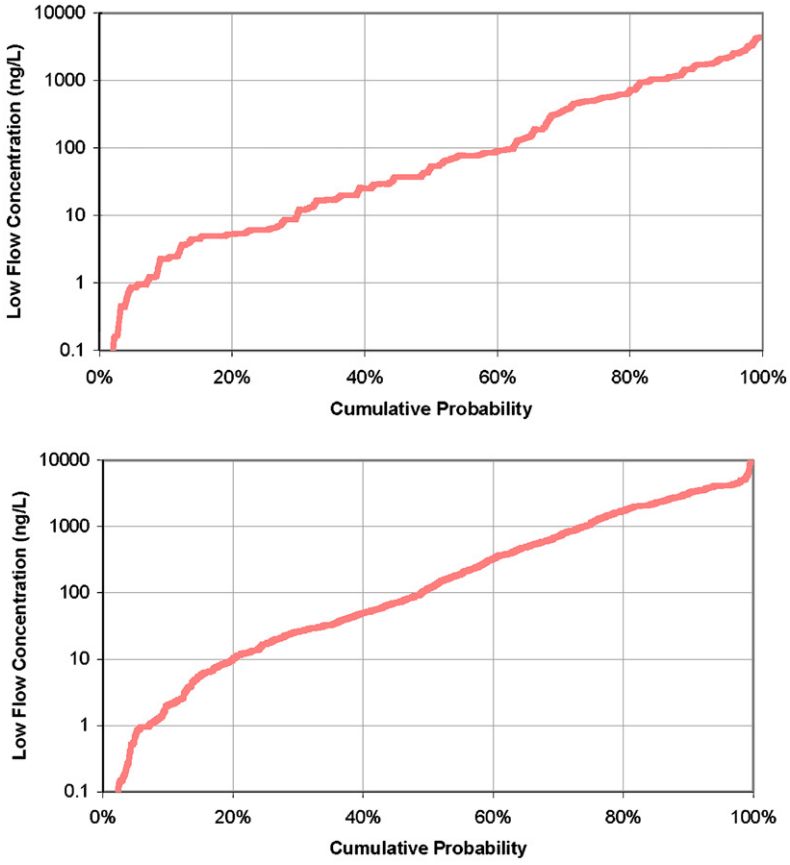

Fig. 1. Example of P*h*ATE output. Upper figure shows cimetidine PEC for low flow (7Q10) conditions at drinking water intakes as a cumulative plot. Lower figure shows cimetidine PEC in all reaches of the modeled watersheds.

for by Kolpin et al. (2002) were detected in greater than 10% of stream segments and seven were not detected at all (Table 7). For six of these seven APIs (excluding digoxin as discussed earlier), 1/2 RL was used as a conservative substitute for the measurement. As shown by Anderson et al. (2004), predicted concentrations for these APIs may be orders of magnitude less than the RL.

Using the measured surface water concentration as a surrogate for drinking water concentration may markedly overestimate concentrations in drinking water for two reasons. First, the processes for purification of drinking water may include carbon adsorption, ozonation, reverse osmosis, etc. which can dramatically decrease the concentration of organic compounds in water (Andreozzi et al., 2002; Huber et al., 2003; Ternes et al., 2002). Second, the risk assessments presented here for the combined drinking water and fish consumption exposure assume that surface waters from all river reaches included in P*h*ATE are used as a source of drinking water. This is unlikely to be true for most reaches; less than 10% of reaches included in P*h*ATE have public drinking water supplies on them. This assumption overestimates PEC to PNEC ratios by about twofold (compare maximum drinking water to surface water PECs in Table 7 and PEC distributions shown in Fig. 1).

The PECs generated by P*h*ATE were calculated using conservative assumptions of low river flow (7Q10) and no depletion mechanisms (i.e., no human metabolism, no removal from POTW or drinking water treatment, and no instream decay). Incorporation of more realistic human metabolic and environmental fate data can result in substantially lower concentrations. For example, the maximum PEC presented here for diltiazem is 12,000 ng/L, as compared to a maximum PEC of approximately 100 ng/L calculated using realistic estimates of metabolism, POTW removal, and instream decay (Anderson et al., 2004).

