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Short Communication

A comparison of octanol–water partitioning between organic chemicals and their metabolites in mammals

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ABSTRACT

Bioaccumulation models take various elimination and uptake processes into account, estimating rates from chemical lipophilicity, expressed as the octanol–water partition ratio (K_{ow}). Here, we focussed on metabolism, which transforms parent compounds into usually more polar metabolites, thus enhancing elimination. The aim of this study was to quantify the change in lipophilicity of relevant organic pollutants undergoing various biotransformation reactions in mammals. We considered oxidation reactions catalyzed by three enzyme groups: cytochrome P450 (CYP), alcohol dehydrogenase (ADH), and aldehyde dehydrogenase (ALDH). Estimated log-K_{ow} values of a selected dataset of parent compounds were compared with the logK_{ow} of their first metabolites. The logK_{ow} decreased by a factor that varies between 0 and −2, depending on the metabolic pathway. For reactions mediated by CYP, the decrease in K_{ow} was one order of magnitude for hydroxylated and epoxidated compounds and two orders of magnitude for dihydroxylated and sulphoxidated xenobiotics. On the other hand, no significant change in lipophilicity was observed for compounds N-hydroxylated by CYP and for alcohols and aldehydes metabolized by ADH and ALDH. These trends could be anticipated by the calculus method of logK_{ow}. Yet, they were validated using experimental logK_{ow} values, when available. These relationships estimate the extent to which the elimination of pollutants is increased by biotransformation. Thus, the quantification of the K_{ow} reduction can be considered as a first necessary step in an alternative approach to anticipate biotransformation rates, which are hard to estimate with existing methods.

1. Introduction

Risk assessment of xenobiotics present in the environment needs comprehensive evaluation of accumulation potential in organisms. Recently developed *in silico* mechanistic models estimate the bioaccumulation factors of chemicals, calculated as the difference between uptake and elimination rates from organisms (Hendriks et al., 2001). In addition to the excretion via urine, egestion via feces and growth dilution, labile compounds can be eliminated by metabolism. Yet, prediction of biotransformation rates is difficult (van der Linde et al., 2001).

The importance of biotransformation in drug activity (Madden and Cronin, 2006) and in assessing human risk of environmental toxicants (Ginsberg et al., 2004) has led to a growing interest in the metabolic pathways of chemicals in bacteria, fish, mammals and other species (Safe, 1994; Kaiser et al., 1996; Snyder and Hedli, 1996; Snedeker, 2001; Xue and Warshawsky, 2005; Seo et al., 2009). Quantitative Structure–Activity Relationships (QSARs) have been developed to predict metabolic rates of drugs as well as environmental pollutants, like pesticides and PAHs. Metabolic rates have also been estimated as the difference between the predicted elimination rate neglecting biotransformation and the observed experimental value (van der Linde et al., 2001).

However, up to date no direct comparison has been made between the physicochemical properties of xenobiotics and their metabolites. Yet, such comparisons could shed light on general patterns of metabolism. The objective of the present study was to estimate the difference in lipophilicity, expressed by the octanol–water partition coefficient (K_{ow}), between parent compounds and their metabolites for a number of organic pollutants. Parent compounds are usually transformed by enzymes into more polar metabolites to be excreted more rapidly; the present work quantifies this difference. The approach can also be considered as a first indication of increased elimination to be used in exposure and risk assessment if empirical data and refined models are lacking.

2. Materials and methods

2.1. Theory

The octanol–water partition coefficient (K_{ow}) is often used in risk assessment to predict intake, accumulation, and excretion rates of chemicals (Hendriks et al., 2001). Elimination rate constants for persistent chemicals generally decrease with the K_{ow} (Fig. 1) (Fears, 1985; Walther et al., 2008). Biotransformation usually reduces the

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lipophilicity of the compound, facilitating its excretion via aqueous fluids (Giroud et al., 1998). If the parent compound is immediately and totally metabolized, it can be assumed that the elimination of the metabolite is similar to that of a persistent compound which is as lipophilic as the metabolite. As an example, Fig. 1 shows the increase of the elimination rate constant by a factor of 10, from about 0.08 to 0.80, as a result of the reduction of the K_{ow} by two orders of magnitude, i.e. from 10^5 to 10^3. The dashed line refers to elimination rate constants representing total physical–chemical elimination of persistent compounds, i.e. without biotransformation, in 10^{-1} kg mammals (Hendriks et al., 2001).

