# Design of Sustainable Chemical Products—The Example of Ionic Liquids

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## *Contents*



## *1. Introduction*

Striving for a sustainable development is a necessary task for mankind. Even if it might appear unrealistic to achieve sustainability looking at the rates at which rain forests are being harvested and the global climate is changing, there is an ethical imperative that as much life as possible should continue.[1] The globalized economy and global society have intimate ties with chemical products and processes. Because of these close relationships and because of some well-known adverse interactions of chemical products and processes with global ecology, chemistry is explicitly addressed in Agenda 21,[2] which was a result of the UN conference on Environment and Development in Rio de Janeiro held in 1992.

Chemical industry, governments, academia, and nongovernmental organizations (NGOs) have taken different approaches to address the challenges at the interface of chemistry and sustainability. Among them are the principles of green chemistry,[3] the global Responsible Care initiative by the International Council of Chemical Associations (ICCA), and the OECD conferences on sustainable chemistry. Further, national laws and international conventions on the regulation of chemical products and processes address the sustainability of chemistry, as well as public-awareness actions of NGOs concerning specific products or production sites.

One of the tasks in striving for sustainable chemistry is the development of sustainable chemical products. So far, few case studies of risk-conscious design,[4] reviews of sustainable design strategies,[5−7] and textbooks for university teaching[8−10] provide some guidance as how to proceed in this emerging field. However, current authors in the field of green chemistry are not necessarily aware of the variety and difficulty of the questions that need to be addressed for a sustainability assessment.[11]

Figure 1 shows an idealized diagram of a cyclic design process for sustainable chemical products. This diagram supposes that a technical purpose exists, which is to be fulfilled by the substance to be found. It should be noted that in the case of ionic liquids (ILs) this is not always the case, as synthesis routes to new ILs are frequently published without a clear-cut technical purpose. Therefore, we have to keep in mind that the sustainability of an ionic liquid is strongly dependent on the purpose of the technical process in which it is applied. Without a definition of its technical purpose, it is impossible to fully characterize a development process as a sustainable one.

For a given technical application, the sustainable design process sketched in Figure 1 can be applied. Its first main message is the equal importance attributed to testing of the application specific performance of a substance, its potential impact on human health, and its potential impact on the environment. Results from testing in all three categories have to be equally respected in the iterative process of substance selection.

The second main message is the importance of an evaluation procedure, generating a synopsis of the available information, and reflecting it with regard to decisions to use or not to use certain substances for a specific purpose. On this level, it has to be ascertained that economical, social, and ecological aspects are being equally and adequately taken into account.

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Stefan Stolte finalized his studies in Chemistry and Biochemistry in 2004. His diploma thesis in the department of Prof. Dr. Bernd Jastorff dealt with the metabolism of ionic liquids. At the moment, he is working as a Ph.D. student at the Center of Environmental Research and Technology in the fields of (eco)toxicity, biodegradation, and analytical methods for ionic liquids.

Reinhold Störmann received his Ph.D. on transformation of structurally related compounds by the monooxygenase system of the liver from the University of Bremen in 1988. During a postdoc position at the University of Bremen, he worked on metabolization of environmental chemicals. In 1992 he conducted an internship at the National Institute of Health in Bethesda, MD. He received further training as an IT-specialist for natural sciences and founded the CHEOPS GmbH in 1994, working as director and software engineer with chemical databases. His main interests are applications of T-SAR, xenobiotic metabolism, and ionic liquids.

Jürgen Arning graduated in Chemistry and Biochemistry in the group of Prof. Dr. Detmar Beyersmann at the Center for Biomolecular Interactions at the University of Bremen in 2004. Since then, he has been working as a Ph.D. student in the group of Prof. Dr. Bernd Jastorff at the Center of Environmental Research and Technology at the University of Bremen. His work is currently funded by a fellowship of the Deutsche Bundesstiftung Umwelt. His research is focused on enzyme inhibiton, cytotoxicity, and interactions of biocides and ionic liquids with biomolecules.

The focus of our review is on the right side of Figure 1 and is further specified below. Nevertheless, conclusions for technological applications, possible human health impacts, and economical and social implications may also be derived from the information given.

## 1.1. The Case of Ionic Liquids

Since the pioneering study of Wilkes and co-workers,[12] ionic liquids have not only become increasingly popular as reaction and extraction media in research and development, they have also widely been promoted as "green solvents", which can easily be verified by browsing the contents of a recent issue of the journal *Green Chemistry* or looking through the abstracts of recent conferences on green and/or sustainable chemistry. The rationale for calling them green generally consists of three arguments:

(i) their vapor pressure is generally negligible, and thus inhalative exposure of workers is reduced as compared to conventional molecular solvents;

(ii) they have been shown to be non-flammable, and thus the risk of fast, exothermic oxidations in the case of an accident is strongly reduced; and

(iii) they are claimed to be relatively nontoxic.

While these arguments are certainly important in the discussion, point iii, in particular, has been repeatedly challenged. Using them as a basis for calling ionic liquids green solvents raises several questions:

- What are boundary conditions and exceptions to the statements cited above?
- What additional aspects have to be taken into account?
- Do we have enough relevant data?
- How do green solvents relate to sustainable development?

Such questions have been posed before, leading to an early conference contribution named "Are ionic liquids green solvents?",[13] the definition of an assessment strategy and a preliminary assessment from our group,[14] the timely review "Ionic liquids: the neglected issues",[15] and a later view-

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point.[16] Important aspects of the greenness of ILs have been incorporated in recent articles by leading authors in the field.[17,18] However, given the number of studies on toxicity, degradation, and ecotoxicity of ionic liquids that have recently appeared, a review focusing on a comparative risk analysis of ionic liquids and conventional molecular solvents, as well as other comparable industrial chemicals, is warranted. We suggest that there are no short answers to the questions raised above. This review was written to systematically gather existing contributions to their answers.

It has become common, although not universally adopted, to define ionic liquids as liquids that are entirely composed of ions, with a melting point lower than 373 K (100 °C). The much smaller group of room-temperature ionic liquids (RTILs) exhibit melting points up to 298 K. In this review, we comprehensively consider molten salts with melting points up to 373 K that are published using the keyword ionic liquid(s), with full conscience of the fact that not all literature about chemical substances falling under our definition will be retrieved by this strategy.

We will use a random selection of conventional molecular solvents with their risk related properties as a reference throughout this article. Acetone has previously been chosen as a reference solvent.[19] Here, we additionally consider the commonly used solvents toluene, methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF), dichloromethane, and acetonitrile as references, where data are available. Another set of reference substances that are not functionally analogous to ILs, but have structural analogies, are ionic surfactants. While anionic surfactants are to our knowledge not typically used for their biological activity, there are many cationic quaternary ammonium compounds (QACs) that are used as sanitizing swimming pool additives[20] or as germicides and deodorizers[21] and which are known for their toxicities toward algae[22] and other organisms. Here, we have chosen benzalkonium chlorides, preferably benzyldimethylhexadecylammonium chloride (BDMAC), as reference substances. On a case by case basis, we also use other cationic or anionic surfactants as reference compounds for comparison.

We will reproduce the most informative literature data as numeric tabular material, but in many cases it will be sufficient to systematically summarize results and point the interested reader to the relevant sources. The exact coverage of this review is given by the substance group defined above, and the scope of the risk indicators is described in the following.

## 1.2. Current Ecotoxicological Risk Profiles of Ionic Liquids

Generally, risk analyses of chemical substances are carried out along the paradigm of comparing daily intake or exposure concentrations with reference doses or effect concentrations, respectively.[23] This concept of an absolute risk analysis requires that a certain minimal set of data about both exposure and effects of a chemical under scrutiny is available. Since the large majority of ILs is still in a very early phase in the development process of a new industrial chemical, it is not yet clear which of them will ever be produced on an industrial scale. Thus, a more flexible method of risk analysis is needed that can be applied to substances with sparse and heterogeneous data availability.

Such a method has been devised for a comparative risk evaluation of chemical substances based on five risk indicators forming ecotoxicological risk profiles for each substance.[24,25] These risk indicators and their interrelation with the development cycle of chemical substances are shown in Figure 2, and they will be introduced below. At the same time, this graph and the underlying concept of an ecotoxicological risk define the scope of this review. The technosphere simply stands for all technically controlled systems. An ecotoxicological risk is constituted by a potential release of chemical substances from any of these systems, if this release is under the influence of a conscious decision.

The decisions that we want to inform with comparative ecotoxicological risk profiles are generally decisions about the selection of chemical substances for a specific technical purpose. As the characteristics of a potential release are highly dependent on the type of technical application for which the substance is considered, it is impossible to derive ecotoxicological risk profiles that are valid for all the multitude of (potential) applications that have been described or will be described for ionic liquids. Therefore, this review can only aim to systematically gather and interpret the relevant information, so decisions on the use of ionic liquids can be made on a case by case basis.

### *1.2.1. Release*

Most information about potential releases due to the decision that a specific substance is being used will be application specific rather than chemical specific. However, there are certain intrinsic properties of chemicals that make a release more or less likely. One example of such a property is its vapor pressure, which has already been mentioned above. Furthermore, a risk relevant release from a technically controlled system can be caused not only by the substance itself but also by its impurities—products of thermal decomposition or of other transformation reactions within the technical system. The tendency of all of these to be released has to be taken into account.

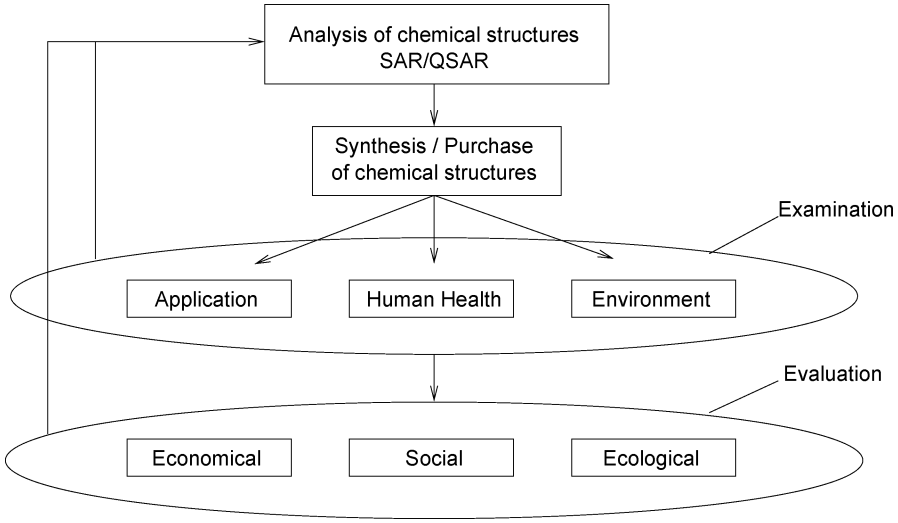


**Figure 1.** Iterative scheme for the development of sustainable chemical products. Adapted from ref 19.

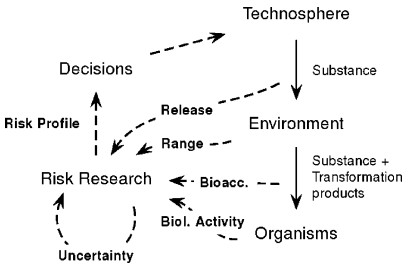


**Figure 2.** Graphical illustration of the risk management cycle and its correlation with the ecotoxicological risk indicators. Adapted from ref 25.

### 1.2.2. Spatiotemporal Range

*Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.*

Green Chemistry Principle[3] No. 10

The spatiotemporal range component of an ecotoxicological risk describes the tendency of the potentially released substance and its environmental transformation products to spread in space and time. The quantification of a spatiotemporal range is generally already a very complex task. As we have argued above, several substances can be released due to the application of one single substance (and all of them can be further transformed in the environment). But also the environment itself is made up of so many different chemical milieus, and there are so many possibilities for transport and reaction, that the term overcomplexity has been introduced as a property of environmental systems.[26] An operational definition that has been proposed earlier for the spatiotemporal range indicator is the joint residence time of the primary substance and its transformation products in a spatially and chemically defined environmental system, under the assumption of steady-state.[25] While this operationalization is equivalent to the definition of a joint persistence, as introduced by Fenner et al.,[27] the spatiotemporal range can alternatively be quantified by different ad hoc methods, as oftentimes either an appropriate environmental fate model is lacking or the substance specific data are not available.

### 1.2.3. Bioaccumulation

The bioaccumulation potential of a substance is frequently evaluated using either the partitioning constant between 1-octanol and water (log $K_{ow}$) or the bioconcentration factor (BCF), ideally describing the steady-state concentration in fish tissue in relation to the concentration in the surrounding medium. Neither 1-octanol nor living fish tissue is a really satisfying biochemically representative phase for living organic matter in the environment. Therefore, an alternative, more general definition of bioaccumulation has been proposed,[25] interpreting bioaccumulation as the quotient of the capacities of the global pool of living organic matter and the remainder of the natural environment. This capacity factor can be expressed by the quotient of the total mass of the substance including transformation products[28] in living organisms in steady-state, $m_{bio}$, divided by their steady-state mass in the environment, $m_{env}$. Using this definition for bioaccumulation, the available log $K_{ow}$ and BCF data of primary substances and transformation products will still be the most important input for its assessment. The reason is that frequently no other data are available. The remaining uncertainty caused by their limited significance for an evaluation of true bioaccumulation has to be kept in mind.