This assessment also considers fish consumption as a potential source of exposure, again using the maximum reported concentration. However, some of the stream segments for which PECs could be predicted likely have too little flow to support a significant fishery for the general population. Furthermore, the evaluation assumes that people are drinking water and eating fish from the stream segments with the highest PECs. Despite these conservative assumptions, the combined PECs for drinking water and fish consumption result in PEC/PNEC

Table 8
Comparison of measured or predicted concentration to PNEC for children for three exposure scenarios: drinking water, fish consumption, and combined drinking water/fish consumption

Compound	Drinking water ratio		Fish consumption ratio		Combined ratio	
	Kolpin et al.	P*h*ATE model	Kolpin et al.	P*h*ATE model	Kolpin et al.	P*h*ATE model
Acetaminophen	2.0E−03	4.4E−02	4.1E−05	1.9E−03	2.1E−03	9.7E−02
Albuterol	3.5E−04[a]	2.9E−03	7.3E−06[a]	1.3E−04	3.6E−04[a]	6.2E−03
Cimetidine	1.4E−03	1.0E−02	2.8E−05	4.5E−04	1.4E−03	2.2E−02
Ciprofloxacin	1.3E−03	1.5E−01	2.6E−05	6.7E−03	1.3E−03	3.3E−01
Codeine	3.4E−02	3.8E−02	7.0E−04	1.7E−03	3.5E−02	8.4E−02
Dehydronifedipine	2.1E−05	7.5E−04	5.8E−06	4.5E−04	2.6E−05	2.0E−03
Digoxigenin	3.9E−03[a]	6.1E−03	3.6E−05[a]	1.2E−04	3.9E−03[a]	1.3E−02
Digoxin	[b]	6.1E−03	[b]	1.5E−04	[b]	1.3E−02
Diltiazem	2.4E−04	2.9E−02	4.9E−06	1.2E−03	2.4E−04	6.0E−02
Doxycycline	1.1E−04[a]	2.3E−03	2.3E−06[a]	9.9E−05	1.2E−04[a]	4.9E−03
Enalaprilat	4.5E−05	2.9E−05	9.3E−07	1.3E−06	4.6E−05	6.3E−05
Erythromycin-H_2O	2.9E−03	6.0E−03	6.0E−05	2.6E−04	3.0E−03	1.3E−02
Fluoxetine	2.8E−04	1.5E−02	5.8E−06	6.3E−04	2.9E−04	3.1E−02
Gemfibrozil	9.8E−04	1.0E−02	2.0E−05	4.4E−04	1.0E−03	2.2E−02
Ibuprofen	6.2E−04	3.9E−02	1.3E−05	1.7E−03	6.4E−04	8.3E−02
Lincomycin	2.0E−03	2.7E−05	4.1E−05	1.2E−06	2.0E−03	5.9E−05
Metformin	1.7E−04	5.2E−02	3.4E−06	2.2E−03	1.7E−04	1.1E−01
Norfloxacin	4.3E−05	2.7E−05	8.9E−07	1.2E−06	4.4E−05	5.9E−05
Oxytetracycline	7.8E−04	2.1E−06	1.6E−05	9.1E−08	7.9E−04	4.5E−06
Paroxetine metabolite	3.1E−03[a]	1.3E−02	6.3E−05[a]	5.3E−04	3.1E−03[a]	2.7E−02
Ranitidine	6.2E−05	4.9E−02	1.3E−06	2.0E−03	6.4E−05	1.0E−01
Sulfamethoxazole	1.0E−03	4.5E−03	2.1E−05	1.9E−04	1.0E−03	9.7E−03
Sulfathiazole	3.4E−05[a]	1.8E−05	7.0E−07[a]	7.9E−07	3.5E−05[a]	3.9E−05
Tetracycline	2.5E−04	7.1E−03	5.2E−06	3.1E−04	2.6E−04	1.5E−02
Trimethoprim	1.2E−02	2.9E−02	2.4E−04	1.2E−03	1.2E−02	6.2E−02
Warfarin	2.1E−04[a]	5.1E−02	4.4E−06[a]	2.2E−03	2.2E−04[a]	1.1E−01

[a] Indicates that the API was not detected by Kolpin et al. Value shown is calculated using 1/2 of the RL.
[b] RL:PNEC ratios are not calculated for digoxin -see text for explanation.

ratios well below 1. Thus, the combined fish and drinking water PNECs lead to a very conservative evaluation that probably does not apply to most stream segments and to most people living in the watersheds evaluated by P*h*ATE.

PECs generated by P*h*ATE are based on the average per capita human use of an API in the US (Anderson et al., 2004). This assumption would cause P*h*ATE to underestimate exposure in areas where per capita use is higher than the national average. However, the potential for regional differences in per capita use does not necessarily mean that the maximum PECs used in this assessment underestimate the maximum exposure within the watersheds included in P*h*ATE. This would only be the case if per capita use is higher than the national average within the same geographic areas where the highest model PECs occur. Furthermore, considering the large margins of safety determined by this risk assessment, differences in regional per capita use are not expected to affect the conclusions presented here. For example, according to U.S. Census (2004) data, 12.4% of the total US population is over the age of 65. The state and county with the highest percentage of elderly in the US is Florida (17.6% elderly or 1.4 times the national average) and Charlotte County, FL (34.7% elderly or 2.8 times the national average), respectively (U.S. Census, 2004). If the per capita use of drugs primarily used in elderly patients, e.g., warfarin, digoxin, were to be higher in such geographic areas, this would alter the PEC_{SW}/$PNEC_{DW+F}$ ratios by, at most, a factor of 2.8. Warfarin is an anticoagulant used to reduce the risk of heart attack and stroke, conditions associated with elderly populations. If the per capita use of warfarin were 2.8 times the national average in the same geographic area where the maximum PEC occurs, the PEC_{SW}/$PNEC_{DW+F}$ ratio would increase from 0.11 to 0.31. It is also noted that this drug is excreted primarily as inactive metabolites which would result in an even lower ratio.