2.2. Data collection

Information on the metabolic pathways of a set of environmental pollutants (parent compounds) was taken from the scientific literature and from two publicly available databases: Hazardous Substances Data Bank (HSDB, http://toxnet.nlm.nih.gov/) and Toxin Target Database (T3DB, http://www.t3db.org/). We built a database including those pollutants that have one main metabolic pathway in mammals and that are oxidized by the enzymes alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), and cytochrome P450 (P450) (Klaassen, 2008). The parent compounds were grouped according to their first "metabolite", i.e. to the reaction they undergo. We considered the following biotransformation reactions: alcohol oxidation (by ADH), aldehyde oxidation (by ALDH), and the more common types of P450 reactions (Guengerich, 2001; Brown et al., 2008), i.e. hydroxylation, dihydroxylation, epoxidation, and heteroatom (N, S) oxygenation. The Supporting Information (SI) provides a scheme with the biotransformation reactions on chemical moieties (Table S1). The parent compounds and the relative metabolites can be also found in the SI (Table S2), together with their $\log K_{ow}$ values and literature references.

The octanol–water partition coefficients of parent compounds and metabolites were taken from the ChemSpider database (freely accessible at http://www.chemspider.com/). ChemSpider reports the experimental $\log K_{ow}$ values (when available in the database), as well as the predicted values calculated by the ACD/log P program (Petrauskas and Kolovanov, 2000), without the relative uncertainties. This program has the advantage of accounting for the positional (topological) effect of substituents on a chemical structure (Machatha and Yalkowsky, 2005).

2.3. Data treatment

The log-transformed octanol–water partition coefficients of the metabolites, $\log K_{ow(metabolite)}$ were related to the parent compounds, $\log K_{ow(parent)}$, according to

$$\log K_{ow(metabolite)} = a \log K_{ow(parent)} + b. \quad (1)$$

The linear parameters a (slope) and b (intercept), as well as the statistical standard error (SE), the correlation coefficient (r^2), 95% the confidence interval (95%CI), and the significance level (p) were determined. Slopes and intercepts were analyzed for significant deviation from $a = 1$ and $b = 0$, respectively, i.e. from the bisector representing a 1:1 relation between the $\log K_{ow}$ values of parent compounds and metabolites.

We developed one regression per enzyme (general regressions) and one per biotransformation reaction. A first set of regressions was built using $\log K_{ow}$ values calculated by the ACD/log P program and a second one using experimental $\log K_{ow}$ values, when available for at least five parent compounds and their relative metabolites. An analysis of covariance (ANCOVA) (Lowry, 2012) was performed to compare the regressions with experimental $\log K_{ow}$ values with the regression with predicted values. If the p_{ancova} resulting from the test for homogeneity of regression was lower than 0.05, we considered the two regressions significantly different from each other.

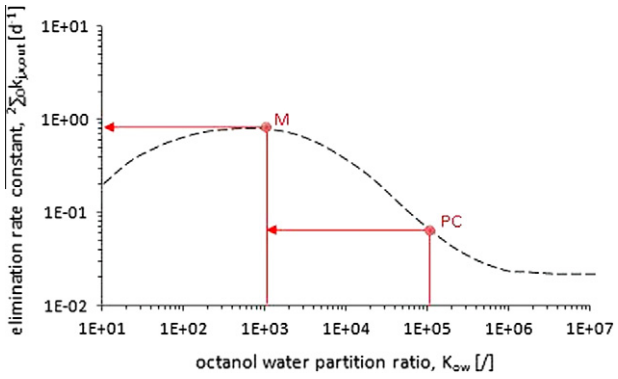

Fig. 1. Effect of a K_{ow} reduction from parent compound (PC) to metabolite (M) on the elimination rate constant. Background graph taken from (Hendriks et al. 2001).