### 1.2.4. Biological Activity

*Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*

Green Chemistry Principle[3] No. 3

Green chemistry is often thought of as chemistry using nontoxic chemicals. This means in turn that toxicological expertise and practice must be an integral part of the competence of scientists working on green chemistry. In reality, some contributions to green chemistry do not mention risk related properties of the chemicals at all, or treat toxicity as if it were a physical property. This indicates that not all green chemistry authors are aware of the multitude of toxicological and ecotoxicological end points that can be used for an assessment of toxicity, mirroring the biochemical, biological, and ecological diversity of living beings.

Besides the large variety of different toxicological end points, it should be noted that it is advantageous to define risk indicators that are independent of each other. This means that instead of using the indicators bioaccumulation and toxicity, which generally correlate, biological activity is preferably defined as the activity of chemical substances that

are already taken up into an organism. The concepts of critical body residue, lethal body burden, internal effect concentrations, toxic ratio, and intrinsic toxicity[29−33] aim for such an assessment strategy. An operational definition of biological activity that fulfills this requirements, and has the further advantage of being additive, is the definition based on critical dilution factors $r^{crit}$, meaning the biomass needed to dilute a defined amount of substance to a level not producing any observable chronic effect. The biological activity of the released substances and their environmental transformation products is then defined as the weighted mean of the critical dilution factors of a chemical in all types of biomass taken into consideration. The weights are the fractions $f_{i,j}$ of substance $i$ in biomass type $j$, as expressed by

$$f_{i,j} = m_{i,j}/m_{bio}$$

where $m_{i,j}$ is the mass of substance $i$ in biomass type $j$ and $\Sigma_{i,j} f_{i,j} = 1$. Index $i$ covers the original substance as well as impurities and environmental transformation products (including metabolic transformation products that have been produced by other organisms), and the joint biological activity $A$ can then be defined by[28]

$$A = \log \Sigma_{i,j} f_{i,j} r^{crit}{}_{i,j}$$

As critical dilution factors are not available as such in the literature, they are approximated by subtracting bioaccumulation effects from toxicity or ecotoxicity data. This can generally only be done in a semiquantitative way. However, we feel that it is better to estimate relevant risk indicators than to work with less relevant data, even if they are more easily obtained and better defined.

#### 1.2.5. Uncertainty

The uncertainty indicator $U$ is defined as the resulting uncertainty from the evaluation of the four preceding risk indicators. While a quantitative measure has recently been proposed for the uncertainty indicator,[34] it will be sufficient in this review to regard the range of the perceivable indicator values for each substance for each indicator and to take the mean of these ranges as the overall uncertainty, as proposed earlier.[24,25]

### 1.3. Thinking in Structure−Activity Relationships (T-SAR)

The structural variety of ionic liquids, defined as compounds exclusively composed of ions that are liquid at temperatures below 100 °C, has been repeatedly pointed out. In order to reduce the complexity of this structural variety, we have proposed to use the structural elements "cation head group", "cation side chain(s)", and "anion" for a structural description.[35] If the influences of these structural elements on technical and (eco)toxicological risk indicators could be assessed in a general manner and independent of each other, they could be used for estimations of risk indicators for untested ionic liquids. It has even been proposed that specific technicophores, toxicophores, and ecotoxicophores may be identified,[19] as substructures that are responsible for the pertinent properties. In light of this terminology, it is interesting to ask if technicophores and (eco)toxicophores are sufficiently distinct from one another so that they can be independently optimized.

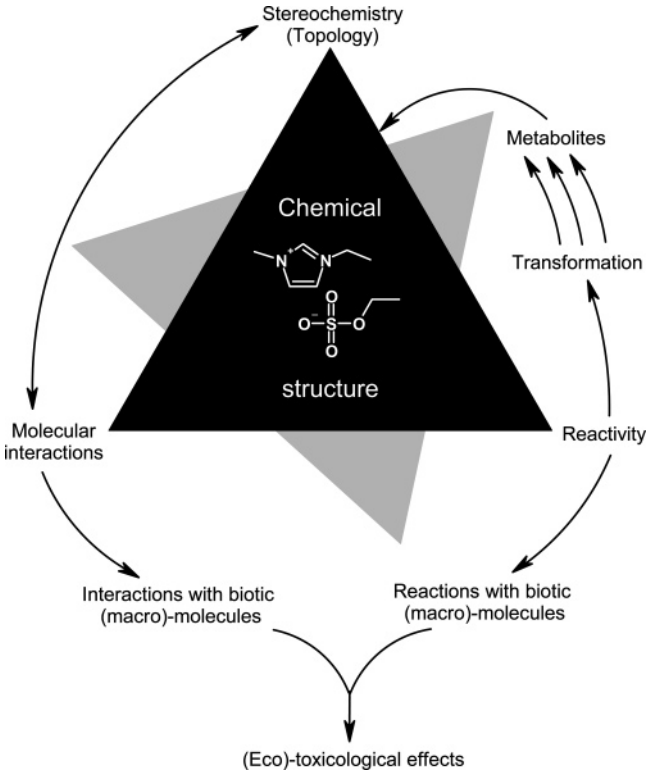


**Figure 3.** Structure−activity relationship (SAR) triangle. Adapted from ref 9.

The importance of stereochemistry, molecular interaction potentials, and reactivity for structure−activity relationships has been illustrated in the structure−activity relationship (SAR) triangle, as shown in Figure 3. It also shows the indirect influence of reactivity via transformation products (metabolites) and via interactions with biological macromolecules.

If we imagine the enormous amount of resources that would be needed to test each substance in each potentially relevant test system, the advantage of obtaining generalized knowledge along these lines becomes obvious. Therefore, in addition to the review of the published information available on each of the risk indicators listed above, we will report to what degree this information has been or can be rationalized in terms of such structure−activity relationships.

Many structure−activity relationships either are linear free energy relationships (LFERs) or are closely related to them. The potential reduction of evaluation complexity that can be offered by single parameter LFERs such as the well-known narcosis QSARs for aquatic toxicity, but also by more elaborated free energy relationships leading to concepts such as the critical body residue or to multiparameter LFERs, leads us to focus our attention on studies allowing for conclusions related to such theories.[29,30,36,37]

In summary, we propose to compare ionic liquids to organic solvents and ionic surfactants regarding five risk indicators:

- release,
- spatiotemporal range,
- bioaccumulation,
- biological activity, and
- uncertainty

In this process, thinking in structure−activity relationships (T-SAR) is used in order to gather risk relevant information that is as general as possible.

## 2. Release from Technical Systems

Of the five ecotoxicological risk indicators defined above, the release indicator is the one whose evaluation suffers most from lacking knowledge about the technical systems in which the ionic liquids will be used. Therefore, it is only possible at this point to summarize the characteristics of certain ILs which will influence their potential release from technical systems.

One of the most important scenarios of ionic liquid application in general is its use in chemical production processes. From the above definition of the release indicator, the solid waste stream will not directly contribute to the release, since it will either directly go to a landfill or end up as slag/ash after incineration. We assume the landfill to be an engineered landfill and thus a technically controlled system. Therefore, waste gas and wastewater are the release relevant streams, obviously stemming from a wide variety of technical processes, and they will be considered further. Additionally, a direct release of ionic liquids to soils, surface water, or groundwater could result from accidents, as soon as significant amounts of the ionic liquids are transported by rail, truck, or ships, or if they are incorporated in consumer products, which are generally subject to considerably less technical control than chemical processing facilities.

### 2.1. Gaseous Release

In general, ionic substances are not expected to occur in gaseous phases, and therefore, ionic liquids are not expected to occur in gaseous waste streams or other gaseous releases. It has recently been shown that ionic liquids do occur in the gas phase, based on the observations that three 1-alkyl-3-methylimidazolium bis(trifluoromethyl)sulfonylimides (bistriflamide) could be distilled at 200−300 °C and 0.1 mbar at appreciable rates and also that several other ILs, including tetraalkylammonium bistriflamides (where a proton transfer from cation to anion and thus a transport via uncharged molecular species is not conceivable), were distilled at unpublished rates under similar conditions.[38] However, a waste gas stream operating at such conditions will hardly occur, so a release by this mechanism seems unlikely. It has also been shown that, for 1-ethyl-3-methylimidazolium chloride−$AlCl_3$ systems with a high excess of $AlCl_3$, the neutral species $Al_2Cl_6$ exerted a measurable vapor pressure above 193 °C.[39] Of course it can be argued that such a liquid is not strictly an ionic liquid any more, because of the presence of the neutral $Al_2Cl_6$ species. In the case of an operation of such melts at such elevated temperatures, this release pathway has nevertheless to be kept in mind.

In the latter case, the ions making up the ILs are not vaporized, but rather the neutral products of an equilibrium reaction are affected by elevated temperatures. Just as ionic liquids can directly be obtained by reaction of a base (most often an amine base) and a (possibly functionalized) alkyl halide in an equilibrium reaction, this equilibrium can simply be shifted toward the reverse direction at high temperatures, leading back to a base and the organohalide. For the case of some tetraalkylammonium ILs, strong indications for such an equilibrium shift have been reported.[40] Investigations of volatile emissions from ionic liquids at temperatures from 180 to 250 °C carried out in our own group (unpublished results) have shown that anions with moderate nucleophilicity, such as chloride, tetrafluoroborate, and bromide, statistically produce an increase in volatile compounds, detected by flame ionization detection as pentadecane equivalents, between 15 and 70 mg/g, while methylsulfonate, butylsulfonate, octylsulfonate, trifluorotris(pentafluoroethyl)-phosphate, and bis(pentafluoroethyl)phosphinate did not show such an influence. It has to be noted, however, that the anion type only explained around 20% of the total variability in volatiles in these analyses, which seems mainly to be due to differences in washing, drying, and other purification steps. Other observations pointing to decomposition reactions involving nucleophilic halide species are the dependence of the thermogravimetric onset temperature on the anion type[41] as well as the susceptibility of the 1-butyl-3-methylimidazolium cation to reaction with several organic nucleophiles.[42] Also, the cation type and, at least in the case of the hexafluorophosphate anion, the presence of aluminum have an influence on the thermal stability.[41] These observations and the fact that long-term, isothermal thermogravimetric analyses have shown that decomposition to volatiles does occur, e.g., for 1-ethyl-3-methylimidazolium tetrafluoroborate at 0.013 wt %/min at 250 °C,[17] clearly show that gaseous release from ionic liquids has to be taken into account at elevated process temperatures. A comprehensive overview of thermal degradation processes has been given in the recent review by Scammels et al.[15]

### 2.2. Ionic Liquids in Wastewater

Wastewater from chemical production processes, as well as landfill leachate, will in general be subject to wastewater treatment. For wastewaters carrying organic carbon, a biological unit is commonly used. Other common treatment processes are wet oxidation and reverse osmosis. While the retention of the relatively large ions used in ionic liquids in reverse osmosis processes does not seem problematic, their complete removal from wastewater streams by wet oxidation is less obvious. Stepnowski and Zaleska investigated three different advanced oxidation processes for the degradation of 1-alkyl-3-methylimidazolium cations. The best results were obtained with a combination of UV light and 0.5% hydrogen peroxide, where 85% of 1-butyl-3-methylimidazolium was removed after 360 min.[43] Morawski et al. investigated the oxidation of a larger variety of ionic liquids under the influence of UV light and in the presence of $TiO_2$ and found removal rates between 30 and 73% total organic carbon, as well as some structural influence of alkyl chain length, functional groups, and anion type on removal efficiencies.[44] Pernak and co-workers have also reported on the possible removal of conventional quaternary nitrogen ILs, alkoxy-3-methylimidazolium and dialkoxyimidazolium ILs, by oxidation with $KMnO_4$, with a permanganate index ranging from 1.4 (*N*-butyl-4-methylpyridinium tetrafluoroborate) to 11.1 (1,3-di(pentyloxymethyl)imidazolium tetrafluoroborate). Apparently, the anions are not oxidized under these conditions and the water immiscible dialkoxyimidazolium bistriflamides prevented measurement of the permanganate index.[45] It might be interesting to note that the permanganate index is generally used for the determination of the quality of potable and surface water. Since 3 mmol of each ionic liquid was used, the permanganate index indicates the amount of oxidizable carbon in each cation/anion combination, which easily explains the observed chain length dependency but puts the relevance of the permanganate index for wastewater treatment into question, since it was not related to the theoretically possible consumption of oxidizing agent. Nevertheless, we generally assume that any

remaining oxidation products are more hydrophilic and less toxic than the original cations. We are not aware of removal methods proposed for largely hydrolytically stable ionic liquid anions such as bistriflamide and trifluorotris(pentafluoroethyl)phosphate. Very recently, Li et al. have reported the chemical oxidation of 1,3-dialkylimidazolium ionic liquids by hydrogen peroxide assisted by ultrasonic irradiation.[46] They observed nearly 99% conversion at 50 °C after 72 h, which was independent of the side chain length (ethyl to hexyl) and the anion ($Cl^-$, $Br^-$, $BF_4^-$, and $PF_6^-$). They also identified degradation products via GC-MS, and they propose a mechanistic pathway to the final degradation products such as acetoxyacetic acid and biurea.