5. Conclusions

Two intrinsic characteristics of most pharmaceuticals explain why exposures to humans are below the predicted no effect concentrations. First, safe exposure levels for APIs are normally directly related to therapeutic dose. Second, because many APIs or their metabolites are ionic compounds, bioconcentration in fish tissue is not generally an important exposure pathway for human consumption (Cunningham, 2004).

The preferred safety profile for pharmaceuticals is that the therapeutic effect is the first effect observed (i.e., at the lowest dose). The very complete set of toxicology data and information from human clinical trials allow great certainty in determining the point of departure for calculating the ADI. As Webb et al. (2003) noted, the most sensitive therapeutic dose will normally be the point of departure for the ADI calculation. This was true for 12 of the APIs evaluated here that exert their activity via specific mechanisms in humans (i.e., receptor mediated). When the ADI is based on the therapeutic dose, there is also a positive and direct correlation between the ADI and the total amount of the API entering the environment. For a given use rate by the population, only low production volumes are needed for potent pharmaceuticals. For the same population use rate, a high therapeutic dose requires more production. So, the total amount of an API entering the environment is generally inversely correlated to its potency.

Nineteen of the 26 APIs evaluated here are among the top 200 drugs (by number of prescriptions dispensed) in 2000 (as found on www.rxlist.com), demonstrating that even with high use rate, exposures would not be anticipated to exceed the ADI. This relationship contrasts to industrial chemicals for which a correlation does not necessarily exist between the ADI defining the safe dose to humans and use rate, production volume, or the amount entering the environment.

Human pharmaceuticals enter the environment primarily as a result of excretion following therapeutic use. For receptor mediated APIs, levels entering the environment will always be diluted, and probably metabolized, well below levels that could result in any physiological effects from drinking water. Another exposure route for humans is from the consumption of fish that potentially accumulate APIs. Pharmaceuticals need to be fairly soluble in water to be readily orally absorbed by humans, and consequently are often ionic compounds (Benet et al., 1996). Ionic compounds do not significantly bioconcentrate in fish, nor do compounds that are quickly metabolized and excreted by fish. As shown in Table 8, the highest dose of a pharmaceutical from fish consumption, in conjunction with the highest possible dose from drinking water, still does not result in a total dose that is higher than the ADI for any of the APIs evaluated here.

Characteristics of some human-use pharmaceuticals could trigger a more thorough evaluation of their risk to human health. APIs that have a non-human target effect (antibiotics), that have a therapeutic dose at or above a toxic dose (e.g., cytotoxics), that have a high potential for allergic responses, or that have a very high bioaccumulation potential may need to be individually evaluated. Also, APIs that are developed for just one gender or age class (e.g., estrogens) may also require individual evaluation, since the therapeutic dose for the target population may not be the point of departure to calculate the ADI for the non-targeted population.

Even though these exceptional characteristics may lead to individual evaluations, it is likely that realistic assessments will conclude that exposure to trace concentrations of these types of pharmaceuticals pose no appreciable risk to human health. Several antibiotics were evaluated in this review, and while the therapeutic doses were not the point of departure for calculating the ADI, substantial margins of safety exist (Table 8). Christensen (1998) evaluated chemicals with exceptional characteristics that would lead to thorough individual evaluations. Christensen (1998) found that environmental residues of 17 α-ethinylestradiol, a potent estrogen agonist that can bioconcentrate in fish, present a negligible risk to humans. Christensen (1998) also found that environmental residues of the antibiotic, phenoxymethylpenicillin (an allergen), and the antineoplastic, cyclophosphamide (therapeutic dose above a toxic dose), pose a negligible risk to humans. Even when evaluated as a genotoxic carcinogen, cyclophosphamide residues were so small that they were considered to be negligible. Schulman et al. (2002); Webb et al. (2003); and Christensen (1998) all concluded that exposure to environmental residues of pharmaceuticals pose no appreciable risk to humans.

Recent improvements in analytical chemistry allow detection of trace levels of chemicals in surface waters. Evaluations presented here and by other authors support the conclusion that trace concentrations of pharmaceuticals in surface water and drinking water present no appreciable risk to human health. Individual evaluations are required for certain classes of pharmaceuticals (e.g., estrogens and cytotoxics). Potential interactions among trace levels of individual pharmaceuticals in surface waters are just as difficult to evaluate as interactions among other trace chemicals in surface water and will require further research and risk assessment techniques to quantify any potential risk to human health.