3. Results

In Fig. 2, the $\log K_{ow}$ of the parent compound is plotted against the $\log K_{ow}$ of the metabolite, using calculated (empty symbols, thin lines) and experimental values (full symbols, thick lines). Tables 1 and 2 provide the regression equations and statistical parameters obtained for all metabolic pathways considered, using calculated and experimental $\log K_{ow}$ values, respectively. All regressions were significant at the 0.01 level ($p < 0.01$).

The regressions with predicted $\log K_{ow}$ had high correlation coefficients: r^2 was higher than 0.85, except for dihydroxylation ($r^2 = 0.71$) and N-hydroxylation ($r^2 = 0.63$). The slopes were equal to 1 within a 95% CI. The general regression lines (Fig. 2) gathered around the intercepts $b = 0$ (ADH and ALDH) and $b = -1$ (CYP), indicating metabolic pathways that do not change the K_{ow} of substrates and metabolic pathways that lower the K_{ow} by a factor of 10, respectively. More in detail (Table 1), for hydroxylation and epoxidation the intercept was statistically similar to −1 within a 95% CI, while for dihydroxylation and sulphoxidation it was around −2. In contrast, the intercepts were about 0 for N-hydroxylation and for the oxidation of alcohols to aldehydes and to ketones.

Using experimental $\log K_{ow}$ data, we also set up nine validation regressions (Table 2 and thick lines in Fig. 2). These regressions were significant at the 0.01 level, with explained variance ranging from 70 to 99%. The regressions with experimental and with predicted K_{ow} values were statistically similar, with the exception of aromatic hydroxylation and the regressions mediated by ADH, which had $p_{ancova} < 0.05$.

4. Discussion

4.1. Calculation methodology

In this study, we related the $\log K_{ow}$ of parent compounds to the $\log K_{ow}$ of their first metabolites in mammals, dividing the data according to the metabolic pathway. We also built general regressions merging data per enzyme group (CYP, ADH, ALDH).

All regressions developed with predicted $\log K_{ow}$ values were robust and statistically significant and had slopes containing the value of 1 in their 95% confidence intervals (Table 1). The dispersion of the data in Fig. 2 (empty symbols, thin lines) was generally similar both at low and high K_{ow}, indicating that the total lipophilicity depends on electronic interactions among substituents of the chemical structure. Errors and uncertainties affecting the calculated values of K_{ow} were not provided by the Chemspider database.