Concerning biological wastewater treatment, continuous (CAS) and semicontinuous (SCAS) activated sludge tests have been devised to test the elimination of organic chemicals in such treatment facilities.[47] The only information available about the behavior of ionic liquids in such tests is actually on surfactants that seem to have a melting point lower than 100 °C (see above) but are not known as ionic liquids. For example, benzyldimethylhexadecylammonium chloride was completely eliminated in the "coupled units test" (OECD 303 A, before revision in 2001) up to an effluent concentration of 1 mg/L, with an elimination rate still reaching 77% at 20 mg/L effluent concentration[48] (consistent with earlier work by Gerike et al.). It has to be noted, however, that these tests include a sludge separation step to simulate the sludge separation step in full scale facilities.[47] Therefore, elimination in these tests is due to both sorption and degradation. Generally, data on the removal of QACs in wastewater treatment have shown that the removal of nontoxic levels should exceed 90%.[21] Although a fairly extensive degradation of benzyldimethylhexadecylammonium under somewhat optimized conditions has been shown by radioactive labeling,[49] it has been found by measurements[50] and modeling[51] that removal by sorption could account for 8−29% for benzyldimethylhexadecylammonium bromide, benzyldimethyldodecylammonium chloride, and benzyldimethyldecylammonium chloride[21] or for 9.5−71.2% for di(hydrogenated tallow)−dimethyl ammonium chloride.[52] Such removal by sorption would lead to anaerobic sludge processing, incineration, or landfilling of the residual material. If it is assumed that these post-treatment processes are technically controlled to a high degree and releases from them are negligible, we still have to assume a release of up to ten percent of the ammonium cations from ILs entering wastewater treatment facilities via their effluent water. This percentage could also be higher in several cases:

Toxic levels of ionic liquid cations with one or more long alkyl chains may be reached to which the sludge microorganisms are not acclimated. Wells and Coombe have recently shown that the ILs 1-hexadecyl-3-methylimidazolium chloride, 1-octadecyl-3-methylimidazolium chloride, and trihexyltetradecylphosphonium chloride and ECOENG(R) 500 inhibited glucose/glutamate biodegradation of sludge bacteria to 100% at 10, 1, 10, and 10 mg/L, respectively.[53] At these levels, toxicity of benzalkonium toward sludge metabolic capacity has been observed, if no acclimation was performed.[48] This is consistent with the observation[54] that while the cytotoxicity of a large variety of typical ionic liquid cations is generally lower than the cytotoxicity of benzalkonium cations, the cytotoxicity of the trihexyltetradecylphosphonium, octylchinolinium, 1-decyl-3-methylimidazolium, and 1-decyl-2-ethylimidazolium cations (and longer chain imidazolium cations; see the section on biological activity below) is comparable to that of benzalkonium chloride ($EC_{50}$ values smaller than 10 $\mu$M). We suggest that these cytotoxicity values are proxy measures also for toxicity toward microorganisms, as they correlate well with inhibition of luminescent bacteria.[55,56] Further evidence that sludge microorganisms could be inhibited by long chain ionic liquid cations is provided by the studies of Pernak and co-workers, showing that some long chain ionic liquid cations, among them the 1-dodecyloxymethylimidazolium cation, reach the same level of antimicrobial activity as benzalkonium chloride, when judged by their minimum inhibitory concentrations against Gram-positive cocci.[57] While the analogy to QACs suggests that under normal circumstances they are unlikely to pose a significant risk of toxicity to microorganisms in wastewater treatment systems, a sudden increase in levels of toxic ILs in wastewater could affect sludge microorganisms and lead to a breakthrough, similar to the case proposed for QACs.[21]

The second possibility of higher release rates than 10% of the influent would be a significantly lower sorption of the ILs as compared to the case of typical cationic surfactant QACs. For many ionic liquid cations, this seems quite likely, since, in principle, lipophilicity dominates sorption to organic matter, and their lipophilicity as established by gradient HPLC is generally much lower than that of benzalkonium cations, with the exception of trihexyltetradecylphosphonium, which showed higher lipophilicity.[54]

A third possibility of increased release rates would be a lower inherent biodegradability of the ionic liquid cations as compared to typical QACs. The term "inherent biodegradability" (OECD tests 301 A-F) is used in contrast to "ready biodegradability" (OECD tests 302 A-C). Testing for inherent biodegradability is less stringent than that for ready biodegradability, because either the inoculum is allowed to acclimate to the tested substance, or the amount of inoculum is higher, or both. While we are not aware of any data on inherent biodegradability of ionic liquids, several publications have reported results from tests for ready or even ultimate biodegradability.[53,58−62] This information is summarized in Table 1, together with data for two surfactants and five conventional solvents for comparison. It must be noted that none of these studies investigate toxicity during the incubation period, so the possibility of a toxification by metabolization has not been empirically excluded in any of these cases.

Comparison of IL degradability with the degradability of one of the main compounds in benzalkonium chloride, benzyldimethyldodecylammonium chloride, shows that while conventional ionic liquid cations with unmodified alkyl groups as side chains generally are less biodegradable than this compound, the degradability of the imidazolium ILs with ester side chains reaches a similar level. Imidazolium ILs with an ester side chain and the octylsulfate anion that were specifically designed for degradability can even be classified as ultimately biodegradable, since $CO_2$ evolution reaches levels higher than 60% of the theoretical maximum.[61] Together, the data suggest that only the ester side chain and the octylsulfate are degraded in the 28 ready biodegradability test, while the imidazolium ring seems to stay intact under these conditions. This is confirmed by the recent study of Docherty et al.,[62] showing that 1-alkyl-3-methylimidazolium ILs are not readily biodegradable and can only be partially mineralized, even if extending the incubation period past the standard 28 days. NMR analyses showed that the imidazo-

**Table 1. Biodegradability of Ionic Liquids in Ready Biodegradability Screening Tests Using Activated Sludge in Comparison to Surfactants and Conventional Solvents**

| name | closed bottle OECD 301 D | $CO_2$-headspace ISO 14593 | others |
|---|---|---|---|
| 1-butyl-3-methylimidazolium hexafluorophosphate | 0%[59] | | 0%[a] |
| 1-butyl-3-methylimidazolium tetrafluoroborate | 0−3%[59,61] | 0−3%[61] | |
| 1-butyl-3-methylimidazolium bromide | 0−3%[59,61] | 0−3%[61] | 0%[b] |
| 1-butyl-3-methylimidazolium chloride | | | 0%[a] |
| 1-butylpyridinium chloride | | | 0%[b] |
| 1-hexyl-3-methylimidazolium bromide | | | 54%[b] |
| 1-octyl-3-methylimidazolium bromide | | | 41%[b] |
| 1-butyl-3-methylpyridinium bromide | | | 0%[c] |
| 1-hexyl-3-methylpyridinium bromide | | | ∼50%[b,c] |
| 1-octyl-3-methylpyridinium bromide | | | 96%[b] |
| methyltrioctylammonium bistriflamide | | | 0%[a] |
| ethyltributylphosphonium diethylphosphate | | | 9%[a] |
| 1-[(3-propyloxy)-2-oxoethyl]-3-methylimidazolium bromide | | | |
| 1-[(3-propyloxy)-2-oxoethyl]-3-methylimidazolium tetrafluoroborate | | | |
| 1-[(3-alkyloxy)-2-oxoethyl]-3-methylimidazolium bromide, alkyl = methy, ethyl, propyl | ∼16−22%[59] | | |
| 1-[(3-alkyloxy)-2-oxoethyl]-3-methylimidazolium bromide, alkyl = butyl, pentyl, hexyl, octyl | ∼28−32%[59] | | |
| 1-butylcarbamoylmethyl-3-methylimidazolium bromide | ∼0%[59] | | |
| 1-[(butylmethylcarbamoyl)methyl]-3-methylimidazolium bromide | ∼0%[59] | | |
| 1-dimethylcarbamoylmethyl-3-methylimidazolium bromide | ∼0%[59] | | |
| 1-butyl-3-methylimidazolium salts: bromide, tetrafluoroborate, hexafluorophosphate, bistriflamide, dicyanamide | <5%[60] | | |
| 1-butyl-3-methylimidazolium octylsulfate | 25%[60] | | |
| 1-[(3-propyloxy)-2-oxoethyl]-3-methylimidazolium salts: bromide, tetrafluoroborate, hexafluorophosphate, bistriflamide, dicyanamide | ∼10−34%[60] | | |
| 1-[(3-propyloxy)-2-oxoethyl]-3-methylimidazolium octylsulfate | 49%[60] | | |
| 1-[(3-propyloxy)-2-oxoethyl]-3-methylimidazolium bromide | 24%[61] | 24%[61] | |
| 1-[(3-propyloxy)-2-oxoethyl]-2,3-dimethylimidazolium bromide | 23%[61] | nd | |
| 1-[(2-pentyloxy)-2-oxoethyl]-3-methylimidazolium bromide | 32%[61] | 41%[61] | |
| 1-[(2-pentyloxy)-2-oxoethyl]-2,3-dimethylimidazolium bromide | 33%[61] | nd | |
| 1-[(3-propyloxy)-2-oxoethyl]-3-methylimidazolium octylsulfate | 49%[61] | 64%[61] | |
| 1-[(3-propyloxy)-2-oxoethyl]-2,3-dimethylimidazolium octylsulfate | 55%[61] | 62%[61] | |
| 1-[(2-pentyloxy)-2-oxoethyl]-3-methylimidazolium octylsulfate | 54%[61] | 67%[61] | |
| 1-[(2-pentyloxy)-2-oxoethyl]-2,3-dimethylimidazolium octylsulfate | 56%[61] | 61%[61] | |
| sodium dodecylsulfate | ∼70%[59,60], ∼80%[61] | ∼90%[61] | |
| benzyldimethyldodecylammonium chloride | | | ∼50%,[d] ∼80%[e] |
| acetone | | | ∼70−80%[f] |
| acetonitrile | | | 30−100%[g] |
| dichloromethane | | | 0−92%,[126] completely[76] |
| *tert*-butyl methyl ether | | | ∼ 1%[76;126] |
| tetrahydrofuran | | | 0−64%[77] |

[a] Manometric respirometry test (OECD 301 F).[53] [b] DOC die-away test (OECD 301).[62] [c] Initial concentration 10 mg/L.[48] [d] 97% after 38 days. [e] Initial concentration 2.5 mg/L.[48] [f] Incubation time > 5 days.[76] [g] Incubation time > 5 days.[77]

lium ring remained intact while the hexyl and octyl side chains were partially degraded. In this study, it was also shown that 1-octyl-3-methylpyridinium bromide is readily biodegradable according the OECD definition, and they could show that the pyridinium ring was metabolized. They found no evidence of metabolization of 1-butyl-3-methylpyridinium bromide.

Some additional information is available on the biodegradability of typical ionic liquid anions in wastewater treatment facilities. Sodium dodecylsulfate (SDS) is used as a readily biodegradable reference in screening tests, and SDS as well as alkyl sulfonate were consistently biodegradable in a method comparison study.[63] Similarly, sodium methyl sulfate was found to be biodegradable.[53] Furthermore, from the data in Table 1, the positive influence of the octylsulfate anion on biodegradability is obvious. On the other hand, biodegradation of the free acid of the bistriflamide anion was not observed,[53] and biodegradation of tetrafluoroborate and hexafluorophosphate anions is not to be expected.

Overall, a potential release of ionic liquid cations and anions from wastewater treatment facilities cannot be excluded based on the currently available information. We have to note that, in particular, the commonly used 1-butyl-3-methylimidazolium cation will likely not be retained in common wastewater treatment facilities, because of its low hydrophobicity and low biodegradability. Also, inorganic anions such as tetrafluoroborate and hexafluorophosphate might not be sufficiently retained, because of their lack of biodegradability and unknown sorption to sewage sludge.

## 2.3. Accidental Releases to Soil or Water

As the third major potential release pathway, the accidental release of the pure ionic liquid has to be taken into account. The probability of such a release will mainly be dependent on factors that are not specific to ionic liquids. However, the probability of accidents with ILs that tend to decompose to gaseous products such as, e.g., bis(trifluoromethyl)imide

ILs (personal communication by N. V. Ignat'ev) will be elevated because of the potential of a pressure buildup.

### 2.4. Uncertainty of Release Estimates

As mentioned above, the evaluation of the release of ionic liquids suffers from a lack of information about the exact future use scenarios of ionic liquids. However, it was illustrated that, depending on the thermal stability and the presence of nucleophiles, gaseous releases from ILs can occur at elevated temperatures and that there is a potential release of ILs via wastewater treatment that (a) are highly toxic to sewage sludge microorganisms, or (b) are weakly sorbing to sewage sludge, or (c) possess a low biodegradability, or (d) show a combination of these factors. Even in the case of the methylimidazolium octylsulfates with an ester side chain, the release of an environmentally relevant refractory degradation product of the cation cannot be excluded, noting that the $CO_2$ evolution only surpasses 60% in combination with the readily biodegradable octylsulfate anion.