Acknowledgments

The authors dedicate this paper to the memory of our colleague Bradley W. Schwab, whose contributions to this paper and to the development of the P*h*ATE model are gratefully acknowledged. The following individuals contributed data and expertise used to develop ADIs presented here: Fred Joachim, Abbott Laboratories; William Galdenzi and Gary Toczylowski, Bayer Pharma; Michael Olson, GlaxoSmithKline; Annette Bucca-Janacek, Hoffmann-La Roche Inc.; Mark Yuschak, Johnson & Johnson; David Dolan, Bruce Naumann, Edward Sargent, Merck & Co., Inc.; and Geoffrey Huse, Pfizer Inc. Identification of published

articles that report surface water concentrations for the APIs evaluated here was greatly facilitated by a database maintained by Richard Williams, Pfizer Inc. The Pharmaceutical Research and Manufacturers of America provided financial support for the preparation of the manuscript.

References

Agency for Toxic Substances and Disease Registry (ATSDR), 1996. Minimal risk levels for priority substances and guidance for derivation. Federal Register 61, 25873–25881.

Anderson, P.D., D'Aco, V.J., Shanahan, P., Chapra, S.C., Buzby, M.E., Cunningham, V.L., DuPlessie, B.M., Hayes, E.P., Mastrocco, F.J., Parke, N.J., Rader, J.C., Samuelian, J.H., Schwab, B.W., 2004. Screening analysis of human pharmaceutical compounds in U.S. surface waters. Environ. Sci. Technol. 38, 838–849.

Andreozzi, R., Marotta, R., Pinto, G., Pollio, A., 2002. Carbamazepine in water: persistence in the environment, ozonation treatment and preliminary assessment on algal toxicity. Water Res. 36, 2867–2877.

American Society of Health-System Pharmacists (ASHP), 2003. AHFS Drug Information.

Avdeef, A., Barrett, D.A., Shaw, P.N., Knaggs, R.D., Davis, S.S., 1996. Octanol-chloroform- and propylene glycol dipelargonat-water partitioning of morphine-6-glucuronide and other related opiates. J. Med. Chem. 39, 4377–4381.

Avdeef, A., 1993. pH-metric log *P*. II: refinement of partition coefficients and ionization constants of multiprotic substances. J. Pharm. Sci. 82 (2), 183–190.

Benet, L.Z., Kroetz, D.L., Sheiner, L.B., 1996. Pharmacokinetics: the dynamics of drug absorption, distribution and elimination. In: Hardman, J.G., Limbird, L.E., Molinoff, P.B., Ruddon, R.W., Gilman, A.G. (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics, ninth ed. McGraw-Hill, Elmsford, NY, p. 5.

Bern, M., Bierbaum, B., Wetzner, S., 1997. Fixed very low dose vs. variable dose warfarin for deep vein thrombosis (DVT) prophylaxis. Thromb. and Haemost. 0 (Suppl.), 330PS.

Boyd, G.R., Reemtsma, H., Grimm, D.A., Mitra S, 2003. Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. Sci. Total Environ. 311 (1–3), 135–149.

Bratton, K.D., Lillquist, A.S., Williams, T.D., Lunte, C.E., 2003. The determination and quantification of human pharmaceuticals in aqueous environmental samples. ACS Symp. Ser. 850, 188–206.

Buser, H.R., Poiger, T., Muller, M.D., 1999. Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. Environ. Sci. Technol. 33, 2529–2535.

Calamari, D., Zuccato, E., Castiglioni, S., Bagnati, R., Fanelli, R., 2003. Strategic survey of therapeutic drugs in the rivers Po and Lambro in northern Italy. Environ. Sci. Technol. 37 (7), 1241–1248.

Christensen, F.M., 1998. Pharmaceuticals in the environment—a human risk?. Regul. Toxicol. Pharmacol. 28, 212–221.

Cunningham, V.L., Constable, D.J.C., Hannah, R.E., 2004. Environmental risk assessment of paroxetine. Environ. Sci. Technol. 38, 3351–3359.

Cunningham, V.L., 2004. Special characteristics of pharmaceuticals related to environmental fate. In: Kuemmerer, K. (Ed.), Pharmaceuticals in the environment: sources, fate, effects and risks, second ed. Springer, Berlin, pp. 13–23 (Chapter 2).

Dourson, M.L., Felter, S.P., Robinson, D., 1996. Evolution of science-based uncertainty factors in non-cancer risk assessment. Regul. Toxicol. Pharmacol. 24, 108–120.

Eli Lilly and Company, 2000. Fluoxetine Hydrochloride Capsules and Tablets. Material Safety Data Sheet.

European Agency for the Evaluation of Medicinal Products (EMEA), 1997. The European agency for the evaluation of medicinal products veterinary medicines evaluation unit. Maximum Residue Limits. Trimethoprim. Summary report (2). EMEA/MRL/255/97-Final.

