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Occurrence and Environmental Behavior of the Chiral Pharmaceutical Drug Ibuprofen in Surface Waters and in Wastewater

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Pharmaceutical compounds can reach detectable concentrations in rivers and lakes if production and use are sufficiently large and the compounds show some mobility and persistence in the aquatic environment. In this study, we report on the occurrence and on the enantiomer composition of the chiral pharmaceutical drug ibuprofen (IB) in surface waters and in samples from wastewater treatment plants (WWTPs). Enantioselective gas chromatography and detection by mass spectrometry/mass spectrometry was used for analysis. IB was present in influents of WWTPs at concentrations of up to 3 μg/L with a high enantiomeric excess of the pharmacologically active *S* enantiomer ($S \gg R$), as from human urinary excretion. The principal human urinary metabolites of IB, hydroxy-IB and carboxy-IB, were observed in WWTP influents at even higher concentrations. In contrast to other pharmaceutical compounds such as clofibric acid and diclofenac, IB and its metabolites are then efficiently degraded (>95%) during treatment in WWTPs. Laboratory incubation experiments confirmed this rapid degradation. In rivers and lakes, IB was detected at concentrations of up to 8 ng/L, generally with some excess of the *S* enantiomer; the IB metabolites were not detected (<1 ng/L). Incubation of lake water fortified with (*rac*)-IB indicated a faster dissipation of the *S* enantiomer, thus resulting eventually in residues with a reversed ($R > S$) enantiomer composition as compared to that from human metabolism. Inefficient WWTPs and direct discharges of untreated wastewater from storm events, however, can still be a source for increased levels of IB in surface water.

Introduction

Ibuprofen (IB; (*rac*)-2-(4-isobutylphenyl)propionic acid, structure see Chart 1) is a nonsteroidal antiinflammatory (NSAID), analgesic, and antipyretic drug widely used in the treatment of rheumatic disorders, pain, and fever (*1*, *2*). It has an estimated annual global production of several kilotons, and it is the third-most popular drug in the world (*3*). It is an important nonprescription drug and has a relatively high therapeutic dose (600−1200 mg/d) (see ref *1*). It is excreted to a significant degree (70−80% of the therapeutic dose) as the parent compound (free or conjugated) or in the form of metabolites (*2*, *4*, *5*). Its physicochemical properties suggest a rather high mobility in the aquatic environment, and in fact, IB has been detected in wastewater and in rivers along with several other pharmaceutical compounds (*6*−*8*). There is growing concern on the occurrence, fate, and possible effects of such substances in the environment (*8*).

IB has an asymmetrically substituted carbon atom and is chiral (see Chart 1). The desired pharmacological effects reside almost exclusively in the *S* enantiomer, yet the racemic compound is used as the drug (*2*). It has been shown that in humans and other mammals the inactive (*R*)-(−)-IB undergoes extensive (unidirectional) chiral inversion to yield the active (*S*)-(+) compound (*2*, *9*). The principal metabolites of IB are hydroxy-IB, carboxy-IB, and carboxy-hydratropic acid (carboxy-HA) (structures, see Chart 1; see also refs *2* and *4*), all of which are chiral. In case of carboxy-IB (two chiral centers), two diasteromeric pairs of enantiomers exist.

In this study, we report on the application of an enantioselective ("chiral"), highly selective analytical method toward the analysis of a chiral pharmaceutical compound in environmental samples. We confirm that IB is enantioselectively metabolized in the human body. We show that not only the parent compound but also its metabolites are detected at wastewater treatment plants (WWTPs), with the parent compound predominantly in the form of the *S* enantiomer, as from human metabolism. Although these compounds then undergo significant degradation in these installations, IB remained detectable in surface waters (rivers, lakes). The data, and those from laboratory experiments, indicated that the enantiomeric composition of IB then can be further changed in the aquatic environment. The data show that IB is not very persistent and has a clearly different behavior as compared to some other pharmaceutical compounds such as 2-(4-chlorophenoxy)-2-methylpropionic acid (clofibric acid, CA) and 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid (diclofenac).

Experimental Section

Materials and Reference Compounds. The sources and purities of the compounds were as follows: CA (97%), (*rac*)- and (*S*)-(+)-IB (both 99%), Aldrich, Buchs, Switzerland; $^{13}C_6$-(*rac*)-2-(2,4-dichlorophenoxy)propionic acid ($^{13}C_6$-DCPP), Cambridge Isotope Laboratories, Cambridge, MA; and 4-bromophenylacetic acid (BPAA; >98%), Fluka, Buchs, Switzerland.

Waters Sampled. The waters from several lakes and rivers in Switzerland and from the North Sea were analyzed. The lakes have been the subject of several previous studies (*10*−*13*), and their morphologies and hydraulics were previously described (*14*). Some samples, including those from the North Sea, were from previous studies on phenoxyalkanoic acid herbicides and pharmaceutical compounds, and the extracts were kept and stored in a freezer at −20 °C (*10*−*12*). Reanalysis indicated no change in the enantiomeric composition over extended periods of time (up to 6 months) and thus chiral stability of IB under these conditions.