## *3. Information Regarding the Spatiotemporal Range of Ionic Liquids*

The first task in evaluating the spatiotemporal range of a group of substances is to characterize their abiotic and biotic degradation pathways and kinetics in the various environmental systems. As gaseous releases from ionic liquids are a special case and the chemical composition of the potentially released gases is not known, we will not treat them further at this point, except that we note that they will add to their spatiotemporal range as well as to the uncertainty of their spatiotemporal range.

Ionic liquids themselves will mainly be released to surface water and soils. We therefore start with a summary of the knowledge which has become available on abiotic and biotic degradation in water and soil compartments. Then, the tendency to evade degradation processes by sorption to solid matter is described.

Generally, the ionic nature of the ionic liquid constituents will lead to a largely independent fate of cations and anions in natural environments, as soon as they have been dissolved in water.

### 3.1. Abiotic Hydrolysis of Ionic Liquid Constituents

It was an important step in the history of ionic liquids to overcome the hydrolytic instability of the chloroaluminate melts which directly preceded the era of todays ILs.[64] The $AlCl_3$-based anions in such melts have been largely replaced by a large variety of anions. Here we summarize information on hydrolysis that has been published on the most prominent anions in the ionic liquid literature. Of course, in the context of an ecotoxicological risk analysis, a remaining tendency to hydrolyze would be a positive feature, since it would reduce the spatiotemporal range of the anions in aqueous environments. On the other hand, the environmental relevance of hydrolysis products has to be evaluated, if they are not obviously harmless. Ionic liquid cations are generally not subjected to abiotic hydrolysis. There is, however, one report showing that the stability of 1-butyl-3-methylimidazolium chloride in aqueous solution is limited to the pH range from 6 to 10.[65]

The hexafluorophosphate anion has been characterized as hydrolytically stable in comparison to $AlCl_3$ systems[64] and also in comparison to $AsF_6$ and $SbF_6$ anions.[66] However, its hydrolysis has been proven by the presence of HF in the crystal structure of hexafluorophosphate ionic liquids and the formation of HF has been recognized as a risk by the group of R. Rogers.[67] Hydrolysis of the hexafluorophosphate anion has also been subject to earlier investigations in the context of Li $PF_6$ as an electrolyte for rechargeable batteries. A recent mechanistic study concludes that the hydrolysis of Li $PF_6$ is acid catalyzed and that the formation of HF during hydrolysis leads to acid conditions which autocatalytically increase the rate of hydrolysis.[68] This might be the cause for observations that glassware containing hexafluorophosphate ionic liquids can be punctually dissolved if hydrolysis occurs (Urs Welz-Biermann, personal communication). The study of Platovnik and co-workers also gives the hydrolysis products $PO_2F_2^-$ and $PO_3F_2^-$, which apparently are much more stable toward hydrolysis in weakly alkaline solutions.[68]

Two comparative studies of the hydrolytic stability of the hexafluorophosphate and tetrafluoroborate anions have found a faster hydrolysis of the tetrafluoroborate anion.[69,70] Baker and Baker have also included the anions trifluorotris(pentafluoroethyl)phosphate and bistriflamide into their comparative study, which were the most stable but still caused a pH shift at 50 °C.[70] Hydrolysis of bistriflamide ions would probably lead to the xenobiotic and possibly environmentally relevant trifluoromethylsulfonate anion. Ignat'ev et al. reported the hydrolytic stability of the trifluorotris(pentafluoroethyl)phosphate anion over 5 h at 100 °C.[71] Our own studies with oxoborate complexes as ionic liquid anions have shown that they are not stable in water. In particular, the bis[1,2-benzenediolato(2-)-*O*,*O*′]borate anion yields brown to black solutions, which we explain by the known autoxidative polymerization of the hydrolysis product catechol (unpublished results).

Finally, the hydrolytic instability of lower homologues of alkylsulfate anions at 80 °C led Wasserscheid and co-workers to choose the octylsulfate anion as a hydrolytically stable alternative to the halogen containing anions cited above.[18]

### 3.2. Photodegradation

Stepnowski and Zaleska have investigated the direct photolysis of 1-alkyl-3-methylimidazolium cations by UV irradiation. Using HPLC analysis of the cations, they found primary photodegradation between 15 and 55% after 6 h.

### 3.3. Biodegradation in the Environment

The data that have been generated on ready biodegradability and ultimate biodegradability was already discussed above in the context of IL degradability in wastewater treatment. Gathergood, Scammels, and co-workers have shown that 1-alkyl-3-methylimidazolium ionic liquids are better degradable if the alkyl chain is functionalized with an ester group. It must however be noted that the bromides of these cations are not readily biodegradable,[59−61] so it has to be assumed that, in the 28 day test, metabolites were formed that are refractory to some degree. While 1-butylpyridinium and 1-butyl-3-methylpyridinium bromides, as well as tributylethylphosphonium diethylphosphate, were not readily metabolized, the degradation of the pyridinium ring was shown for 1-octyl-3-methylpyridinium.[62] Among the quaternary ammonium compounds used as cationic surfactants, alkylpyridinium compounds have been found to be the least biodegradable, with generally lower biodegradability

than dialkyldimethylammonium and alkyldimethylbenzylammonium quaternaries, which are still less biodegradable than monoalkyltrimethylammonium quaternaries.[47] Summarizing IL cation biodegradability, we state that while several ionic liquid cations show low biodegradability, medium chain length alkylpyridinium cations seem to be good candidates for creating readily biodegradable ionic liquids.

Concerning the anions, methylsulfate and octylsulfate show the best biodegradability of the more frequently used IL anions. Research on anionic surfactants has shown[72] that linear alkylsulfates show excellent biodegradability, and linear alkylsulfonates show good biodegradability, as do linear alkylbenzene sulfonates, that are in use in high volumes as detergents but have also been used for the preparation of ionic liquids. No information was found on the chemical behavior of the typical fluorine-containing ionic liquid anions in organisms. The increased stability of the bistriflamide and the trifluorotris(pentafluoroethyl)phosphate anions toward abiotic hydrolysis and the fact that they do not contain structural features that are known to be biodegraded[47] suggest that these and similar anions will presumably not be biodegraded when released to the natural environment.

Comparison to conventional molecular solvents (Table 1) shows that MTBE is also not readily biodegradable in typical screening tests, while acetone, acetonitrile, and dichloromethane have been mainly found to be readily biodegradable under such conditions. It might be worthy to note that more detailed studies on the aerobic degradation of MTBE have shown that under certain conditions degradation can be observed, but the high release rates of this compounds in its function as a gasoline additive and its slow degradation in subsurface groundwater have caused concern (compare the review by Deeb et al.[73]).

## 3.4. Sorption to Minerals and Organic Matter

Only recently, a few studies of sorption of 1-alkyl-3-methylimidazolium cations to various materials important for their geochemical behavior were published. From the analogy to long-chain QACs, we expect that at least the long chain ionic liquid cations will show strong and rapid sorption to natural soils and sediments.[21] This behavior has actually been found in the so far most comprehensive study of Stepnowski,[74] who investigated the sorption behavior of 1-propyl-3-methylimidazolium, 1-butyl-3-methylimidazolium, 1-pentyl-3-methylimidazolium, 1-hexyl-3-methylimidazolium, and 1-butyl-3-ethylimidazolium cations applied as tetrafluoroborate salts. The highest sorption, with a $K_D$ value of 2467 L kg$^{-1}$, was found for the sorption of 1-hexyl-3-butylimidazolium to a sea sediment from the southern Baltic Sea. Also for the three investigated soil types, sorption of 1-hexyl-3-butylimidazolium was higher as compared to that of the other cations investigated. The author suggests that the influence of the mineral content of soils and sediments on sorption is more important than the influence of their content of organic matter. Matzke et al. have recently presented sorption experiments with different amounts of smectite and kaolinite added to a standard soil, supporting that both organic matter content and clay mineral content foster sorption of 1-butyl-3-methylimidazolium and 1-octyl-3-methylimidazolium to soils, while 1-octyl-3-methylimidazolium sorption was greater than 1-butyl-3-methylimidazolium sorption. In the same study it could be shown that addition of smectite, being an expanding lattice clay, increases sorption to soils more than addition of kaolinite. Similar differences have previously been observed in the older literature for QACs, although it is unclear if the mechanism of intercalation of QACs into swelling clay is also available to dialkyl quaternaries.[21]

It is commonly assumed that electrostatic interactions between negatively charged mineral surfaces and large organic cations mainly contribute to their sorption. It can be added that although the limited influence of soil organic matter content suggests that interactions with the soil organic matter do not significantly contribute to the sorption behavior,[74] the smaller water solubility and therefore the higher activity coefficient of the more lipophilic cations still explains the observed dependence of sorption strength on alkyl chain length. A further study of 1-butyl-3-methylimidazolium chloride sorption to bacteria, gibbsite (positive surface charge), quartz (negative surface charge), and montmorillonite revealed sorption only to the montmorillonite, with $K_D$ values of 1735 and 1133 L kg$^{-1}$ for ionic strengths of $10^{-1}$ and $10^{-4}$ M, respectively.[65] Very recently, Stepnowski et al. confirmed that sorption of the three cations 1-butyl-3-methylimidazolium, 1-hexyl-3-methylimidazolium, and 1-butyl-4-methylpyridinium to four different soil types is influenced by both cation exchange capacity and organic matter content.[75] They found sorption to exceed the cation exchange capacity in almost all cases, reflecting the contribution of the hydrophobic side chains to sorption that has been discussed by Schwarzenbach et al. (p 434)[36] using alkyl ammonium compounds as an example.

The sorption behavior of ionic liquid anions has not been studied to our knowledge. It is however to be expected that, because of the prevalence of negative surface charges in natural environmental media, sorption of the small anions will generally be much weaker.

Little data is available concerning sorption of conventional molecular solvents to soils and sediments, but it is assumed that sorption is rather low for acetone, acetonitrile, dichloromethane, tetrahydrofuran, and MTBE.[76,77]

## 3.5. Uncertainty in the Evaluation of the Spatiotemporal Range of Ionic Liquids

For a reliable evaluation of the spatiotemporal range of ionic liquids, several steps are necessary. First, spatial patterns of their release to the environment would have to be defined. Then a multicompartment model would have to be specified including the compartments most relevant for their potential environmental impact. Finally, the available data on transformation reactions and thermodynamic partitioning, including such data on any environmentally relevant metabolite (e.g., trifluoromethylsulfonate from anion decomposition; see above), would have to be fed to the model.

Both the application of adapted versions of one of the widely used models[78,79] and the use of tailor-made models for the case of ionic liquids (compare, e.g., a model proposed specifically for the global fate of antifouling biocides[80]) could be envisaged. Special attention would have to be paid to the fact that some of the more hazardous ionic liquid constituents will be surface active, so sorption to inner surfaces and other interfacial areas would be of primary importance. At current, no modeling attempts for assessing the spatiotemporal range of ILs in the natural environment have been carried out, resulting in a very high evaluation uncertainty, since the interplay of the different factors, such as biodegradation and

**Table 2. Hydrophobicities of Ionic Liquids, Expressed as Cation log $k_0$ Values Derived from Gradient Retention[54] and as log $K_{ow}$ Values (Different Sources)**

| | | log $K_{ow}$ | | | |
|---|---|---|---|---|---|
| cation | log $k_0$ | $Cl^-$ | $BF_4^-$ | $PF_6^-$ | $(CF_3SO_2)_2N^-$ |
| 1-ethyl-3-methylimidazolium | | | | −1.92 to −1.82[d] | −1.05 to −0.96[a] |
| 1-ethyl-2,3-dimethylimidazolium | | | | | −1.15 to −0.92[a] |
| 1-carboxypropyl-3-methylimidazolium | −0.08 | | | | |
| 1-hydroxybutyl-3-methylimidazolium | −0.06 | | | | |
| 1-(3-oxobutyl)-3-methylimidazolium | 0 | | | | |
| 3-methyl-1-propylimidazolium | 0.42 | | | | |
| 2,3-dimethyl-1-propylimidazolium | | | | | −0.92 to −0.62[a] |
| 1-butyl-3-methylimidazolium | 0.67 | −2.4[a] | −2.5[a] | −1.7[a] | −0.96 to −0.2[a] |
| | | −0.31[b] | −2.44[c] | −2.39[c] | 0.33[c] |
| | | | | −2.3 to −1.7[d] | |
| 1-methyl-3-(phenylmethyl)imidazolium | 0.83 | | | | |
| 1-(8-hydroxyoctyl)-3-methylimidazolium | 0.9 | | | | |
| 1-(3-carboxyheptyl)-3-methylimidazolium | 0.92 | | | | |
| 1-pentyl-3-methylimidazolium | 0.92 | | | | |
| 1-methyl-3-(phenylethyl)imidazolium | 1.01 | | | | |
| 1-methyl-3-[(4-methylphenyl)methyl]imidazolium | 1.12 | | | | |
| 1-hexyl-3-methylimidazolium | 1.24 | | | −1.86[c] | 0.15−0.22[a] |
| | | | | | 0.65[c] |
| 1-hexyl-2,3-dimethylimidazolium | 1.37 | | | | 0.13−0.25[a] |
| 1-heptyl-3-methylimidazolium | 1.57 | | | | |
| 3-octyl-1-methylimidazolium | 1.85 | −0.27[b] | | −1.33[c] | 0.8−1.05[a] |
| 3-methyl-1-nonylimidazolium | 2.1 | | | | |
| 1-decyl-3-methylimidazolium | 2.37 | −0.29[b] | | | |
| 1-dodecyl-3-methylimidazolium | | −0.14[b] | | | |
| 1,3-diethylimidazolium | 0.09 | | | | |
| 1-ethyl-3-propylimidazolium | 0.56 | | | | |
| 1-ethyl-3-butylimidazolium | 0.77 | | | | |
| 1-ethyl-3-hexylimidazolium | 1.4 | | | | |
| 1-ethyl-3-decylimidazolium | 2.51 | | | | |
| butylquinolinium | 1.06 | | | | |
| hexylquinolinium | 1.68 | | | | |
| octylquinolinium | 2.22 | | | | |
| 1,1-butylmethylpyrrolidinium | 0.57 | | | | |
| 1,1-hexylmethylpyrrolidinium | 1.17 | | | | |
| 1,1-methyloctylpyrrolidinium | 1.87 | | | | |
| 1,1-dihexylpyrolidinium | 2.41 | | | | |
| 1-butylpyridinium | 0.58 | | | | |
| 1-butyl-2-methylpyridinium | 0.71 | | | | |
| 1-butyl-3-methylpyridinium | 0.73 | | | | |
| 1-butyl-4-methylpyridinium | 0.73 | | | | |
| 1-butyl-3,4-dimethylpyridinium | 0.91 | | | | |
| 1-butyl-3,5-dimethylpyridinium | 0.93 | | | | |
| 1-hexyl-4-methylpyridinium | 1.37 | | | | |
| 1-octyl-4-methylpyridinium | 1.98 | | | | |
| tetrabutylammonium | 2.32 | | | | |
| tetrabutylphosphonium | 2.53 | | | | |
| trihexyltetradecylphosphonium | 6.9 | | | | |
| benzyldecyldimethylammonium | 2.93 | | | | |
| benzyldodecyldimethylammonium | 3.49 | | | | |
| benzyltetradecyldimethylammonium | 4.22 | | | | |