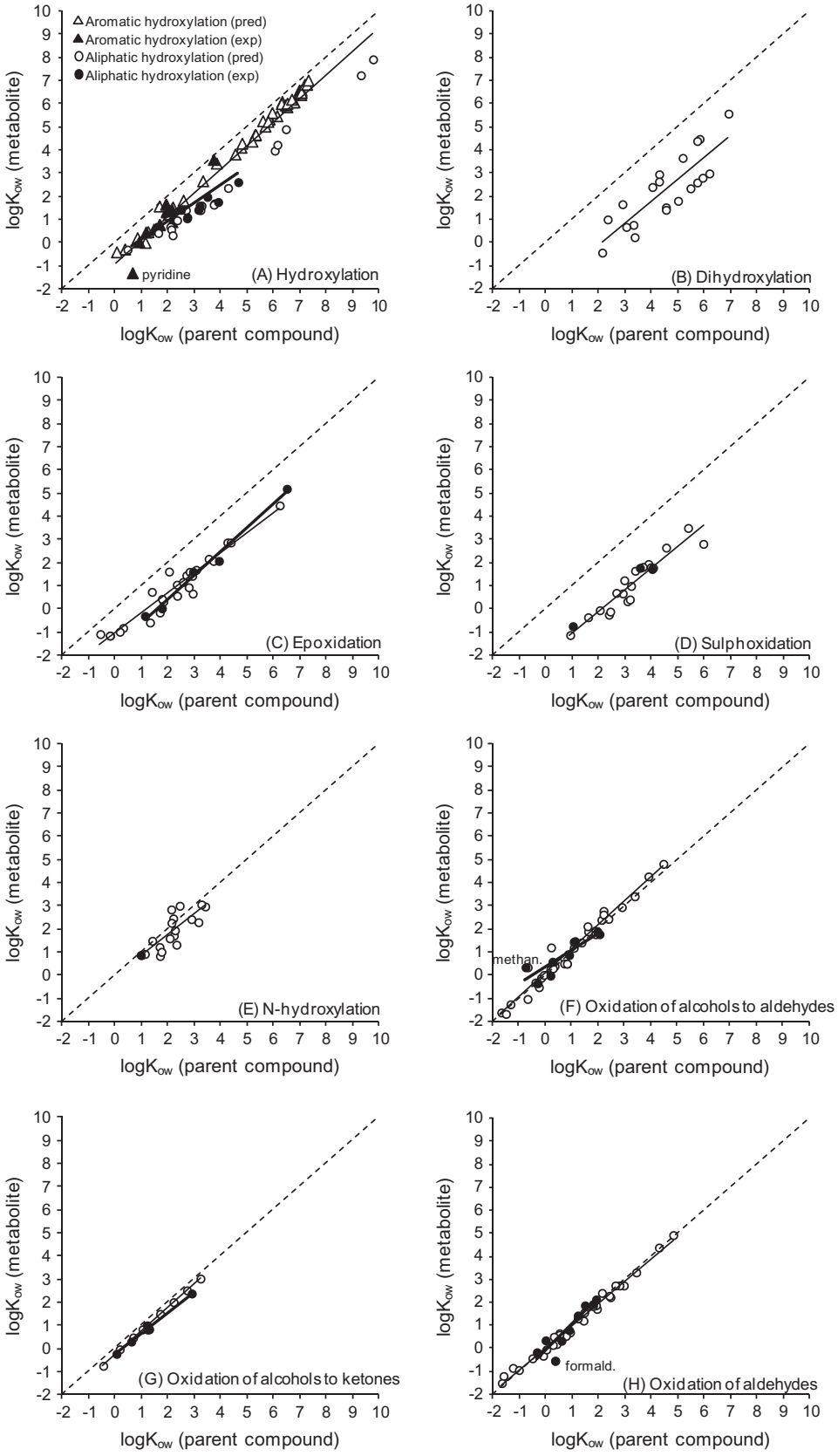

Fig. 2. Log K_{ow} values of metabolites versus parent compounds, using predicted (empty dots) or experimental (full dots) log K_{ow} values, for the following biotransformation reactions: (A) hydroxylation; (B) dihydroxylation; (C) epoxidation; (D) sulphoxidation; (E) N-hydroxylation; (F) oxidation of alcohols to aldehydes; (G) oxidation of alcohols to ketones; and (H) oxidation of aldehydes. Dashed lines indicate the 1:1 bisector ($a = 1$ and $b = 0$), while solid lines indicate the regressions with predicted (thin lines) or experimental (thick lines) log K_{ow} values.

Table 1
Characteristics and statistical parameters of metabolite versus parent compound log(K_{ow}) regressions with slope *a* and intercept *b*. Log K_{ow} are calculated with the ACD/log P program.