European Agency for the Evaluation of Medicinal Products (EMEA), 1998. Maximum Residue Limit. Enrofloxacin. Summary report (2). EMEA/MRL/388/98-Final.

Farre, M., Ferrer, I., Ginebreda, A., Figueras, M., Olivella, L., Tirapu, L., Vilanova, M., Barcelo, D., 2001. Determination of drugs in surface water and wastewater samples by liquid chromatography-mass spectrometry: methods and preliminary results including toxicity studies with *Vibrio fischeri*. J. Chromatogr. A 938 (1–2), 187–197.

Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. 2001. tenth ed., J.G. Hardman, L.E. Limbird (Eds.), McGraw-Hill, Elmsford.

Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. 2005. McGraw-Hill, Elmsford, NY, online version accessed 19 March 2005.

Gross, B., Montgomery-Brown, J., Naumann, A., Reinhard, M., 2004. Occurrence and fate of pharmaceuticals and alkylphenol ethoxylate metabolites in an effluent-dominated river and wetland. Environ. Toxicol. Chem. 23 (9), 2074–2083.

GSK, 2002. Tagamet, Prescribing Information, TG:L93, Glaxo-SmithKline, Research Triangle Park, NC, June 2002.

Halling-Sorensen, B., Nielsen, S.N., Lanzky, P.F., Ingerslev, F., Lutzheft, H.C.H., Jorgensen, S.E., 1998. Occurrence, fate and effects of pharmaceutical substances in the environment—a review. Chemosphere 36, 357–393.

Hansch, C., Leo, A., Hoekman, D., 1995. Exploring QSAR. Hydrophobic, electronic, and steric constants. ACS Professional Reference Book. American Chemical Society, Washington, DC.

Hartig, C., Jekel, M., 2001. Occurrence of bacteriostatic sulfonamide drugs in surface waters and their behavior in bank filtration. NGWA, 2nd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, October 9–11, 2001.

Hartig, C., Storm, T., Jekel, M., 1999. Detection and identification of sulphonamide drugs in municipal waste water by liquid chromatography coupled with electrospray ionisation tandem mass spectrometry. J. Chromatogr. A 854, 163–173.

Heberer, T., 2002. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol. Lett. 131, 5–17.

Heberer, Th., Reddersen, K., Mechlinski, A., 2002. From municipal sewage to drinking water: fate and removal of pharmaceutical residues in the aquatic environment in urban areas. Water Sci. Technol. 46 (3), 81–88.

Hilton, M.J., Thomas, K.V., 2003. Determination of selected human pharmaceutical compounds in effluent and surface water samples by high-performance liquid chromatography-electrospray tandem mass spectrometry. J. Chromatogr. A (Netherlands) 1015 (1–2), 129–141.

Hirsch, R., Ternes, T.A., Haberer, K., Kratz, K.L., 1996. Determination of beta-blockers and B2-sympatomimetics in the aquatic environment. Vom Wasser 87, 263–274.

Hirsch, R., Ternes, T., Haberer, K., Kratz, K.L., 1999. Occurrence of antibiotics in the aquatic environment. Sci. Total Environ. 225, 109–118.

Hoechst, 1999. Cardizem® (diltiazem HCl), Pescribing Information, Hoechst Marion Roussel, Kansas City, MO, May 1999.

Hoffman, B.F., Bigger, J.T., 1990. Digitalis and allied cardiac glycosides. In: Gilman, A.G., Rall, T., Nies, A., Taylor, P. (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics, eighth ed., p. 814.

Huber, M., Canonica, S., Park, G-Y., Von Gunten, U., 2003. Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. Environ. Sci. Technol. 37, 1016–1024.

Hazardous Substances Data Bank (HSDB), 2005. National Library of Medicine, http://toxnet.nlm.nih.gov/, accessed 31 March 2005.

IMS Health Inc., 2003. National Sales Perspectives™, January 2003.

International Programme on Chemical Safety (IPCS), 1994. Assessing human health risk of chemicals: the derivation of guidance values for health-based exposure limits. Environmental Health Criteria No. 170, Geneva.

International Programme on Chemical Safety (IPCS), 2001. Guidance document for the use of data in development of chemical-specific adjustment factors (CSAF) for interspecies differences and human variability in dose/concentration response assessment. WHO/PCS/01.4.

Joint FAO/WHO Expert Committee on Food Additives (JECFA), 1994. Toxicological evaluation of certain veterinary drug residues in food. Sulfadimidine. WHO Food Additives Series, No. 33. World Health Organization, Geneva.

Joint FAO/WHO Expert Committee on Food Additives (JECFA), 1998. Toxicological evaluation of certain veterinary drug residues in food. Tetracyclines: oxytetracycline, chlortetracycline, and tetracycline (addendum). WHO Food Additive Series 41. World Health Organization, Geneva.

Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2000. Toxicological evaluation of certain veterinary drug residues in food. Lincomycin. WHO Food Additive Series 45. World Health Organization, Geneva.

Jux, U., Baginski, R.M., Arnold, H.G., Kronke, M., Seng, P.N., 2002. Detection of pharmaceutical contaminations of river, pond, and tap water from Cologne (Germany) and surroundings. Int. J. Hyg. Environ. Health 205, 393–398.

Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance. Environ. Sci. Technol. 36, 1202–1211 [Including correspondence/rebuttal, 2002. Environ. Sci. Technol. 36, 4007–4008].

Kolpin, D.W., Skopec, M., Meyer, M.T., Furlong, E.T., Zaugg, S.D., 2004. Urban contribution of pharmaceuticals and other organic wastewater contaminants to streams during differing flow conditions. Sci. Total Environ. 328 (1–3), 119–130.

Lehman, A.J., Fitzhugh, O.G., 1954. 100-fold margin of safety. Assoc. Food Drug Off. U.S.Q. Bull. 18, 33–35.

Lindsey, M.E., Meyer, M., Thurman, E.M., 2001. Analysis of trace levels of sulfonamide and tetracycline antimicrobials in groundwater and surface water using solid-phase extraction and liquid chromatography/mass spectrometry. Anal. Chem. 73 (19), 4640–4646.

Loos, R., Hanke, G., Eisenreich, S.J., 2003. Multi-component analysis of polar water pollutants using sequential solid-phase extraction followed by LC-ESI-MS. J. Environ. Monit. (United Kingdom) 5 (3), 384–394.

Martindale, 2005. Cimetidine, in Martindale—the complete drug reference—monographs, 1982–2005. The Pharmaceutical Press, accessed 30 March 2005.

McClung, M.R., Geusens, P., Miller, P.D., Zippel, H., Bensen, W.G., Roux, C., Adami, S., Fogelman, I., Diamond, T., Eastell, R., Meunier, P.J., Reginster, J., for The Hip Intervention Program Study Group, 2001. Effect of risedronate on the risk of hip fracture in elderly women. New Engl. J. Med. 344, 333–340.

Merck, 2004. NOROXIN® (norfloxacin, MSD), International Physician Circular, IPC-NRX-T-042004, Merck & Co., Whitehouse Station, NJ, 12 April 2004.

Merck 2005. RENITEC®, Oral Tablet (enalapril maleate, MSD), Injection (enalaprilat, MSD), International Physician Circular, IPC-RNT-MF-032005, Merck & Co., Whitehouse Station, NJ, 29 March 2005.

Meylan, W.M., Howard, P.H., Boethling, R.S., Aronson, D., Printup, H., Gouchie, S., 1999. Improved method for estimating bioconcentration/bioaccumulation factor from octanol/water partition coefficient. Environ. Toxicol. Chem. 18, 664–672.

Marchese, S., Perret, D., Gentili, A., Curini, R., Pastori, F., 2003. Determination of non-steroidal anti-inflammatory drugs in surface water and wastewater by liquid chromatography-tandem mass spectrometry. Chromatographia 58 (5–6), 263–269.

McFarland, J.W., et al., 1997. Quantitative structure-activity relationships among macrolide antibacterial agents: in vitro and in vivo potency against *Pasteurella multocida*. J. Med. Chem. 40, 1340–1346.

McQuillan, D., Parker, J., Chapman, T.H., Sherrell, K., Mills, D., 2001. Drug residues in ambient water: initial surveillance in New Mexico, USA. NGWA, 2nd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, October 9–11, 2001.

Metcalfe, C.D., Miao, X.S., Koenig, B.G., Struger, J., 2003. Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada. Environ. Toxicol. Chem. 22 (12), 2881–2889.

Mons, M.N., Hoogenboom, A.C., Noij, T.H.M., 2003. Pharmaceuticals and drinking water supply in the Netherlands. BTO 2003.040, Kiwa N.V. Water Research. Nieuwegein, The Netherlands.

Mulroy, A., 2001. When the cure is the problem: antibiotic contamination of surface water and groundwater may be promoting the development of drug resistant pathogens. Water Environ. Technol. 13 (5), 31–36.

Naumann, B.D., Weideman, P.A., 1995. Scientific basis for uncertainty factors used to establish occupational exposure limits for pharmaceutical active ingredients. Hum. Ecol. Risk Assess. 1, 590–613.

Neer, R.M., Arnaud, C.D., Zanchetta, J.R., Prince, R., Gaich, G.A., Reginster, J.Y., Hodsman, A.B., Eriksen, E.I., Ish-Shalom, S., Genant, H.K., Wang, O., Mitlak, B.H., 2001. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. New Engl. J. Med. 344, 1434–1441.