[a] Values from Ropel et al.[83] converted to logarithms. [b] Values obtained from solubility data by Domanska et al.[82] [c] Values from Lee et al. and references cited therein.[84] [d] Values obtained at 303 K by Choua et al.[81]

sorption, can only be judged by intuition to a very limited degree.

## 4. Ionic Liquid Bioaccumulation

Experimentally determined 1-octanol/water partitioning coefficients of several 1-alkyl-3-methylimidazolium ionic liquids have been reported by several groups[81−84] and are reproduced in Table 2. Base 10 logarithms of such partition coefficients (log $K_{ow}$ values) range from −2.5 (1-butyl-3-methylimidazolium tetrafluoroborate) to 0.8−1.1 (1-octyl-3-methylimidazolium bistriflamide, concentration dependent). While the values for the single substances sometimes differ by up to 2 orders of magnitude between groups (see Table 2), the values obtained by Ropel et al.[83] seem to be carefully obtained and are consistent with expectations concerning the influence of alkyl chain length and anion hydrophobicity. Differences in absolute values have been related to different concentration ranges investigated[83] but could also result from the fact that 1-octanol/water partitioning is strongly dependent on concentration and type of counteranions present,[85] so that small ionic impurities in water and/or octanol could have a large influence on experimental results. Domanska et al. obtained log $K_{ow}$ values from solubilities of ILs in 1-octanol and water by a "simple, synthetic, visual method",[82] but the very small range of log $K_{ow}$ values for ILs with cation chain lengths varying from 4 to 12 suggests that their method is not comparable to results from the shake-flask or slow-stirring methods. It must also be noted that if suitable

counterions are present in environmental aqueous phases, partitioning to organic phases would be underestimated by log $K_{ow}$ values determined using deionized water. Divalent, environmentally omnipresent cations such as $Ca^{2+}$ and $Mg^{2+}$ have been shown to have a larger influence on anion partitioning than monovalent cations.[85] In general, the counterions relevant for partitioning of hydrophobic ions from water to solid or organic phases in the environment will differ from the ones present in the original ionic liquid, limiting the relevance of ionic liquid $K_{ow}$ values for environmental processes.

A possibly related influence of ionic strength and water hardness on bioaccumulation in fish has been revealed in studies with anionic surfactants.[86] However, an unambiguous increase for all investigated compounds was only found in the range of low to intermediate hardness.[87] On the other hand, the presence of increased concentrations of dissolved organic carbon or suspended clay minerals has been shown to decrease surfactant bioconcentration.[86]

According to an estimation method of the bioconcentration factor (BCF) in fish from log $K_{ow}$ values by Meylan et al.,[88] ionic substances such as carboxylic acids, sulfonates, and quaternary nitrogen compounds with a log $K_{ow}$ value $< 1$ can be expected to have log BCF values between 0 and 1, corresponding to BCF values between 1 and 10 L $kg^{-1}$. A recent experimental investigation of the sorption of 1-alkyl-3-methylimidazolium cations to mammalian cells has revealed enrichment factors in cellular material between 2.3 (1-butyl-3-methylimidazolium) and 17 (1-octyl-3-methylimidazolium), that are roughly consistent with this estimate.[89] These observations suggest that the potential of this group of ILs to bioaccumulate is very low. Transformation products, resulting from metabolic or abiotic reactions, would generally be expected to exhibit even lower bioaccumulation potentials.

In an attempt to overcome the limited environmental relevance of log $K_{ow}$ values for surfactants as well as experimental problems with their determination, Rosen and co-workers have introduced the parameter $\Delta G°_{ad}/A_{min}$, where $\Delta G°_{ad}$ is the standard free energy of adsorption of a surfactant to the air/water interface and $A_{min}$ is the minimum cross-sectional area of a surfactant.[90,91] This parameter is a hydrophobicity measure that is independent of ionic strength and counterions present in the experimental system. Interestingly, it correlates well with aquatic toxicity values for algae and rotifers across the investigated cationic, nonionic, and anionic surfactants, as well as with bioconcentration factors of anionic surfactants.[92] Since its calculation is merely based on surface tension measurements at varying surfactant concentrations, without the necessity of concentration measurement as necessary for direct log $K_{ow}$ determinations by the shake-flask or slow-stirring methods, the use of this parameter for the constituents of ionic liquids should be evaluated.

Stepnowski and Storoniak have suggested using the group contribution method by Hansch and Leo[93] for estimating log $K_{ow}$ values for ionic liquids.[94] However, since the imidazolium cation is not covered by the original method, they resorted to using the fragment constant for the nitrogen in quaternary ammonium compounds for both of the nitrogens in the imidazolium ring. While the resulting log $P$ parameters should not be used as absolute estimates of experimental log $K_{ow}$values because of this, they do provide a measure of lipophilicity, in analogy to the log $P$ values proposed for surfactants by Roberts.[95,96] Stepnowski and Storoniak have also shown the correlation of their log $P$ parameter to the chromatographic capacity factor log $k'_w$ derived from isocratic elution from immobilized artificial membranes for four 1-alkyl-3-methylimidazolium cations.[94]

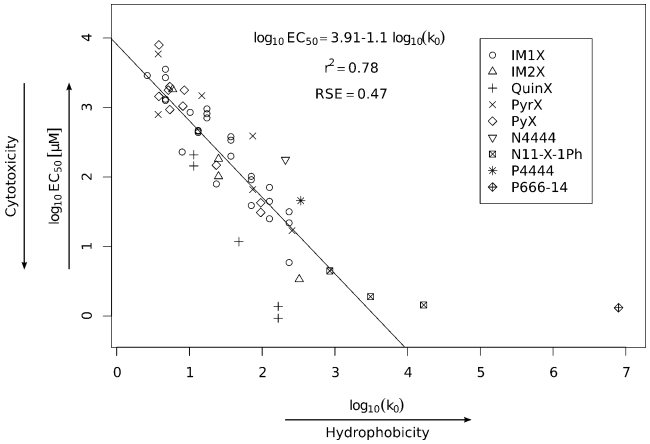


**Figure 4.** Relationship between the chromatographically derived cation hydrophobicity parameter log $k_0$ and cytotoxicity toward a rat cell line. The cation acronyms used in the legend are as follows: IM1X = 1-alkyl-3-methylimidazolium, IM2X = 1-alkyl-3-ethylimidazolium, QuinX = 1-alkylquinolinium, PyrX = 1-alkylpyrrolidinium, PyX = 1-alkylpyridinium, N4444 = tetrabutylammonium, N11-X-1Ph = alkylbenzyldimethylammonium, P4444 = tetraalkylphosphonium, P666-14 = trihexyltetradecylphosphonium.

Only recently, Ranke et al. have published hydrophobicity parameters log $k_0$ for a variety of 44 different ionic liquid cations derived from gradient reversed phase HPLC.[54] They are listed together with the published log $K_{ow}$values in Table 2. The log $K_{ow}$ values for the organic reference solvents are between $-0.77$ (methanol) and 2.73 (toluene).

These log $k_0$ values of the cations are readily obtained, provided that a gradient HPLC system with a suitable detection method is available. They also correlate well with the cytotoxicities of their salts with small anions such as chloride, bromide, tetrafluoroborate, and hexafluorophosphate (Figure 4). The cations making up the common disinfectant benzalkonium chloride are described by the same correlation. This is relevant in the context of bioaccumulation, because it suggests that there is a continuum in nonspecific toxicity of organic cations—including disinfectants and germicides—that is dominated by their uptake controlled by hydrophobicity. This is then modulated by structure-specific effects. From these observations, and from similar correlations of surfactant hydrophobicity with bioaccumulation[97] and toxicity,[96,98] it would be expected, that—in the absence of metabolic or abiotic transformation reactions—the log $k_0$ values given in Table 2 correlate with the tendency of these ions to bioaccumulate.

In this study, the hydrophobicities of some theoretically predicted metabolites of the 1-butyl-3-methylimidazolium and 1-octyl-3-methylimidazolium cations was also determined. As already pointed out, their lipophilicity was lower than that of the parent cation, but their cytotoxicity, and thus likely also their bioaccumulation tendency, was described by the same linear correlation. In this context, it is noteworthy that the first attempts to find some of the theoretically predicted metabolites of the 1-butyl-3-methylimidazolium cation[19] have recently been published.[99]

Comparison to BCF values measured for surfactants shows fish BCF values for long chain alkyltrimethylammonium

cationics of up to 2000[100] and for linear alkylbenzene sulfonate anionics of up to 1000,[101] which correspond to a high bioaccumulation potential. Considering that BCF values for perfluorinated acids (PFAs) range up to 23000[102] and that the consequences of this high bioconcentration and dietary bioaccumulation[103] potential are part of the reasons why the long chain PFAs are being phased out,[103] it is clear that the increasing popularity of perfluorinated side chains, also noticeable in the field of ionic liquids, will not automatically lead to green or sustainable chemistry. Similarly, the large log $k_0$ value of the long chain phosphonium cation trihexyltetradecylphosphonium indicates a very high bioaccumulation potential.

By comparison, all molecular solvents chosen as a reference for comparison do not or are not expected to bioconcentrate.[76,77] This means that the structural variability of ionic liquids causes them to most likely cover both the low and the high ends of the bioaccumulation scale, while the admittedly random set of reference solvents does not cause concerns of bioaccumulation.

While the knowledge on bioaccumulation of surfactants is now quite evolved, bioconcentration or more general bioaccumulation of typical ionic liquid cations and anions has yet to be directly investigated. The further establishment of linear free enthalpy relationships (LFER) for ionic substances would help to reduce the need for animal testing. Almost no knowledge on bioaccumulation of surfactant or ionic liquid metabolites has been generated.

It is important to note that to date no standard bioconcentration studies with ionic liquids have been carried out. This is an important uncertainty in the risk profile of ionic liquids that will have to be filled soon.

## 5. Biological Activity of Ionic Liquids

In the Introduction, we postulated that the biological activity of ILs in the organisms should be evaluated using critical dilution factors, i.e., the amount of biomass needed to dilute the bioaccumulated part of the released substances including their environmental and metabolic transformation products. While the recently proposed inclusion of transformation products into the assessment of biological activity[28] has not been propagated by other authors, the critical dilution factor of the parent compound is simply the inverse critical body residue (CBR), which has been proposed by Lynn McCarty, Don Mackay, and others in the context of an approximative unifying physicochemical theory of the relationship of hydrophobicity as quantified by log $K_{ow}$, bioconcentration, and aquatic toxicity.[29,30]

Currently, it is not possible to include environmental transformation products and metabolites into the assessment of the biological activity of ILs in the environment, since not even degradation pathways, not to speak of the respective degradation kinetics along these pathways (as have been estimated, e.g., for nonyl phenol ethoxylates by Fenner et al.[104]), are known, and only little can be said about the properties of the theoretically predicted transformation products.