WWTP Samples Analyzed. Samples (all 24-h flow proportionally collected) of influent to the biological stage (raw sewage) and treated effluent emitted to the rivers were collected from the WWTP of Gossau, Pfäffikon, and Uster (for locations, see Figure 1 in ref *11*). These installations are modern, three-stage mechanical/biological plants serving populations of about 10 500 (Gossau), 26 000 (Uster), and 8500 persons (Pfäffikon), respectively (*15*).

Analytical Procedures. The solid-phase extraction, derivatization, and cleanup procedure was as previously

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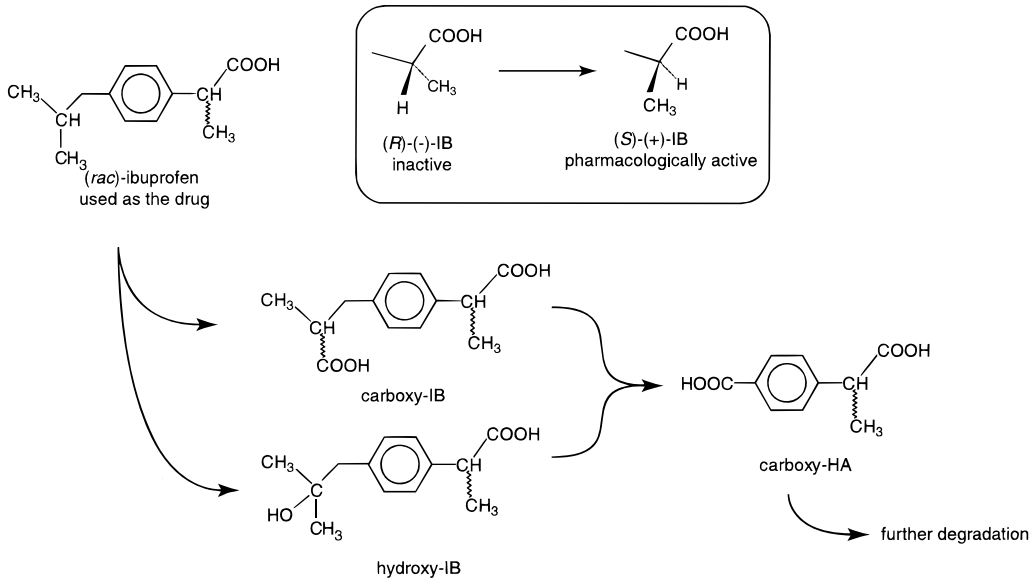
CHART 1. Major Pathways of the Oxidative Metabolism of Ibuprofen in Man (Adapted from Ref *2*)[a]



[a] Inset: Absolute configurations of (*S*)-(+)- and (*R*)-(−)-ibuprofen.

detailed for the analysis of phenoxyalkanoic acid herbicides and other acidic compounds in surface water and in wastewater (*10*−*12*). Briefly, surface water (1 L) was fortified with 20 ng of $^{13}C_6$-DCPP as the internal standard and acidified to pH <2. IB and its metabolites were then extracted using a macroporous polystyrene divinylbenzene copolymer adsorbent (Bio-Beads SM-2; Bio-Rad Laboratories, Hercules, CA) column eluted with methanol/methylene chloride, and methylated with diazomethane, and the samples were cleaned up on silica. In case of the WWTP samples (influent and effluent), portions of ≈300 mL were centrifuged (*11*), and 250 mL of the clear supernatants was treated in the same way as above, except that a designated extraction column was used to avoid cross-contamination of surface water samples and no internal standard was added. Aliquots of the sample extracts, 1−2 μL of a total of 100−1000 μL, were then analyzed by gas chromatography/mass spectrometry (GC/MS).

GC/MS analysis of the analytes as methyl esters (ME) was performed on a VG Tribrid mass spectrometer (VG Fisons, Manchester, England) under electron-impact ionization (EI, 70 eV, 180 °C) and full-scan (*m*/*z* 35−435, 1.16 s/scan; mass resolution $M/\Delta M = 500$), selected ion monitoring (SIM) or selected reaction monitoring (MS/MS SRM) conditions, using a 25-m DB-5 column under conditions as for the analysis of phenoxyalkanoic acid herbicides (*10*, *12*, *16*). In the SRM mode, the formation of daughter ions generated from selected parent ions (generally the molecular ions, $M^{\bullet+}$) was monitored, whereby argon was used as collision gas (*16*). The transitions $220^+ \rightarrow 161^+$ (IB-ME), $228^+ \rightarrow 128^+$ (CA-ME), $228^+ \rightarrow 169^+$ (BPAA-ME), $254^+ \rightarrow 168^+$ ($^{13}C_6$-DCPP-ME), $236^+ \rightarrow 178^+$ (hydroxy-IB-ME), $264^+ \rightarrow 205^+$ (carboxy-IB-ME_2), and $222^+ \rightarrow 163^+$ (carboxy-HA-ME_2) were used to monitor the various compounds.