Metabolic reaction	Chemical class of parent compounds	*n*	Log K_{ow} range of parent compounds	*a* ± *SE*	95%CI[a] *a*	*b* ± *SE*	95%CI[a] *b*	r^2	*SE*	*p*[b]
Reactions mediated by P450 enzymes										
General regression		147	−0.56; 9.76	0.97 ± 0.03	0,90; 1,04	−1.13 ± 0.14	−1,42; −0,85	0.85	0.86	<0.01
Hydroxylation		65	0.05; 9.76	1.02 ± 0.03	0.96; 1.08	−0.97 ± 0.15	−1.27; −0.67	0.95	0.56	<0.01
Aromatic	PCBs, aromatic hydrocarbons, heterocyclic compounds, PCDDs, PCDFs, PBDEs, PBBs.	47	0.05; 7.31	1.04 ± 0.01	1.01; 1.06	−0.74 ± 0.06	−0.86; −0.61	0.99	0.19	<0.01
Aliphatic	Aliphatic hydrocarbons (alkanes and ketones), aromatic hydrocarbons, cyclic compounds, drugs (aliphatic amines, imides).	18	0.47; 9.76	0.92 ± 0.03	0.86; 0.97	−1.33 ± 0.13	−1.61; −1.05	0.99	0.30	<0.01
Dihydroxylation	PAHs, NHAs, nitro PAHs, aromatic hydrocarbons, heterocyclic compounds.	20	2.13; 6.91	0.94 ± 0.14	0.64; 1.23	−1.97 ± 0.67	−3.38; −0.55	0.71	0.84	<0.01
Epoxidation	PAH diols, NHA diols, aromatic hydrocarbons, heterocyclic compounds, aliphatic hydrocarbons (alkenes), cyclic alkenes, vinyl halides.	25	−0.56; 6.23	0.86 ± 0.05	0.76; 0.96	−1.04 ± 0.14	−1.32; −0.76	0.93	0.39	<0.01
Sulphoxidation	Sulphides (carbamate, thiocarbamate, organophosphorous pesticides)	19	0.92; 5.96	0.94 ± 0.08	0.78; 1.11	−2.02 ± 0.27	−2.58; −1.45	0.90	0.40	<0.01
N-hydroxylation	Aromatic amines (primary, secondary), heterocyclic aromatic amines (primary, secondary)	18	0.99; 3.41	0.91 ± 0.17	0.54; 1.28	−0.07 ± 0.39	−0.91; 0.76	0.63	0.49	<0.01
Reactions mediated by ADH enzymes										
General regression		43	−1.69; 4.45	1.02 ± 0.04	0.95; 1.10	0.04 ± 0.06	−0.09; 0.17	0.95	0.33	<0.01
Oxidation of primary alcohols to aldehydes	Aliphatic hydrocarbons (primary alcohols, allylic alcohols, glycols, glycol ethers, halohydrins), benzyl alcohols.	33	−1.69; 4.45	1.04 ± 0.04	0.96; 1.12	0.11 ± 0.07	−0.02; 0.25	0.96	0.32	<0.01
Oxidation of secondary alcohols to ketones	Aliphatic hydrocarbons (secondary alcohols, allylic alcohols, cyclic compounds)	10	−0.45; 3.23	1.02 ± 0.02	0.96; 1.07	−0.27 ± 0.04	−0.37; −0.17	0.99	0.08	<0.01
Reaction mediated by ALDH enzymes										
Oxidation of aldehydes to acids	Aliphatic hydrocarbons (aldehydes), benzyl aldehydes.	32	−1.67; 4.82	0.97 ± 0.03	0.92; 1.03	0.01 ± 0.05	−0.09; 0.12	0.98	0.24	<0.01

[a] Confidence interval for the parameter at 95% confidence.
[b] *p*-Value of statistical significance testing.

Nevertheless, as the same error affects both parent compounds and metabolites, the pattern still remains consistent.

The interpretation of the results is closely related to the method used to calculate the K_{ow}. Since the octanol–water partition coefficient has long been known as an "additive–constitutive" property (Petrauskas and Kolovanov, 2000), the ACD/log P software uses the basic approach of "group contribution", which is valid among different chemical classes and in a large range of log K_{ow} values. If a metabolic process effectively "removes" a group of atoms and "inserts" a different one, the overall lipophilicity change will depend only on the difference between the contribution of both group. For this assumption, each regression is expected to have a slope of exactly one, as the difference is independent of the total lipophilicity of the molecule. In other words, Eq. (1) can be considered in terms of a Hammett equation: $\log(K_{ow(metabolite)}/K_{ow(parent)}) = b$. In this equation K_{ow} coefficients are equilibrium constants which can be related to free energies of solvation by simple thermodynamical laws. Thus, the difference between log K_{ow} becomes the difference between free energies of solvation of the metabolite and parent compound. The intercept "b" is negative when $K_{ow(metabolite)} < K_{ow(parent)}$ and positive when $K_{ow(metabolite)} > K_{ow(parent)}$. In Hammett terms ("total electronic effect") this means that the insertion of an oxygen atom or link has a favoring or disfavoring electronic effect on the solvation by water. Usually, this insertion favors the water solubility for several reasons: raised molecular volume, raised H-bond basicity, raised polarizability, etc. Thus, the intercept "*b*" is expected to be negative for the oxidation reactions considered in our study.