McCarty and Mackay have stated about the CBR method that its principles are applicable not only to aquatic systems but also to all parts of the ecosystem. They also point out that their theory indicates that living organisms are much more similar than it would appear from a superficial examination of toxicity test results.[30]

For anionic as well as cationic surfactants, relationships between acute fish lethality expressed as log $LC_{50}$ and estimated hydrophobicity expressed as log $K_{ow}$ values have been demonstrated,[96,98] suggesting that they could be included into the group of substances acting by (general or polar[105]) narcosis. For a mixture of dodecylbenzene sulfonate isomers, critical body residues for acute aquatic toxicity between 0.21 and 0.59 mmol $kg^{-1}$ were found in a recent study. Critical body residues for chronic toxicity ranged between 0.035 and 0.23 mmol $kg^{-1}$.[106] In an attempt to simplify the establishment of critical body residues for fish, Bernhard and Dyer measured critical cell residues (CCRs) in fish cell cultures. CCR values for the three surfactants studied (among them the anionic sodium dodecylbenzene sulfonate and the cationic N111-16) were between 0.6 and 1.13 mmol $kg^{-1}$.[107] While all these CBRs and CCRs for acute aquatic toxicity fall in the range of values found for polar narcosis (0.2−1.9 mmol $kg^{-1}$), the chronic toxicity CBRs cited rather point to one of the more specific modes of toxic action such as "respiratory uncoupler" or "AChE inhibitor".[30]

Therefore, we draw no definitive conclusion about the mode of toxic action of surfactants, but we note that there is some data supporting the assumption of a rather nonspecific mode of action,[32] at least in some species, confounded by the potentially pivotal work of Rosen et al.[92]

From the only measured bioconcentration of ionic liquids that we are aware of, the enrichment of 1-alkyl-3-methylimidazolium tetrafluoroborates in a glia cell line, the only substance for which concurrent cytotoxicity information in terms of an $EC_{50}$ value is available is 1-octyl-3-methylimidazolium tetrafluoroborate.[89] For this substance, a critical cellular residue of 6.8 mM can be calculated from the product of its $EC_{50}$ (400 $\mu$M) and its enrichment factor of 17. Such a critical cellular residue indicates a narcotic mode of action in these cells.

Of course, this can only be taken as a very first approximation of the mode of toxic action of ionic liquids, that will be in some cases modulated and in other cases radically changed by (a) the chemical reactivity of certain ILs, as has been mentioned above, (b) different targets for toxic action that are not present in the cell lines studied so far, and (c) differences in metabolic capacities, leading potentially to a toxification, but more likely to an increased detoxification by transformation to more hydrophilic compounds.

### 5.1. Ionic Liquid Toxicity toward Enzymes, Microorganisms, and Cell Cultures

On the subcellular toxicity level, enzyme inhibition data have been published for the acetylcholinesterase (AChE)[108] and the AMP deaminase.[109] While 1-butyl-3-methylimidazolium ILs with different anions were inhibiting AMP deaminase only at rather high concentrations,[109] 1-butyl-2-methylpyridinium and 1-octyl-3-methylimidazolium as well as 1-decyl-3-methylimidazolium ILs showed pronounced AChE inhibition only by a factor of 3−10 weaker than Aldicarb, a potent AChE inhibiting insecticide.[108] The latter results suggest that insect toxicity should be investigated and that neurotoxicity has to be regarded as a possible effect of ionic liquids, especially for ILs that feature both an intermediate to high lipophilicity and a strong AChE inhibition, such as, e.g., 1-decyl-3-methylimidazolium tetrafluoroborate. Table 3 lists a comprehensive collection of IPC-81 cytotoxicities for 253 compounds and AChE inhibition values for 292 compounds and from our substance library covering a large variety of ionic liquids and closely related salts. The most important features of this data set have largely been

**Table 3. Cytotoxicities in the Leukemia Rat Cell Line IPC-81 and AChE Inhibition Data[a]**

| cation | anion | log $EC_{50}$[b] IPC-81 | log $EC_{50}$[b] AChE |
|---|---|---|---|
| 3-methyl-1-tetradecylimidazolium | chloride | −0.42 | 0.54 |
| tributyltetradecylphosphonium | alkylbenzenesulfonate | −0.27 | >3.48 |
| 1-hexadecyl-3-methylimidazolium | chloride | −0.19 | 0.68 |
| 1-octylquinolinium | bromide | −0.03 | NA |
| trihexyltetradecylphosphonium | alkylbenzenesulfonate | −0.01 | >3.48 |
| trihexyltetradecylphosphonium | trifluorotris(pentafluoroethyl)phosphate | 0 | >3 |
| 3-methyl-1-octadecylimidazolium | chloride | 0.01 | 0.96 |
| benzyltetradecyldimethylammonium | chloride | 0.16 | NA |
| 1-octylquinolinium | tetrafluoroborate | 0.17 | 0.3 |
| trihexyltetradecylphosphonium | bis(trifluoromethylsulfonyl)amide | 0.24 | >3.48 |
| benzyldodecyldimethylammonium | chloride | 0.28 | NA |
| benzylhexadecyldimethylammonium | chloride | 0.33 | NA |
| trihexyltetradecylphosphonium | tetrafluoroborate | 0.48 | >3.3 |
| 1-decyl-3-ethylimidazolium | bromide | 0.53 | 0.92 |
| benzyldecyldimethylammonium | chloride | 0.64 | 0.73 |
| 1-decyl-3-methylimidazolium | tetrafluoroborate | 0.77 | 1.08 |
| 4-(dimethylamino)-1-hexylpyridinium | chloride | 0.93 | 0.5 |
| 4-(dimethylamino)-1-hexylpyridinium | bis(trifluoromethylsulfonyl)amide | 0.93 | 0.81 |
| 1-ethyl-3-methylimidazolium | bis[1,2-benzenediolato(2-)-O1,O2]borate | 1.02 | 2.09 |
| 1-hexyl-3-methylimidazolium | trifluorotris(heptafluoropropyl)phosphate | 1.04 | >2.4 |
| 1-hexylquinolinium | tetrafluoroborate | 1.07 | 0.48 |
| lithium | bis[1,2-benzenediolato(2-)-O1,O2]borate | 1.13 | >3 |
| tetraethylammonium | bis[1,2-benzenediolato(2-)-O1,O2]borate | 1.17 | 2.9 |
| 1,1-dihexylpyrrolidinium | tetrafluoroborate | 1.23 | 2.08 |
| 1-octylpyridinium | chloride | 1.27 | 1.6 |
| tetrabutylphosphonium | bis[1,2-benzenediolato(2-)-O1,O2]borate | 1.32 | 3.11 |
| 1-decyl-3-methylimidazolium | chloride | 1.34 | 1.09 |
| 3-methyl-1-nonylimidazolium | chloride | 1.4 | 1.36 |
| 1-octyl-4-methylpyridinium | tetrafluoroborate | 1.49 | 1.22 |
| 1-decyl-3-methylimidazolium | hexafluorophosphate | 1.5 | 1.68 |
| 1-hexyl-3-methylimidazolium | trifluorotris(pentafluoroethyl)phosphate | 1.53 | >2.4 |
| 3-methyl-1-octylimidazolium | tetrafluoroborate | 1.59 | 1.53 |
| tetrabutylammonium | bis[1,2-benzenediolato(2-)-O1,O2]borate | 1.61 | NA |
| 1-octyl-4-methylpyridinium | chloride | 1.63 | 1.11 |
| 3-methyl-1-octylimidazolium | bis(trifluoromethylsulfonyl)amide | 1.64 | 2.03 |
| 3-methyl-1-nonylimidazolium | tetrafluoroborate | 1.65 | 1.43 |
| tetrabutylphosphonium | bromide | 1.66 | 2.61 |
| 4-(dimethylamino)-1-butylpyridinium | bis(trifluoromethylsulfonyl)amide | 1.75 | 0.59 |
| 1-butyl-3-methylimidazolium | trifluorotris(pentafluoroethyl)phosphate | 1.81 | NA |
| 1-methyl-1-octylpyrrolidinium | tetrafluoroborate | 1.82 | 2.02 |
| 3-methyl-1-nonylimidazolium | hexafluorophosphate | 1.85 | 1.62 |
| 3-hexyl-1,2-dimethylimidazolium | tetrafluoroborate | 1.9 | 1.27 |
| 4-(dimethylamino)-1-butylpyridinium | chloride | 1.94 | 0.6 |
| 3-methyl-1-octylimidazolium | hexafluorophosphate | 1.96 | 2.03 |
| 3-methyl-1-octylimidazolium | chloride | 2.01 | 1.6 |
| 1-hexyl-3-ethylimidazolium | bromide | 2.01 | 1.77 |
| 1-butylquinolinium | tetrafluoroborate | 2.16 | 0.62 |
| 1-hexyl-4-methylpyridinium | tetrafluoroborate | 2.17 | 1.48 |
| 1-butyl-3-methylimidazolium | bis(trifluoromethyl)amide | 2.19 | 1.6 |
| 1-hexyl-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 2.24 | 2.15 |
| tetrabutylammonium | bromide | 2.25 | 2.3 |
| 1-butyl-3-methylimidazolium | hexafluoroantimonate | 2.26 | 1.81 |
| 1-hexyl-3-ethylimidazolium | tetrafluoroborate | 2.26 | 1.84 |
| 1-hexyl-3-methylimidazolium | 1,2-benzisothiazolonium 1,1-dioxide | 2.29 | 1.96 |
| 1-heptyl-3-methylimidazolium | hexafluorophosphate | 2.3 | 1.91 |
| sodium | hexafluoroantimonate | 2.31 | 2.34 |
| 1-butylquinolinium | bromide | 2.32 | 0.79 |
| lithium | bis[2-hydroxybenzoato(2-)-O1,O2]borate | 2.32 | >3 |
| 1-(8-hydroxyoctyl)-3-methylimidazolium | bromide | 2.36 | 1.28 |
| 1-butyl-1-methylpyrrolidinium | trifluorotris(pentafluoroethyl)phosphate | 2.41 | >3 |
| 1-butyl-3-methylimidazolium | tetracarbonylcobaltate | 2.44 | NA |
| 1-heptyl-3-methylimidazolium | chloride | 2.53 | 2.07 |
| 1-heptyl-3-methylimidazolium | tetrafluoroborate | 2.58 | 2.12 |
| 1-methyl-1-octylpyrrolidinium | chloride | 2.59 | 2.36 |
| 1-methyl-3-[(4-methylphenyl)methyl]imidazolium | chloride | 2.64 | 1.86 |
| 1-methyl-3-[(4-methylphenyl)methyl]imidazolium | hexafluorophosphate | 2.66 | NA |
| 1-methyl-3-[(4-methylphenyl)methyl]imidazolium | tetrafluoroborate | 2.67 | 2.08 |
| 1-butyl-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 2.68 | 1.96 |
| sodium | 1-dodecylsulfate | 2.7 | NA |
| sodium | hexafluorophosphate | 2.82 | 2.16 |
| 1-ethyl-3-methylimidazolium | bis(pentafluoroethyl)phosphinate | 2.83 | 2.09 |
| 4-(dimethylamino)-1-ethylpyridinium | bis(trifluoromethylsulfonyl)amide | 2.84 | 0.93 |