Enantioselective analysis of IB as the methyl ester was done on a homemade 16-m OV1701-DMPen (DMPen = heptakis(2,6-*O*-dimethyl-3-*O*-*n*-pentyl)-β-cyclodextrin; 1:1 diluted with OV1701) fused silica column (0.25 mm i.d) with on-column injection and using SRM. This column was temperature programmed as follows: 70 °C, 2-min isothermal, 20 °C/min to 120 °C, then at 2.5 °C/min to 152 °C, then at 20 °C/min to 230 °C, followed by an isothermal hold at this temperature. IB-ME eluted at 6.5−7.5 min (measured from data acquisition start at 120 °C), depending on age and condition of the column. For the surface water samples, the amounts of analyte were determined from peak area ratios relative to the internal standard ($^{13}C_6$-DCPP, as methyl ester), and in reference to suitable standards. In case of IB, the summed concentrations of both enantiomers are reported. Enantiomeric ratios of IB (ER) were defined as $ER = p_S/p_R$ whereby p_S and p_R are the peak areas of the earlier eluted *S* and the later eluted *R* enantiomer, respectively. The solid-phase extraction and GC/MS procedure allowed the detection of IB in surface water at concentrations of 0.1−1 ng/L, with acceptable recoveries (50−90%). The WWTP samples with much higher concentrations of IB were quantified using external standardization, and the WWTP incubation samples were quantified using BPAA as the internal standard.

Characterization of Urinary Metabolites. Because the principal metabolites of IB were not available, the compounds were characterized from urine of a female occasional user of the drug. This volunteer had ingested a combined dose of 1400 mg of IB during a 24-h time period. A 250-mL aliquot of urine from the 24-h collected sample was treated and analyzed in the same way as the WWTP samples. No attempt was made to cleave possible conjugates of IB or its metabolites.

Incubation of Fortified Lake Water. Two 2.5-L portions of water from lake Greifensee (August 1997) were fortified with (*rac*)-IB (200 ng/L) and CA (100 ng/L). The samples were incubated at room temperature (rt) for up to 37 d in clear Pyrex glass bottles whereby one bottle was kept in the dark and the other one was exposed to daylight. Aliquots of 250 mL were removed from each bottle, the first ones immediately after fortification ($t = 0$) and then after 4, 10, 21, and 37 d. The samples were immediately extracted and methylated as described above. As a sterile control sample, a 1-L portion of lake water was autoclaved (2 h, 120 °C), fortified at the same levels, and daylight exposed for 37 d. A 250-mL aliquot was then extracted and methylated in the same way. All samples were analyzed for IB and CA using the OV1701-DMPen column and SRM, and the data for IB were reported relative to CA for which degradation occurred neither in the dark nor in daylight.

Incubation of IB with Activated Sludge. Influent from the WWTP at Gossau (November 11, 1997) containing IB, its metabolites, and other contaminants was incubated under aerobic conditions with activated sludge. For this purpose,

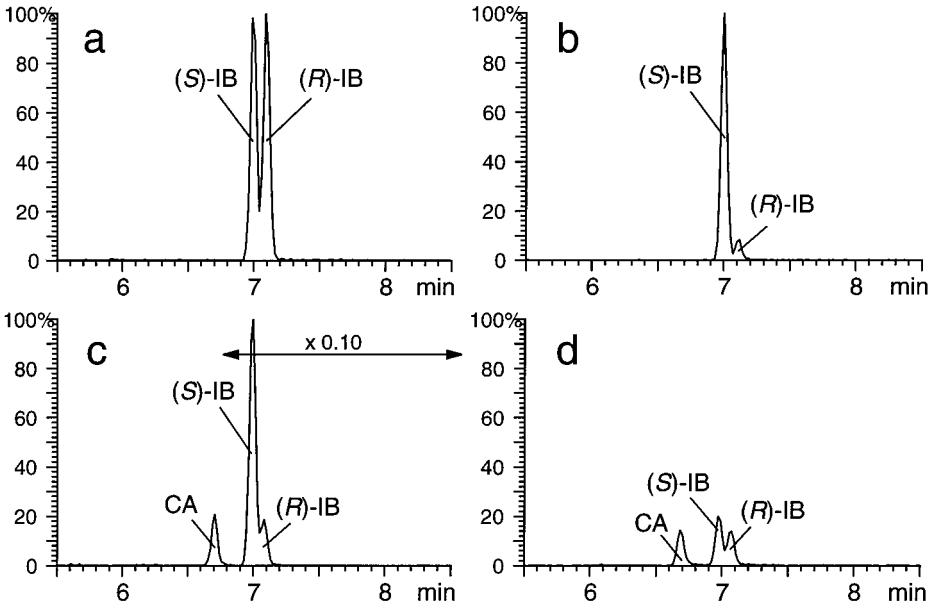


FIGURE 1. EI SRM chromatograms showing elution of IB (upper chromatograms, transition $220^+ \rightarrow 161^+$) and of IB and CA (lower chromatograms, combined trace of transitions $220^+ \rightarrow 161^+$ and $228^+ \rightarrow 169^+$), analyzed as methyl esters using the enantioselective OV1701-DMPen column. Note enantiomer resolution of IB with (*S*)-IB as first-eluting and (*R*)-IB as second eluting enantiomer. (a) Racemic IB, as used as the pharmaceutical drug, (b) IB isolated from human urine showing enantiomeric excess of (*S*)-IB, (c) IB and CA in WWTP influent (Pfäffikon, February 2, 1998; note 10-fold attenuation of IB signals), and (d) IB and CA in WWTP effluent (Pfäffikon, February 2, 1998).

influent (2132 g) was mixed with 307 g of activated sludge from the same installation and air diffused into the mixture at a rate of 220 mL/min. Samples (≈300 mL) were removed, the first one immediately after addition of the sludge ($t = 0$) and then at regular intervals up to 8 h of incubation. They were centrifuged (see before), and 250 mL of the clear supernatant was fortified with 250 ng of BPAA (internal standard) and then extracted and analyzed using the DB-5 column and SRM. The analyses were then repeated using the OV1701-DMPen column and SRM to determine the enantiomeric composition of IB. The results were corrected for water evaporation (≈6 mL/h), normalized to the total concentration of IB ($S + R$) at $t = 0$ (C/C_0), and plotted versus time. Since no quantitative standards were available for the metabolites, their SRM response was normalized to that of IB.