Ollers, S., Singer, H.P., Fassler, P., Muller, S.R., 2001. Simultaneous quantification of neutral and acidic pharmaceuticals and pesticides at the low-ng/L level in surface and waste water. J. Chromatogr. A 911, 225–234.

Physicians' Desk Reference (PDR), 2005a. Main Edition. Published by Thompson Healthcare, Montvale, NJ, online version accessed 29 March 2005.

Physicians' Desk Reference (PDR), 2005b. Main Edition. Published by Thompson Healthcare, Montvale, NJ, online version accessed 31 March 2005.

Physicians' Desk Reference (PDR), 2005c. Main Edition. Published by Thompson Healthcare, Montvale, NJ, online version accessed 06 April 2005.

Pfizer, 2003. LOPID® (Gemfibrozil, USP). Tablets Package Insert, Parke-Davis, Division of Pfizer Inc., NY, October 2003.

Qureshi, F., Pestian, J., Davis, P., Zaritsky, A., 1998. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. New Engl. J. Med. 339, 1030–1035.

Renwick, A.G., 1993. Data-derived safety factors for the evaluation of food additives and environmental contaminants. Food Addit. Contam. 10, 275–305.

Roth, H.J., Fenner, H., 1994. Struktur-Bioreaktivitat-Wirkungsbezogeneneigenschaften Eigenschaften, second ed. Georg Thieme Verlag, Stuttgart 65–68.

Sangster, J., 1994. LOGKOW Databank. A databank of evaluated octanol-water partition coefficients (Log *P*) on microcomputer diskette. Sangster Research Laboratories, Montreal, Quebec, Canada.

Sacher, F., Lochow, E., Bethmann, D., Brauch, H.-J., 1998. Occurrence of drugs in surface waters. Vom Wasser 90, 233–243.

Schulman, L.J., Sargent, E.V., Naumann, B.D., Faria, E.C., Dolan, D.G., Wargo, J.P., 2002. A human health risk assessment of pharmaceuticals in the aquatic environment. Hum. Ecol. Risk Assess. 8, 657–680.

Silverman, K.C., Naumann, B.D., Holder, D.J., Dixit, R., Faria, E.C., Sargent, E.V., Gallo, M.A., 1999. Establishing data-derived adjustment factors from published pharmaceutical clinical trial data. Hum. Ecol. Risk Assess. 5, 1059–1089.

Snyder, S.A., Kelly, K.L., Grange, A.H., Sovocool, G.W., Snyder, E.M., Giesy, J.P., 2001. Pharmaceuticals and Personal Care Products in the Waters of Lake Mead, Nevada. Pharmaceuticals and Personal Care Products in the Environment, ACS Symposium Series 791, Oxford University Press, 116–141.

SOLVD Investigators, 1991. Effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. New Engl. J. Med. 325, 293–302.

Stan, H.J., Heberer, T., 1997. Pharmaceuticals in the aquatic environment. Analusis Mag. 25 (7), M20–M23.

Stumpf, M., Ternes, T.A., Haberer, K., Seel, P., Baumann, W., 1996. Determination of drugs in sewage treatment plants and river water. Vom Wasser 86, 291–303.

Stumpf, M., Ternes, T.A., Wilken, R.D., Rodrigues, S.V., Baumann, W., 1999. Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. Sci. Total Environ. 225, 135–141.

Swarm, R.L., Roberts, G.K.S., Levy, A.C., Hines, L.R., 1973. Observations on the thyroid gland in rats following the administration of sulfamethoxazole and trimethoprim. Appl. Pharmacol. 24, 351–363.

Takacs-Novak, K., Jozan, M., Hermecz, I., Szasz, G., 1992. Lipophilicity antibacterial fluoroquinolones. Int. J. Pharm. 79 (2–3), 89–96.

Ternes, T.A., 1998. Occurrence of drugs in German sewage treatment plants and rivers. Water Res. 32, 3245–3260.

Ternes, T., 2001. Pharmaceuticals and metabolites as contaminants of the aquatic environment. In: Daughton, C.G., Jones-Lepp, T.L. (Eds.), Pharmaceutical and Personal Care Products in the Environment: Scientific and Regulatory. American Chemical Society, Washington, DC, pp. 39–54.

Ternes, T., Meisenheimer, M., McDowell, D., Sacher, F., Brauch, H.-J., Haist-Gulde, B., Preuss, G., Wilme, U., Zulei-Seibert, N., 2002. Removal of pharmaceuticals during drinking water treatment. Environ. Sci. Technol. 36, 3855–3863.

Tixier, C., Singer, H., Oellers, S., Muller, S., 2002. Occurrence and fate of carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen, and naproxen in surface waters. Environ. Sci. Technol. 37 (6), 1061–1068.

U.S. Census Bureau, 2004. Population and Ranking Tables of the Older Population for the United States, States, Puerto Rico, Places of 100,000 or More Population, and Counties (PHC–T–13), http://www.census.gov/population/www/cen2000/phc-t13.html, accessed 02 May 2004.