**Table 3 (Continued)**

| cation | anion | log $EC_{50}$[b] IPC-81 | log $EC_{50}$[b] AChE |
|---|---|---|---|
| 1-hexyl-3-methylimidazolium | chloride | 2.85 | 1.92 |
| lithium | bis[oxalato(2-)]-borate | 2.87 | >3 |
| 4-(dimethylamino)-1-ethylpyridinium | bromide | 2.9 | 0.99 |
| 1-butyl-1-methylpyrrolidinium | tetrafluoroborate | 2.9 | 1.91 |
| 1-hexyl-3-methylimidazolium | hexafluorophosphate | 2.91 | 1.88 |
| 1-hexyl-1-methylpyrrolidinium | chloride | 2.91 | 2.48 |
| 1-methyl-3-(2-phenylethyl)imidazolium | hexafluorophosphate | 2.93 | 1.9 |
| 1-ethyl-3-methylimidazolium | bis[oxalato(2-)]-borate | 2.93 | 2 |
| 1,3,7,9-tetramethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-9-ium | trifluoromethanesulfonate | 2.96 | 1.58 |
| 1-butyl-4-methylpyridinium | tetrafluoroborate | 2.98 | 1.54 |
| 1-hexyl-3-methylimidazolium | tetrafluoroborate | 2.98 | 1.88 |
| sodium | fluoride | 2.99 | 2.76 |
| 1-butyl-4-methylpyridinium | hexafluorophosphate | >3 | 1.43 |
| 1-methyl-3-(phenylmethyl)imidazolium | hexafluorophosphate | >3 | 1.74 |
| 3-methyl-1-pentylimidazolium | hexafluorophosphate | >3 | 1.85 |
| 3-methyl-1-pentylimidazolium | tetrafluoroborate | >3 | 1.86 |
| 1-methyl-3-(2-phenylethyl)imidazolium | chloride | >3 | 1.91 |
| 3-methyl-1-pentylimidazolium | chloride | >3 | 1.96 |
| 1-methyl-3-(phenylmethyl)imidazolium | tetrafluoroborate | >3 | 1.98 |
| 1-methyl-3-(phenylmethyl)imidazolium | chloride | >3 | 2.04 |
| 1,3-diethylimidazolium | bromide | >3 | 2.08 |
| 3-methyl-1-propylimidazolium | hexafluorophosphate | >3 | 2.22 |
| potassium | bromide | >3 | >3 |
| 1-butyl-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.01 | 2.13 |
| 1-butyl-3,4-dimethylpyridinium | tetrafluoroborate | 3.02 | 1.1 |
| 1-butyl-3-methylimidazolium | trifluoromethanesulfonate | 3.02 | 1.93 |
| 1-(ethoxymethyl)-1-methylpyrrolidinium | chloride | 3.05 | 1.86 |
| 1-methyl-3H-imidazolium | tetrafluoroborate | 3.09 | >3 |
| 1-butyl-3-methylimidazolium | hexafluorophosphate | 3.1 | 2.15 |
| 1-butyl-3-methylimidazolium | tetrafluoroborate | 3.12 | 1.98 |
| 1-(ethoxymethyl)pyridinium | bis(trifluoromethylsulfonyl)amide | 3.12 | 2.14 |
| 1-butyl-3-methylimidazolium | dicyanamide | 3.15 | 1.93 |
| 1-butyl-3-methylimidazolium | 2-(2-methoxyethoxy)ethyl sulfate | 3.16 | 1.99 |
| 1-butylpyridinium | tetrafluoroborate | 3.18 | 1.8 |
| 1-(2-ethoxyethyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.18 | 2.12 |
| 1-(2-methoxyethyl)pyridinium | bis(trifluoromethylsulfonyl)amide | 3.19 | 2.09 |
| 4-(2-hydroxyethyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.19 | 2.93 |
| 1-(ethoxymethyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.2 | 2.45 |
| 1-(2-ethoxyethyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.2 | 2.55 |
| 1-butyl-3-methylimidazolium | 1-methylsulfate | 3.21 | 1.95 |
| 1-butyl-3-methylimidazolium | 1-octylsulfate | 3.23 | 1.98 |
| 1-ethyl-3-methylimidazolium | trifluorotris(pentafluoroethyl)phosphate | 3.23 | > 2.4 |
| 1-butyl-2-methylpyridinium | tetrafluoroborate | 3.25 | 0.82 |
| 1-butyl-3,5-dimethylpyridinium | tetrafluoroborate | 3.25 | 1.17 |
| 1-(2-methoxyethyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.25 | 2.47 |
| 1-(2-ethoxyethyl)pyridinium | bis(trifluoromethylsulfonyl)amide | 3.26 | 1.48 |
| 1-butyl-3-ethylimidazolium | tetrafluoroborate | 3.26 | 2.04 |
| 1-(ethoxymethyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.26 | 2.22 |
| 1-(3-methoxypropyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.27 | 2.27 |
| 1-(2-methoxyethyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.28 | 1.93 |
| ethyl(2-ethoxyethyl)dimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.28 | 2.55 |
| 1-butyl-3-methylimidazolium | hydrogensulfate | 3.29 | 1.97 |
| 1-butyl-3-methylimidazolium | toluene-4-sulfonate | 3.29 | 2 |
| 1-butyl-3-methylpyridinium | tetrafluoroborate | 3.3 | 1.27 |
| 1-(2-methoxyethyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.3 | 2.11 |
| 3-ethyl-1-propylimidazolium | bromide | >3.3 | 2.21 |
| sodium | tetrafluoroborate | >3.3 | >3 |
| sodium | iodide | >3.3 | >3 |
| sodium | bromide | >3.3 | >3.48 |
| 1-butyl-3-ethylimidazolium | trifluoroacetate | 3.31 | 2.01 |
| ethyl(2-methoxyethyl)dimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.31 | 2.45 |
| 1-(ethoxymethyl)pyridinium | chloride | 3.32 | 2.06 |
| lithium | bis(trifluoromethylsulfonyl)amide | 3.33 | >3 |
| 1-(2-ethoxyethyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.34 | 2.55 |
| 1-(2-methoxypropyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.34 | 2.58 |
| 4-(ethoxymethyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.34 | 2.88 |
| 1-(3-methoxypropyl)pyridinium | bis(trifluoromethylsulfonyl)amide | 3.38 | 2.06 |
| 1-(3-methoxypropyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.4 | 2.71 |
| (2-hydroxyethyl)dimethylammonium | acetate | 3.4 | >3 |
| 1-butyl-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.41 | 1.78 |
| 1-(ethoxymethyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.41 | 2.16 |
| (2-hydroxyethyl)dimethylammonium | hydroxyacetate | 3.41 | >3 |

**Table 3 (Continued)**

| cation | anion | log $EC_{50}$[b] IPC-81 | log $EC_{50}$[b] AChE |
|---|---|---|---|
| 1-butyl-3-methylimidazolium | thiocyanate | 3.42 | 2 |
| 1-butyl-3-methylimidazolium | bromide | 3.43 | 1.96 |
| 1-butyl-3-ethylimidazolium | trifluoromethanesulfonate | 3.43 | 2.01 |
| butylethyldimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.43 | 2.03 |
| 4-butyl-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.43 | 2.78 |
| lithium | bis[malonato(2-)]-borate | 3.43 | >3 |
| 1-ethyl-3-methylimidazolium | tetrafluoroborate | 3.44 | 2.05 |
| 1-hexyl-3-methylimidazolium | tris(trifluoromethylsulfonyl)methide | 3.44 | >2.4 |
| 3-methyl-1-propylimidazolium | tetrafluoroborate | 3.47 | 2.3 |
| 1-butyl-3-methylimidazolium | iodide | 3.48 | 2.02 |
| 1-(4-hydroxybutyl)-3-methylimidazolium | chloride | >3.48 | 2.74 |
| 3-methyl-1-(3-oxobutyl)imidazolium | bromide | >3.48 | 2.79 |
| tetraethylammonium | chloride | >3.48 | 2.8 |
| 1-(7-carboxyheptyl)-3-methylimidazolium | bromide | >3.48 | >3 |
| 1-(3-carboxypropyl)-3-methylimidazolium | chloride | >3.48 | >3 |
| bis(2-methoxyethyl)ammonium | sulfamate | 3.48 | >3 |
| sodium | 1-octylsulfate | 3.48 | >3.7 |
| 1-ethyl-3-methylimidazolium | tetracyanoborate | 3.5 | 1.98 |
| 1-cyanomethylpyridinium | bis(trifluoromethylsulfonyl)amide | 3.5 | 2.51 |
| 1-butyl-3-methylimidazolium | 1-methanesulfonate | 3.51 | 1.99 |
| 4-(ethoxymethyl)-4-methylmorpholinium | chloride | 3.52 | 2.96 |
| 4-(cyanomethyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.53 | >3 |
| 4-(3-hydroxypropyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.53 | >3 |
| ethyl(3-methoxypropyl)dimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.54 | 2.92 |
| 1-butyl-3-methylimidazolium | chloride | 3.55 | 1.91 |
| 1-(3-hydroxypropyl)pyridinium | bis(trifluoromethylsulfonyl)amide | 3.55 | 2.56 |
| (ethoxymethyl)ethyldimethylammonium | chloride | 3.59 | 2.36 |
| (ethoxymethyl)methylimidazolium | chloride | 3.6 | 2.61 |
| 1-(3-hydroxypropyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.6 | 2.77 |
| butyltrimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.61 | 2.6 |
| 1-(3-hydroxypropyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.63 | 2.56 |
| 1-(2-hydroxyethyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 3.65 | 2.34 |
| 1-(3-hydroxypropyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.66 | 2.74 |
| 4-(2-ethoxyethyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.69 | >3 |
| ethyl(2-hydroxyethyl)dimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.7 | 2.59 |
| 1-(2-hydroxyethyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.72 | 2.61 |
| 1-(2-hydroxyethyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.76 | 2.88 |
| 1-butyl-1-methylpyrrolidinium | bromide | 3.77 | 1.93 |
| 4-(3-methoxypropyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.77 | >3 |
| 1-cyanomethylpyridinium | chloride | 3.79 | 2.47 |
| 1-(2-hydroxyethyl)pyridinium | bis(trifluoromethylsulfonyl)amide | 3.79 | 2.65 |
| (ethoxymethyl)ethyldimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.8 | 2.3 |
| 1-(cyanomethyl)-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | 3.8 | 2.83 |
| 1-ethyl-3-methylimidazolium | toluene-4-sulfonate | 3.81 | 2.22 |
| 4-ethyl-4-methylmorpholinium | toluene-4-sulfonate | 3.81 | 2.59 |
| 4-(2-methoxyethyl)-4-methylmorpholinium | bis(trifluoromethylsulfonyl)amide | 3.81 | 2.9 |
| ethyl(3-hydroxypropyl)dimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.83 | >3 |
| (cyanomethyl)ethyldimethylammonium | bis(trifluoromethylsulfonyl)amide | 3.87 | >3 |
| (2-hydroxyethyl)trimethylammonium | hydroxyacetate | 3.89 | >3 |
| 1-butylpyridinium | bromide | 3.9 | 1.77 |
| 1-(cyanomethyl)-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | 3.9 | 2.88 |
| 1-(3-sulfopropyl)pyridinium | trifluoromethanesulfonate | 3.9 | >3 |
| 1-ethyl-3-methylimidazolium | hexafluorophosphate | 3.92 | 2.05 |
| 1-ethyl-3-methylimidazolium | 1-ethylsulfate | 3.93 | 2.07 |
| 1-ethyl-3-methylimidazolium | hydrogensulfate | 3.99 | 2.13 |
| 1-ethyl-3-methylimidazolium | trifluoroacetate | 4 | 2.03 |
| 1-(cyanomethyl)-1-methylpiperidinium | bis(trifluoromethylsulfonyl)amide | 4 | 2.45 |
| sodium | chloride | >4 | >3 |
| sodium | trifluoromethanesulfonate | >4 | >3.3 |
| sodium | 1-methylsulfate | >4 | >3.48 |
| 1-butyl-1-methylpiperidinium | bromide | 4.03 | 1.83 |
| sodium | 1-hexanesulfonate | 4.08 | >3 |
| 1-ethyl-3-methylimidazolium | trifluoromethanesulfonate | 4.09 | 2.13 |
| 1-(2-ethoxyethyl)-3-methylimidazolium | bromide | 4.14 | 2.27 |
| 1-(2-hydroxyethyl)pyridinium | iodide | 4.15 | 2.69 |
| (2-hydroxyethyl)ammonium | formate | 4.15 | >3 |
| sodium | toluene-4-sulfonate | 4.17 | >3 |
| sodium | dicyanamide | 4.18 | >3.48 |
| 1-butyl-1-methylpyrrolidinium | dicyanamide | 4.23 | 1.98 |
| 1-ethyl-3-methylimidazolium | thiocyanate | 4.23 | 2.12 |
| 1-(cyanomethyl)-1-methylpyrrolidinium | chloride | 4.23 | 2.88 |
| 1-(2-ethoxyethyl)pyridinium | bromide | 4.24 | 1.55 |