Results and Discussion

Enantioselective GC of IB and Detection by SIM and SRM. IB was isolated from water using a macroporous solid-phase extraction procedure and recovered as methyl ester (ME) from silica gel in the same fraction as the phenoxyalkanoic acid herbicides and the pharmaceutical compounds CA and diclofenac (*10*−*12*). Whereas (*rac*)-IB-ME eluted as a single peak from the DB-5 column, the two enantiomers were resolved on several enantioselective GC columns (data not shown). The best resolution was obtained on an OV1701 column with DMPen as the chiral selector, as shown by the chromatograms in Figure 1. Consequently this column was used for most analyses. The enantiomer elution sequence on this column is *S* followed by *R*. This elution sequence corresponds to that of another chiral propionic acid derivative, the herbicide MCPP (MCPP = 2-(4-chloro-2-methylphenoxy)propionic acid) (see ref *12*), when topographically equivalent stereoisomers are considered (note that the configuration of (*S*)-(+)-IB is topographically equivalent to that of (*R*)-(+)-MCPP). However, the enantiomer resolution for IB-ME is lower than that for MCPP-ME (*12*).

The EI mass spectrum of IB-ME is shown in Figure 2a. It shows a molecular ion ($M^{\bullet+}$) at m/z 220 and major fragment ions at m/z 177 ($M^+ - C_3H_7$) and 161 ($M^+ - COOCH_3$), both ions formed via β-(benzylic) cleavage of the side chains. The mass spectra of the two enantiomers, expectedly, were identical. The ion m/z 220, generally used in SIM analyses for IB-ME, is not very characteristic for its detection in GC/MS. This ion is common to many organic compounds; e.g., 1400 compounds are listed in a mass spectral library with molecular masses of 220 Da, 218 compounds even with the exact composition ($C_{14}H_{20}O_2$) of IB-ME (*17*), among which high-resolution MS cannot distinguish.

Not surprisingly, SIM chromatograms of WWTP and environmental samples (lake and river water) generally showed a number of components eluting in the retention time range of IB-ME, interfering with its proper detection (data not shown). In contrast to this, SRM chromatograms were virtually free of interfering signals when the transition $220^+ \rightarrow 161^+$ was monitored (see Figure 1 and below), and the enantiomeric composition of IB could then be determined precisely. MS/MS SRM detection is expected to be more selective than SIM because in SRM not only a particular ion has to be present but a definite parent/daughter ion relationship must exist.

Presence of IB and the Metabolites in Human Urine. When the urine sample was analyzed using the enantioselective OV1701-DMPen column and SRM, residual IB showed a high enantiomeric excess of (*S*)-IB (*S*/*R* = 95:5; ER = 19, see chromatogram in Figure 1b), although the racemic compound was used as the drug. This finding is in accordance with previous data obtained using various other analytical techniques (diastereomeric derivative formation; high-performance liquid chromatography) (*18*−*20*). The urine, when analyzed by full-scan MS using the DB-5 column, showed a complex pattern of components, among which the methyl esters of IB, hydroxy-IB, carboxy-IB (major), and carboxy-HA (minor) were clearly observed (see chromatogram in Figure 3a). In Figure 2b−d, we show EI mass spectra of the three metabolites thus characterized and identified in reference to published spectra (*18*) and/or from retention time considerations. The identification of these compounds as metabolites of IB is supported by the fact that IB and these