We set up nine validation regressions using experimental log-K_{ow} values and analyzed their similarity to the regressions with predicted log K_{ow}. The p_{ancova} resulting from the analysis of covariance (Table 2) confirmed the homogeneity between the two types of regressions, with the exceptions of aromatic hydroxylation and the regressions for ADH, with $p_{ancova} < 0.05$. Fig. 2a and f shows deviations for two data points: pyridine and methanol (experimental log K_{ow} values), undergoing aromatic hydroxylation and alcohol oxidation, respectively. It is interesting to note that formaldehyde presented a deviation in the regression for ALDH compounds with experimental log K_{ow} data (Fig. 2h). Formaldehyde (CH_2O) and

Table 2
Characteristics and statistical parameters of metabolite versus parent compound log(K_{ow}) regressions with slope a and intercept b. LogK_{ow} are experimental values.

Metabolic reaction	Chemical class of parent compounds	n	LogK_{ow} range of parent compounds	$a \pm SE$	95%CI[a] a	$b \pm SE$	95%CI[a] b	r^2	SE	p[b]	p_{ancova}[c]
Reactions mediated by P450 enzymes											
General regression (hydroxylation, epoxidation, heteroatom (N, S) oxygenation)		26	0.65; 6.50	0.84 ± 0.09	0.66; 1.01	−0.86 ± 0.25	−1.38; −0.35	0.80	0.60	<0.01	0.28
Hydroxylation		17	0.65; 4.66	0.79 ± 0.13	0.51; 1.07	−0.65 ± 0.35	−1.40; 0.09	0.71	0.59	<0.01	0.07
Aromatic	Aromatic hydrocarbons, heterocyclic compounds.	10	0.65; 3.72	1.40 ± 0.16	1.03; 1.76	−1.52 ± 0.31	−2.23; −0.80	0.91	0.41	<0.01	<0.01
	Without pyridine	9	0.90; 3.72	1.23 ± 0.13	0.92; 1.55	−1.13 ± 0.27	−1.77; −0.48	0.92	0.31	<0.01	0.04
Aliphatic	Aliphatic hydrocarbons (alkanes), aromatic hydrocarbons, cyclic compounds.	7	2.49; 4.66	0.61 ± 0.13	0.28; 0.94	−0.35 ± 0.44	−1.48; 0.77	0.82	0.23	<0.01	0.06
Epoxidation	Aromatic hydrocarbons, aliphatic hydrocarbons (alkenes), cyclic alkenes, vinyl halides.	5	1.13; 6.50	1.03 ± 0.07	0.82; 1.24	−1.64 ± 0.25	−2.42; −0.86	0.99	0.28	<0.01	0.10
Reactions mediated by ADH enzymes											
General regression		14	−0.77; 2.90	0.74 ± 0.10	0.52; 0.97	0.17 ± 0.13	−0.13; 0.46	0.82	0.37	<0.01	0.01
Oxidation of primary alcohols to aldehydes	Aliphatic hydrocarbons (primary alcohols, allylic alcohols, glycols, glycol ethers, halohydrins), benzyl alcohols.	8	−0.77; 2.03	0.74 ± 0.15	0.38; 1.09	0.34 ± 0.17	−0.07; 0.75	0.81	0.39	<0.01	0.02
	Without methanol	7	−0.31; 2.03	0.94 ± 0.12	0.64; 1.24	0.08 ± 0.14	−0.28; 0.45	0.93	0.29	<0.01	0.31
Oxidation of secondary alcohols to ketones	Aliphatic hydrocarbons (secondary alcohols, cyclic compounds)	6	0.05; 2.90	0.91 ± 0.04	0.80; 1.02	−0.26 ± 0.06	−0.43; −0.10	0.99	0.09	<0.01	0.04
Reaction mediated by ALDH enzymes											
Oxidation of aldehydes to acids	Aliphatic hydrocarbons (aldehydes), benzyl aldehydes.	9	−0.34; 1.90	1.14 ± 0.19	0.70; 1.58	−0.09 ± 0.21	−0.59; 0.41	0.84	0.41	<0.01	0.21
	Without formaldehyde	8	−0.34; 1.90	1.03 ± 0.11	0.76; 1.30	0.11 ± 0.13	−0.21; 0.44	0.94	0.24	<0.01	0.62