U.S. EPA, 1989. Risk Assessment Guidance for Superfund, vol. I. Human Health Evaluation Manual. EPA/540/1-89/002, December 1989.

U.S. EPA, 2000. Methodology for deriving ambient water quality criteria for the protection of human health. Office of Water, Office of Science and Technology. EPA-822-B-00-004, October 2000.

U.S. EPA, 2002. A review of the reference dose and reference concentration processes. EPA/630/P-02/002F, p. 192.

U.S. FDA, 1997. 21CFR Part 25.20-31. Actions requiring preparation of an environmental assessment and categorical exclusions.

U.S. FDA, 1998. Guidance for industry: environmental assessment of human drug and biologics applications. Revision 1. p. 42 (www.fda.gov/cder/guidance/1730fnl.pdf).

U.S. FDA, 1999. Benefit vs. Risk: how CDER approves new drugs. In: From test tube to patient: improving health through human drugs. U.S. Food and Drug Administration Center for Drug Evaluation and Research Special Report. pp. 33–40 (www.fda.gov/cder/about/whatwedo/testtube-full.pdf).

Vanderford, B.J., Pearson, R.A., Rexing, D.J., Snyder, S.A., 2003. Analysis of endocrine disruptors, pharmaceuticals, and personal care products in water using liquid chromatography/tandem mass spectrometry. Anal. Chem. 75 (22), 6265–6274.

Watts, C.D., Crathorne, B., Fielding, M., Steel, C.P., 1983. Identification of non-volatile organics in water using field desorption mass spectrometry and high performance liquid chromatography. Presented at the 3rd European Symposium on Organic Micropollutants in water, Oslo, Norway, September 19–21. In: Angeletti, G., Bjørseth, A. (Eds.), Analysis of Organic Micropollutants in Water. DD Reidel Publishing Co., Dordrecht. pp. 120–131.

Webb, S., Ternes, T., Gibert, M., Olejniczak, K., 2003. Indirect exposure to pharmaceuticals via drinking water. Toxicol. Lett. 142, 157–167.

Weigel, S., Kuhlmann, J., Huhnerfuss, H., 2002. Drugs and personal care products as ubiquitous pollutants: occurrence and distribution of clofibric acid, caffeine and DEET in the North Sea. Sci. Total Environ. 295 (1–3), 131–141.

Weigel, S., Berger, U., Jensen, E.;, Kallenborn, R., Thoresen, H., Huhnerfuss, H., 2004a. Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromso/Norway with emphasis on ibuprofen and its metabolites. Chemosphere 56 (6), 583–592.

Weigel, S., Kallenborn, R., Huehnerfuss, H., 2004b. Simultaneous solid-phase extraction of acidic, neutral and basic pharmaceuticals from aqueous samples at ambient (neutral) pH and their determination by gas chromatography-mass spectrometry. J. Chromatogr. A 1023 (2), 183–195.

Weigel, S., Aulinger, A., Brockmeyer, R., Harms, H., Loffler, J., Reincke, H., Schmidt, R., Stachel, B., Von Tumpling, W., Wanke, A., 2004c. Pharmaceuticals in the river Elbe and its tributaries. Chemosphere 57 (2), 107–126.

Williams, R.T., 2005. Human health pharmaceuticals in the environment: An introduction. In: Williams, R.T. (Ed.), Science for Assessing the Impacts of Human Pharmaceuticals on Aquatic Ecosystems. Society of Environmental Toxicology and Chemistry (SETAC), Pensacola, FL, forthcoming.

Winkler, M., Lawrence, J.R., Neu, T.R., 2001. Selective degradation of ibuprofen and clofibric acid in two model river biofilm systems. Water Res. 35 (13), 3197–3205.

Yang, S., Carlson, K., 2003. Evolution of antibiotic occurrence in a river through pristine, urban and agricultural landscapes. Water Res. (United Kingdom) 37 (19), 4645–4656.

Yang, S., Carlson, K., 2004a. Routine monitoring of antibiotics in water and wastewater with a radioimmunoassay technique. Water Res. 38 (14–15), 3155–3166.

Yang, S., Carlson, K., 2004b. Solid-phase extraction-high-performance liquid chromatography-ion trap mass spectrometry for analysis of trace concentrations of macrolide antibiotics in natural and waste water matrices. J. Chromatogr. A 1038 (1–2), 141–155.

Yu, H.C.M., Chan, T.Y.K., Critchley, J.A., Woo, K.S., 1996. Factors determining the maintenance dose of warfarin in Chinese patients. Q. J. Med. 89, 127–135.

Zuccato, E., Calamari, D., Natangelo, M., Fanelli, R., 2000. Presence of therapeutic drugs in the environment. Lancet 355, 1789–1790.