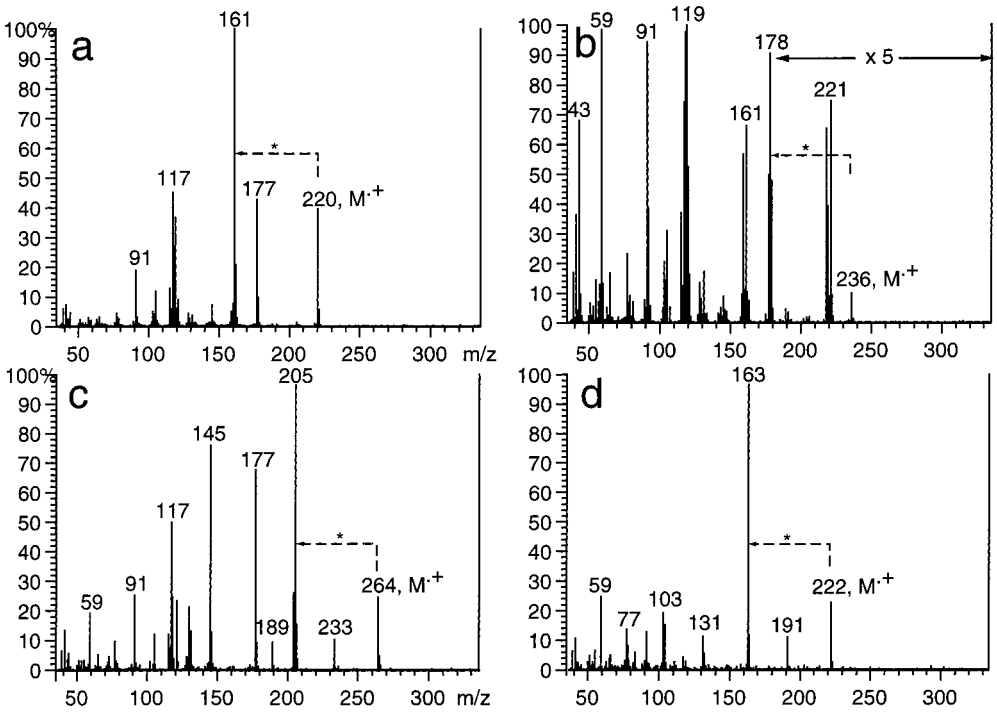


FIGURE 2. EI mass spectra of ibuprofen and metabolites, analyzed as methyl esters. (a) IB-ME ($M^{\bullet+}$ = 220), (b) hydroxy-IB-ME ($M^{\bullet+}$ = 236), (c) carboxy-IB-ME_2 ($M^{\bullet+}$ = 264), and (d) carboxy-HA-ME_2 ($M^{\bullet+}$ = 222) identified in urine (see text). Ion transitions for SRM indicated by dotted lines.

compounds were no longer detected in urine of the same person 7 d after use of the drug. The EI mass spectra in Figure 2b−d show $M^{\bullet+}$, $M^{\bullet+} - COOCH_3$ $(M - 59)^+$, and other fragment ions; hydroxy-IB-ME also shows a characteristic $(M - 58)^{\bullet+}$ even-mass fragment ion due to the loss of C_3H_6O (formally acetone) from the hydroxylated side chain. In Figure 2b−d, we also indicate the SRM transitions used for the selective detection of the metabolites. Enantiomer resolution of the metabolites, when analyzed as the methyl esters using OV1701-DMPen, was incomplete and not further attempted, and the nonenantioselective DB-5 column was used for the analysis of these compounds.

Detection of IB and Its Metabolites in WWTPs. IB, hydroxy-IB, carboxy-IB (major), and smaller amounts of carboxy-HA were consistently detected in the influents of the WWTP installations at Gossau, Pfäffikon, and Uster as shown by a representative chromatogram in Figure 3b. IB was found at concentrations of 1−3.3 μg/L (see Table 1), and hydroxy- and carboxy-IB were found even at higher concentrations as judged from such chromatograms. The residual IB in these samples showed a predominance of the *S* enantiomer (ER = S/R = 5.5−8; as an example, see chromatogram in Figure 1c), as in the human urine (see Figure 1b). Also detected in these samples were CA (6−105 ng/L) and diclofenac (310−1920 ng/L, see ref *11*).

The concentrations of IB of 1−3.3 μg/L for the 24-h averaged influents and the known throughputs of wastewater amount to inputs of 2.9−21 g/d to these plants (see Table 1). When normalized for the populations serviced by these plants, the inputs amount to 2.8−11 g (10 000 persons)$^{-1}$ d^{-1}. This is in good agreement with the overall consumption of IB as estimated from other data (19−38 g (10 000 persons)$^{-1}$ d^{-1}, see refs *6* and *8*), assuming some metabolization in man and degradation in the sewer system.

IB and the principal metabolites, hydroxy-IB and carboxy-IB, were also detected in the effluents from these installations but at much lower concentrations (IB, 2−81 ng/L). A comparison of the chromatogram of an influent of a WWTP (Figure 3b) to that of the effluent from the same installation (Figure 3c) sampled at the same time clearly indicates the efficient removal of these and other compounds during treatment. As indicated in Table 1 and examplified by the chromatogram in Figure 1d, the residual IB in the effluents shows a lower enantiomeric excess of (*S*)-IB (ER = 0.9−2) than the residual IB in the influents (ER = 5.5−8), indicating that (*S*)-IB is somewhat faster degraded than (*R*)-IB. CA was detected at similar concentrations in the effluents as in the influents, indicating little, if any, elimination of this particular compound in WWTPs. The concentration of IB (C_{IB}) relative to the concentration of CA (C_{CA}), the ratio C_{IB}/C_{CA}, is thus decreased during treatment, as is also indicated by a comparison of the chromatograms in Figure 1, panels c and d.

The actual amounts of IB emitted into rivers or lakes with sewage effluent are low and estimated at 0.01−0.3 g d^{-1} installation^{-1} (see Table 1). Low emissions are also indicated by the generally low concentrations (<0.2−2.4 ng/L) in the tributary Aabach of Greifensee (see Table 2) to which three of the WWTPs are emitting.