[a] Confidence interval for the parameter at 95% confidence.
[b] p-Value of statistical significance testing.
[c] p-Value of statistical homogeneity of regression testing.

methanol (CH_3OH) are the simplest aldehyde and the simplest alcohol, respectively. Thus, these molecules may not adhere to general trends because of their small size. In order to test the sensitivity, regressions were developed removing pyridine, methanol and formaldehyde from their respective datasets with experimental logK_{ow}. The results are reported in Table 2: the fit was improved, as well as the homogeneity of the regressions (higher p_{ancova}).

4.2. Intercepts

The regression lines reflect an increase (intercept > 0) or decrease (intercept < 0) of the lipophilicity after biotransformation. The oxidation reactions of alcohols and aldehydes did not lead to a significant lipophilicity change, having intercepts of about zero. While this may be at odds with the high metabolic rates usually noted for alcohols (Klaassen, 2008), one has to keep in mind that this hydrophobicity trend allows the reverse reduction of aldehydes to alcohols driven by the alcohol dehydrogenase (Kollock et al., 2008). Furthermore, the majority of acids deprotonate at cytosolic pH, the ionic form being more water-soluble, thus more easily excretable.

The decrease in lipophilicity differed for the single reactions mediated by CYP enzymes. Hydroxylation and epoxidation reduced the lipophilicity by one order of magnitude ($b = -0.97$ and $b = -1.04$, respectively). Dihydroxylation and sulphoxidation reduced the K_{ow} by two orders of magnitude ($b = -1.97$ and -2.02, respectively). The two orders of magnitude difference for sulphoxidation was confirmed by a similar study on the oxidation of alkyl sulphides (Caron et al., 1997). Experimental logK_{ow} values of eight phenyl and biphenyl alkyl amines (tertiary) were a linear function of their N-oxidized metabolites in a neutral form, with $r^2 = 0.93$ and $p < 0.01$ (Caron et al., 1999). Caron et al. concluded that the neutral N-oxides had a logK_{ow} value lower than that of the parent amine by a factor ranging from 2.61 to 2.77. This decrease is higher than those observed with our correlations, due to the differences in chemical structure with respect to the chemicals in this study's dataset. We analyzed the N-oxygenation of primary and secondary amines to hydroxylamines, which is the only reaction mediated by CYP enzymes that cause no change in logK_{ow}, with the intercept close to zero. Overall, logK_{ow} was shown to be reduced by one unit for chemicals that are typically metabolized by CYP, the intercept being −1.13. The biotransformation reactions considered in the present study are the more common reactions mediated by CYP enzymes.

The excretion of stable compounds decreases with hydrophobicity (Hendriks et al., 2001). Vice versa, a reduction of the K_{ow} by biotransformation will thus enhance elimination to an extent that may be anticipated by the same relationship (Fig. 1). Obviously, empirical confirmation by future studies is needed. As metabolism rates are hard to anticipate with existing methods,

we feel that the present paper provides the first necessary step in an alternative approach (van der Linde et al., 2001).

5. Conclusions

Comparisons of lipophilicity and preliminary discussions on their significance play a key role in understanding the natural logic of metabolism. The present study shows that the $\log K_{ow}$ is reduced by a factor that varies between 0 and −2, depending on the metabolic pathway. The magnitude of the reduction can be anticipated by analyzing the way the K_{ow} is calculated. Knowing the magnitude of the reduction is a first necessary step in an alternative approach to estimating biotransformation rates.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2012.03.033.

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