The consistently lower concentrations of IB and metabolites in the effluents point to an efficient elimination (96−99.9%) of these compounds in WWTPs. In principle, higher emissions can result from direct discharges of wastewater to rivers and lakes either during high-water events (overflow conditions) or from households that are not connected to sewage treatment plants. Because influent concentrations were 25−1000 times higher than effluent concentrations, a direct discharge of just a small amount of untreated wastewater can lead to a mass loading of IB to rivers and lakes similar to or higher than the total amount of IB and metabolites discharged with a much larger volume of treated wastewater. In the catchment area of Greifensee, the direct discharge of raw wastewater was estimated to be as high as ≈10% (mainly from overflow) (*21*), and the amount of IB thus emitted directly into the lake may exceed the amount discharged via treated wastewater by a factor of 2−100.

Degradation of IB and Its Principal Metabolites in Activated Sludge. In Figure 4, we plotted the data from the

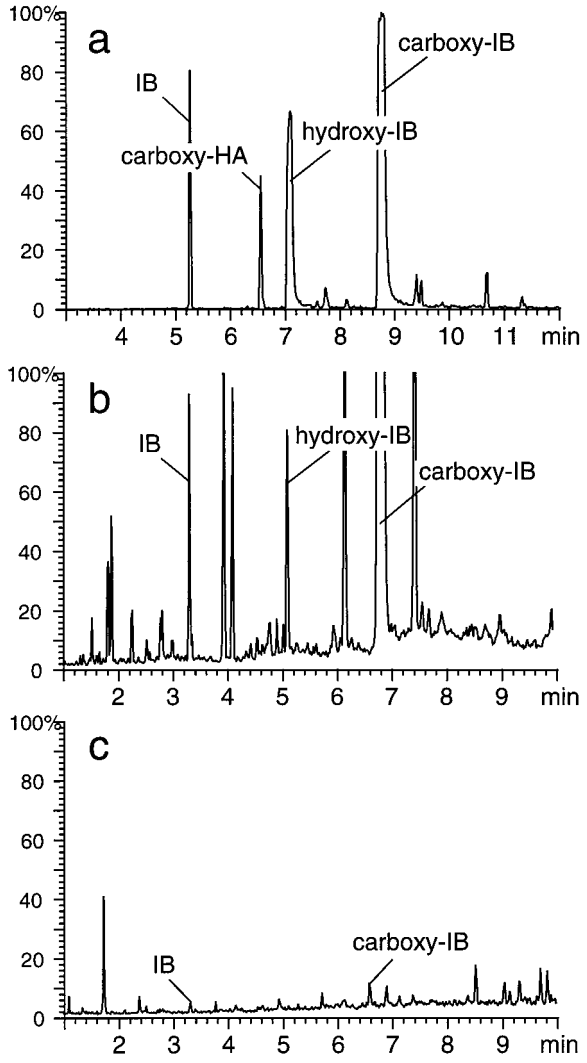


FIGURE 3. EI GC/MS chromatograms (combined traces *m/z* 178 + 220 + 222 + 264, reconstructed from full-scan mass spectra) of ibuprofen and metabolites, analyzed as methyl esters using the nonenantioselective DB-5 column in (a) human urine after use of the drug, (b) WWTP influent (Gossau, December 5, 1997), and (c) WWTP effluent (Gossau, December 5, 1997). Note different retention time in chromatogram (a) because data acquisition was started at 100 °C.

laboratory incubation of IB in WWTP influent mixed with activated sludge. The data indicated some initial phase with little or no dissipation followed by rapid dissipation of IB and its principal metabolites to levels <1−3% after 8 h of incubation. In addition, the enantiomeric composition of IB changed during incubation from an initial ER of 5.7 to an ER of 2.7. The rapid and almost complete dissipation and the changed enantiomeric composition point to biologically mediated degradation rather than other processes such as sorption or uptake by the sludge, which is also supported by findings in similar experiments with the related compound MCPP (*22*). The faster degradation of (*S*)-IB observed in this experiment is consistent with the results from the WWTP samples where a trend to lower ERs in the effluents was observed. The degradation kinetics in Figure 4 also indicate that, for complete removal of IB, a residence time of wastewater in excess of 6 h is required. In WWTPs with a lower residence time or with other deviating conditions, IB may be degraded less efficiently, if at all. This may explain the relatively higher concentrations (up to 3.35 μg/L) in effluents from some German installations (*6, 8*).

Degradation of IB in Fortified Lake Water. In Figure 5, we plotted the data from the incubation experiments of (*rac*)-IB in fortified lake water. The data from the sterile control sample showed no degradation of IB for up to 37 d, even when exposed to daylight. However, IB was degraded under nonsterile conditions in daylight as well as in the dark. Under both conditions a faster degradation of the *S* enantiomer was observed, leading to an excess of (*R*)-IB in the residues ($ER_{dark} \approx 0.6$; $ER_{light} \approx 0.1$). Whereas overall degradation (summed concentrations of both enantiomers) is not very different with half-lives (τ) of ≈20 d under both conditions, the enantioselectivity is much higher under daylight exposure, as indicated by the lower ER value. Because degradation is highly enantioselective and was not observed in sterilized water under daylight exposure, it is largely biological. The results indicate eventual compositions $R > S$ from the racemic compound and thus an enantioselectivity which is reversed from that of the metabolism in man (see above). It can be speculated that these transformation processes involve enantiomerization (e.g., conversion from *S* to *R*), as was observed with the 2-phenoxypropionic acids MCPP and DCPP (*12*). The degradation of IB in lake water shows an enantioselectivity (*S* faster degraded than *R*) in the same sense as MCPP (*R* faster degraded than *S*) when considering topographically equivalent stereoisomers (*12*).

Occurrence of IB in Surface Waters. Several lakes and rivers contained IB at detectable concentrations, as reported in Table 2. The metabolites, however, were not detected (estimated limit of detection, less than 1 ng/L). The concentrations of IB were low (up to 7.8 ng/L), which is in contrast to data from German rivers with concentrations up to 139 ng/L (see ref *6*). Greifensee, the most thoroughly examined lake in our study, showed concentrations of IB of 2−8 ng/L with no obvious seasonal pattern. These residues mostly showed an excess of (*S*)-IB with ERs up to 2.1. There appears to be some trend toward lower ERs (closer to racemic) in the warmer season when the lake is stratified and shows more biological activity. Samples from the tributary Aabach of Greifensee showed the presence of IB at all locations with concentrations up to 2.4 ng/L (see Table 2) except at one location upstream of a WWTP installation (<0.2 ng/L at site L3, see ref *11*). This confirms that WWTPs are the source of IB.

IB was also detected in Zürichsee (3.3−4.0 ng/L), Baldeggersee (1.5−3.2 ng/L), and Pfäffikersee (4.0 ng/L). The residues in these lakes in general showed an enantiomeric excess of (*S*)-IB with ERs up to 2.0 (excepting a value of 4.2 for Baldeggersee, see below) as observed in WWTP effluents. However, IB was neither detected (<0.2 ng/L) in Sempachersee nor in the North Sea. The absence in Sempachersee, the lake with the longest water residence time (17 yr), and in the North Sea, the final sink, suggest further degradation of IB during extended residence in the aquatic environment.

Comparative Environmental Stability of IB and Other Pharmaceutical Compounds. IB and its principal metabolites were detected in all WWTP samples, and IB was also detected in some of the lakes and rivers at lower concentrations. While the *S* enantiomer of IB is excreted in a much greater concentration than the *R* enantiomer, the *S* enantiomer degrades faster in the sewage system and apparently in surface water. This has important implications for the relative toxicity of these species including possible endocrine disrupting acivity of the enantiomers to both human and wildlife.

Also detected in WWTP samples and in surface water were the pharmaceutical compounds CA and diclofenac (*10, 11*). The widespread occurrence of these compounds points to inputs from therapeutic uses via WWTPs. The data suggest a different environmental behavior of these compounds: whereas IB is largely eliminated in WWTPs, CA and diclofenac

TABLE 1. Concentrations (ng/L) and Amounts (g/d) of Ibuprofen in Wastewater

installation, location	population serviced (persons)	date	throughput Q (m^3/d)	influent (ng/L)	influent (g/d)	influent ER (*S*/*R*)	effluent (ng/L)	effluent (g/d)	effluent ER (*S*/*R*)
Gossau	10500	Oct 28, 1997	3236	3300	10.7	6.2	≈2	0.01	≈1.5
		Nov 11, 1997	2912	990	2.9	5.7	na[a]	na	
		Dec 5, 1997	3917	2900	11.4	8.0	≈2	0.01	≈2
Uster	26000	Feb 2, 1998	15440	1360	21.0	7.9	13	0.2	0.9
Pfäffikon	8500	Feb 2, 1998	3161	2040	6.5	5.5	81	0.3	1.0

[a] na, not analyzed.

TABLE 2. Ibuprofen in Lakes and Rivers, and in the North Sea

lake, river	date	ibuprofen concn (ng/L)	ibuprofen ER (*S*/*R*)
Greifensee (outlet)	Aug 2, 1996	4.3	≈0.7
	Sep 18, 1996	4.7	≈1.0
	Dec 12, 1996	7.8	2.0
	Mar 3, 1997	4.3	2.1
	Apr 15, 1997	7.8	2.0
	May 6, 1997	2.0	1.6
	Jul 2, 1997	5.2	1.6
	Aug 12, 1997	5.2	1.1
	Dec 5, 1997	4.7	1.8
Aabach Tributary	Aug 1996–Oct 1997[a]	nd[b]–2.4	0.9–3.0
Pfäffikersee	Aug 12, 1997	4.0	1.4
Zürichsee	Dec 1996–Oct 1997[c]	3.3–4.0	1.0–1.3
Baldeggersee	Jun 1997–Nov 1997[d]	1.5–3.2	1.8–4.2
Sempachersee	Aug 1996–Jul 1997[c]	nd	
North Sea	Dec 1996/Apr 1997[e]	nd	
mountain lakes	Jul–Aug 1997[e]	nd	

[a] 9 samples. [b] nd, not detected (<0.2 ng/L). [c] 5 samples. [d] 3 samples. [e] 2 samples.

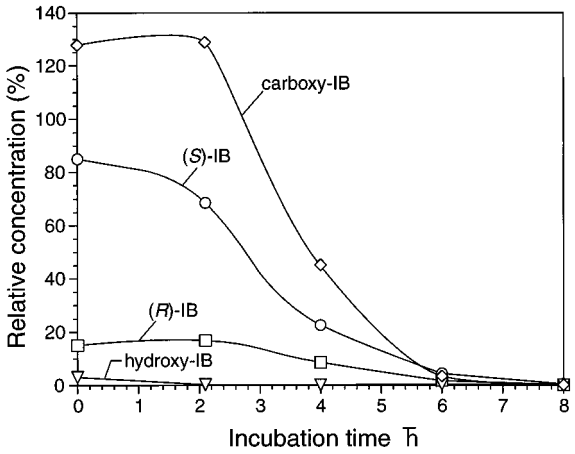


FIGURE 4. Degradation of (*S*)- and (*R*)-IB and the principal metabolites, carboxy- and hydroxy-IB, in WWTP influent incubated with activated sludge under aerobic laboratory conditions. Relative concentrations plotted versus incubation time (h); summed concentration of (*S*)- and (*R*)-IB = 100% at $t = 0$; equal SRM responses assumed for all analytes. Note faster degradation of (*S*)- than of (*R*)-IB.

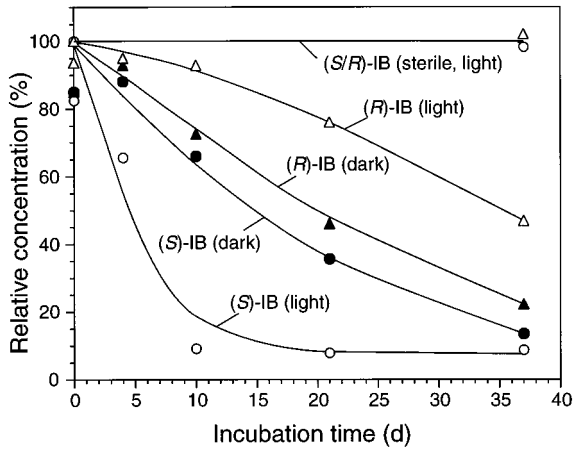


FIGURE 5. Degradation of IB in lake water fortified with (*rac*)-IB and incubated under laboratory conditions. Relative concentrations (C/C_0) plotted versus incubation time (d). Note faster degradation of (*S*)-IB than (*R*)-IB when incubated under nonsterile conditions in the dark (full circles and triangles) and in daylight (empty circles and triangles). No degradation under sterile conditions (top curve). Circles, (*S*)-IB; triangles, (*R*)-IB.

are more resistant and largely survive sewage treatment. Diclofenac is then degraded in the lakes, most likely by photodegradation (*11*). Clearly, CA is the most persistent compound of the three and was even present in the North Sea (*10*), and IB is the least persistent of these compounds. The relative concentration of IB, as expressed by the ratio C_{IB}/C_{CA}, should thus decrease not only during treatment in WWTPs but also with increased residence in a water body.

In Figure 6, SRM chromatograms document the presence (or absence) of IB and CA in Greifensee (1.1 yr), Zurichsee (1.2 yr), Baldeggersee (3.8 yr), Sempachersee (17 yr) (mean water residence times given in parentheses), and in the North Sea. The order chosen in Figure 6 (top to bottom) is the order of increasing water residence times in the lakes, with the North Sea at the end of this chain. As seen in Figure 6, there is a general trend to lower C_{IB}/C_{CA} ratios with increased mean water residence time, consistent with a lower environmental stability of IB. A possible exception is Baldeggersee where the concentration of IB is higher (up to 3.2 ng/L) than expected from the long mean water residence time and low population density within the catchment area. In this case, the relatively higher ER of 4.2 of one of the samples may

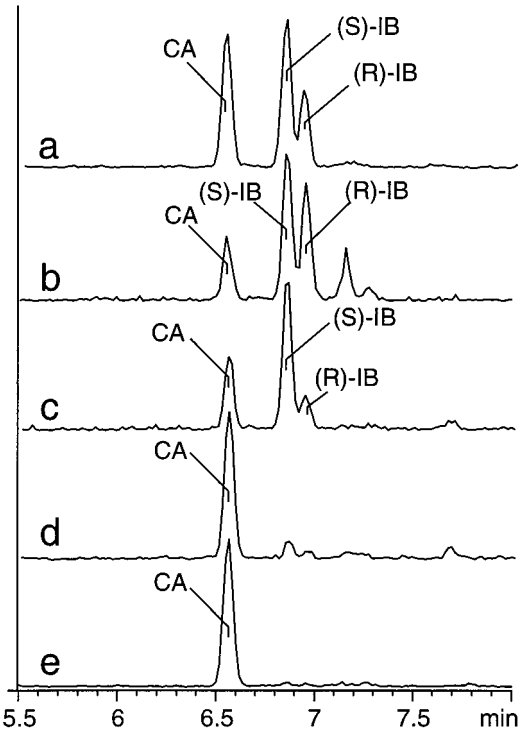


FIGURE 6. EI SRM chromatograms (combined traces of transitions $220^+ \rightarrow 161^+$ and $228^+ \rightarrow 169^+$) of IB and CA, analyzed as methyl esters using the enantioselective OV1701-DMPen column, in various surface waters. From top to bottom: Greifensee (December 12, 1996; ratio $r = C_{IB}/C_{CA} = 0.6$), Zurichsee (October 8, 1997; $r = 1.7$), Baldeggersee (June 30, 1997; $r = 1.0$), Sempachersee (December 12, 1996; $r < 0.1$), and the North Sea (Station 101, December 1, 1996; $r < 0.1$). Note the decreased ratio r in Sempachersee and the North Sea; for details, see text.

point to some input of untreated or insufficiently treated wastewater.

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