**Table 3 (Continued)**

| cation | anion | log $EC_{50}$[b] IPC-81 | log $EC_{50}$[b] AChE |
|---|---|---|---|
| 1-butyl-1-methylpyrrolidinium | chloride | >4.3 | 1.92 |
| butylethyldimethylammonium | chloride | >4.3 | 2.06 |
| 1-(2-methoxyethyl)pyridinium | chloride | >4.3 | 2.07 |
| 3-methyl-1-propylimidazolium | chloride | >4.3 | 2.27 |
| 1-(2-methoxyethyl)-1-methylpyrrolidinium | chloride | >4.3 | 2.38 |
| ethyl(2-ethoxyethyl)dimethylammonium | chloride | >4.3 | 2.56 |
| ethyl(2-methoxyethyl)dimethylammonium | chloride | >4.3 | 2.57 |
| 1-(2-methoxyethyl)-3-methylimidazolium | chloride | >4.3 | 2.58 |
| 1-(2-ethoxyethyl)-1-methylpyrrolidinium | bromide | >4.3 | 2.6 |
| 1-(2-hydroxyethyl)-1-methylpyrrolidinium | iodide | >4.3 | 2.63 |
| 1-(3-hydroxypropyl)pyridinium | chloride | >4.3 | 2.65 |
| ethyl(2-hydroxyethyl)dimethylammonium | iodide | >4.3 | 2.67 |
| 4-butyl-4-methylmorpholinium | bromide | >4.3 | 2.71 |
| 1-(3-hydroxypropyl)-1-methylpyrrolidinium | chloride | >4.3 | 2.86 |
| 1-(cyanomethyl)-3-methylimidazolium | chloride | >4.3 | 2.89 |
| 4-(2-hydroxyethyl)-4-methylmorpholinium | iodide | >4.3 | 2.96 |
| 1-(2-hydroxyethyl)-3-methylimidazolium | iodide | >4.3 | 2.96 |
| 4-(2-methoxyethyl)-4-methylmorpholinium | chloride | >4.3 | 2.98 |
| 1-(3-hydroxypropyl)-3-methylimidazolium | chloride | >4.3 | 2.99 |
| sodium | 1-methanesulfonate | >4.3 | >3 |
| 4-(2-ethoxyethyl)-4-methylmorpholinium | bromide | >4.3 | >3 |
| (cyanomethyl)ethyldimethylammonium | chloride | >4.3 | >3 |
| 4-(cyanomethyl)-4-methylmorpholinium | chloride | >4.3 | >3 |
| 4-(3-hydroxypropyl)-4-methylmorpholinium | chloride | >4.3 | >3 |
| (2-hydroxyethyl)trimethylammonium | 2-hydroxypropanoate | >4.3 | >3 |
| sodium | thiocyanate | >4.3 | >3.48 |
| 1-(2-ethoxyethyl)-1-methylpiperidinium | bromide | 4.31 | 2.6 |
| 1-(3-methoxypropyl)-1-methylpiperidinium | chloride | 4.4 | 2.2 |
| 4-(3-methoxypropyl)-4-methylmorpholinium | chloride | >4.48 | >3 |
| 1-(2-methoxypropyl)-3-methylimidazolium | chloride | 4.49 | 2.61 |
| 1-(2-hydroxyethyl)-1-methylpiperidinium | iodide | 4.58 | 2.34 |
| 1-(cyanomethyl)-1-methylpiperidinium | chloride | 4.58 | 2.43 |
| 1-(2-methoxyethyl)-1-methylpiperidinium | bromide | >4.6 | 2.06 |
| 1-(3-methoxypropyl)pyridinium | chloride | >4.6 | 2.15 |
| 1-(3-hydroxypropyl)-1-methylpiperidinium | chloride | >4.6 | 2.53 |
| ethyl(3-methoxypropyl)dimethylammonium | chloride | >4.6 | 2.97 |
| 1-(3-methoxypropyl)-1-methylpyrrolidinium | chloride | >4.7 | 2.74 |
| 1-octyl-3-methylpyridinium | chloride | NA | 0.64 |
| 1-butyl-2-methylpyridinium | chloride | NA | 0.7 |
| 1-butyl-3,4-dimethylpyridinium | chloride | NA | 0.85 |
| 1-butyl-3,5-dimethylpyridinium | chloride | NA | 0.99 |
| 1-hexyl-3-methylpyridinium | chloride | NA | 1.06 |
| 1-butyl-3-methylpyridinium | chloride | NA | 1.15 |
| 1-butyl-3-methylpyridinium | dicyanamide | NA | 1.22 |
| 1-butyl-3-methylpyridinium | hexafluorophosphate | NA | 1.24 |
| 1-octylpyridinium | bis(trifluoromethylsulfonyl)amide | NA | 1.4 |
| 1-hexyl-4-methylpyridinium | chloride | NA | 1.44 |
| 1-butyl-4-methylpyridinium | chloride | NA | 1.44 |
| 1-butyl-4-methylpyridinium | tetracyanoborate | NA | 1.46 |
| 1-pentylpyridinium | bromide | NA | 1.52 |
| 1-pentylpyridinium | bis(trifluoromethylsulfonyl)amide | NA | 1.55 |
| 1-butyl-4-methylpyridinium | trifluorotris(pentafluoroethyl)phosphate | NA | 1.64 |
| 1-butylpyridinium | chloride | NA | 1.7 |
| 1-hexylpyridinium | chloride | NA | 1.72 |
| 1-butylpyridinium | 1-methylsulfate | NA | 1.75 |
| 1-hexylpyridinium | hexafluorophosphate | NA | 1.76 |
| 1-hexylpyridinium | trifluoromethanesulfonate | NA | 1.84 |
| 1-butylpyridinium | hexafluorophosphate | NA | 1.84 |
| 1-hexylpyridinium | bis(trifluoromethylsulfonyl)amide | NA | 1.85 |
| 1-butylpyridinium | trifluoromethanesulfonate | NA | 1.87 |
| 1-methyl-3-(2-phenylethyl)imidazolium | tetrafluoroborate | NA | 1.97 |
| 1-butyl-3-methylimidazolium | tetrachloroferrate | NA | 2.01 |
| 1-ethyl-3-methylimidazolium | bis(trifluoromethylsulfonyl)amide | NA | 2.03 |
| 1-ethyl-3-methylimidazolium | chloride | NA | 2.06 |
| 1-ethyl-3-methylimidazolium | 2-(2-methoxyethoxy)ethyl sulfate | NA | 2.09 |
| 1-ethylpyridinium | chloride | NA | 2.1 |
| 1-(ethoxymethyl)-1-methylpiperidinium | chloride | NA | 2.14 |
| 1-propylpyridinium | bis(trifluoromethylsulfonyl)amide | NA | 2.21 |
| 1-propylpyridinium | bromide | NA | 2.22 |
| 3-methyl-1-(2-propenyl)imidazolium | chloride | NA | 2.3 |
| ethyldimethylpropylammonium | bis(trifluoromethylsulfonyl)amide | NA | 2.34 |
| trihexyltetradecylphosphonium | 1-methanesulfonate | NA | 2.58 |

**Table 3 (Continued)**

| cation | anion | log $EC_{50}$[b] IPC-81 | log $EC_{50}$[b] AChE |
|---|---|---|---|
| 1-hexyl-1-methylpyrrolidinium | bis(trifluoromethylsulfonyl)amide | NA | 2.6 |
| trihexyltetradecylphosphonium | bromide | NA | 2.85 |
| sodium | 1-butanesulfonate | NA | >3 |
| sodium | 1-octanesulfonate | NA | >3 |
| pyridinium | chloride | NA | >3 |
| (2-hydroxyethyl)dimethylammonium | formate | NA | >3 |
| (2-hydroxyethyl)trimethylammonium | hydroxide | NA | >3 |
| trihexyltetradecylphosphonium | bis(2,4,4-trimethylpentyl)phosphinate | NA | >3.3 |
| trihexyltetradecylphosphonium | dicyanamide | NA | >3.3 |
| trihexyltetradecylphosphonium | hexafluorophosphate | NA | >3.3 |
| sodium | acetate | NA | >3.48 |
| sodium | trifluoroacetate | NA | >3.48 |
| trihexyltetradecylphosphonium | decanoate | NA | >3.6 |

[a] log $EC_{50}$ values are base 10 logarithms of $EC_{50}$ values in $\mu$M. The approximate confidence regions of the cytotoxicity values were established to be about $\pm$0.15.[54] [b] NA means not available (not determined).

discussed by earlier contributions from our group,[35,54−56,108,110] but the datasets presented here cover the largest ionic liquid variability tested in single laboratory tests for biological activity. It should be noted that the values from Table 3 do not exactly coincide with previously published data, as on some substances additional data was generated after the original publications which caused the values to be slightly shifted as compared to the values first published. The IPC-81 cytotoxicities cover more than 4 orders of magnitude, while the AChE inhibitory concentrations span more than 3 orders of magnitude. Since we interpret the IPC-81 cytotoxicities as basal cytotoxicities, they were used for sorting the substances in Table 3 with decreasing cytotoxicity.

Effect concentrations that have been published as minimum inhibitory concentrations or log $EC_{50}$ values have been reported in a number of publications and cannot be reproduced here. Table 4 lists the references that we are aware of.

Table 4 shows that the use of conventional molecular solvents as a reference for IL toxicity to microorganisms and cell cultures has become common practice. On the other side of the activity spectrum, both cationic surfactants with antimicrobial or germicidal activity and reactive biocides have been chosen for convenient comparison of biological effects. The numerical results given in these studies suggest that IL toxicities toward microorganisms and cell cultures cover the whole range of biocidal potencies from rather inactive molecular solvents, such as ethanol or dimethyl sulfoxide that are biocompatible up to very high aqueous concentrations, up to highly active biocides, leading even to the proposal of some ionic liquids as wood preservatives.[111]

Couling et al. have developed quantitative structure−property relationship (QSPR) models for IL toxicity toward *Vibrio fischeri* using various parameters calculated from the IL structure.[112] While such models are useful for the estimation of *Vibrio fischeri* toxicity for untested but structurally similar compounds, their relation to modes of toxic action or molecular interaction potentials of ionic liquids,[37] and therefore their applicability to other test systems is unclear.

These highlight the necessity of a careful differentiation between types of ionic liquids when referring to their antimicrobial effects. At the time of this writing, it is not clear how much of this variation in biological activity can actually be explained by bioaccumulation in these organisms, since only the data from our group have been analyzed in this respect. The omnipresent chain length effect and the good correlation between cation hydrophobicity and cytotoxicity in a dedifferentiated mammalian cell line cited earlier suggest that a comprehensive investigation of critical cell residues would show a reduction in the range of biological activity values from four or more orders of magnitude observed for cytotoxicity values to little more than 1 order of magnitude for critical cell residues. Our results on the anion effects on cytotoxicity as well as the study of Rosen et al.[92] even suggest that for various test systems several ionic liquids could be regarded as a mixture of cations and anions with a similar mode of action according to the concentration addition concept developed in mixture toxicity.[35]

## 5.2. Aquatic Toxicity

References containing data on the aquatic toxicity of ionic liquids are collected in Table 5. The largest database concerning IL toxicity toward aquatic organisms has been collected for the water flea *Daphnia magna*. The substances with the highest toxicities toward this species, but also with partially very high toxicities toward the monocellular algae *Selenastrum capricornutum*, have been investigated by Wells and Coombe.[53] These authors found that *Daphnia magna* $EC_{50}$ values decreased up to a chain length of 18 for the tested 1-alkyl-3-methylimidazolium chlorides down to 1.7 $\mu$g $L^{-1}$ (1-octyl-3-methylimidazolium chloride), while the lowest $EC_{50}$ values for the tested algae were obtained for 1-dodecyl-3-methylimidazolium chloride (1.1 $\mu$g $L^{-1}$). Tetradecyltrihexylphosphonium chloride was less toxic in both the Daphnia and algal assays (72 and 42 $\mu$g $L^{-1}$, respectively). Obviously, these differences between the test systems cannot be explained by physicochemical parameters, but the possibility of fairly constant critical body residues cannot be excluded. The latter would mean that not so much the biological activity but rather the bioaccumulation tendency is the cause of concern for these substances.

Comparison to data available for ionic surfactants toward algae[22] shows that effect concentrations smaller than 1 mg $L^{-1}$ are frequently reported, but toxicity values below 10 $\mu$g $L^{-1}$ are rarely encountered. In general, cationic surfactants are frequently more toxic toward algae than anionic surfactants.[22] Ideally, such a comparison should be related to a common hydrophobicity parameter.

A noncomprehensive screening of the abundant surfactant toxicity data on invertebrates indicates that they range down

**Table 4. Studies of Biological Effects of Ionic Liquids on Microorganisms and Cell Cultures**

| reference | test systems | end point, parameter[a] | no. of tested ILs | head groups | side chains | anions | reference compds |
|---|---|---|---|---|---|---|---|
| Pernak et al., 2001[127] | 5 cocci, 1 bacillus 4 rods, 2 funghi | growth, MIC, MBC | 22 | pyridinium | alkoxyalkyl carbamoyl, | 12 | benzalkonium |
| Pernak et al., 2001[128] | 5 cocci, 1 bacillus, 4 rods, 2 funghi | growth, MIC, MBC | 11 | pyridinium benz imidazolium | alkoxymethyl, nicotionyl aminomethyl | $Cl^-$ | benzalkonium |
| Pernak et al., 2003[129] | 5 Gram-positive cocci, 4 Gram-negative rods, 2 fungi | growth, MIC, MBC | 36 | imidazolium | alkoxymethyl | $Cl^-$, $BF_4^-$, $PF_6^-$ | benzalkonium chloride |
| Ranke et al., 2004[55;56] | IPC-81 cells, C6 cells, *Vibrio fischeri* | WST-1 reduction/ luminescence, $EC_{50}$ | 27 8 13 | imidazolium | alkyl | $Cl^-$, $Br^-$, $BF_4^-$ $PF_6$-, toluenesulfonate | 4 organic solvents |
| Stepnowski et al., 2004[130] | HeLa cells | WST-1 reduction | 6 | imidazolium | alkyl | $Cl^-$, $BF_4^-$, $PF_6^-$ | sodium salts of $Cl^-$, $BF_4^-$ $PF_6^-$; 4 organic solvents |
| Pernak et al., 2004[57] | 5 Gram-positive cocci, 5 Gram-negative rods, 2 fungi | growth, MIC, MBC | 42 | imidazolium | alkyl, alkoxymethyl | L-lactate, DL-lactate | benzalkonium chloride |
| Matsumoto et al., 2004[131] | 9 lactic acid producing bacteria | rel. activity at saturation | 3 | imidazolium | alkyl | $PF_6^-$ | 14 organic solvents |
| Cieniecka-Roslonkiewicz et al., 2005[122] | 5 Gram-positive cocci, 1 Gram-positive bacillus, 4 Gram-negative rods, 2 fungi | growth, MIC, MBC | 21 | phosphonium | alkyl | $Cl^-$, $Br^-$, 10 other anions | benzalkonium chloride |
| Lee et al., 2005[84] | *E. coli* | growth, $EC_{50}$ | 13 | imidazolium | alkyl | bistriflamide, $PF_6^-$, $BF_4^-$, methylsulfate, $[CF_3SO_3]^-$, $SBf_6^-$ | 8 organic solvents |
| Docherty and Kulpa, 2005[132] | *Vibrio fischeri* (5 other bacteria) | luminescence, $EC_{50}$ (CFU at 1 g/L) | 14 (6) | imidazolium, pyridinium | alkyl | $Cl^-$, $Br^-$, dicyanamide | 12 organic solvents |
| Garcia et al., 2005[60] | *Vibrio fischeri* | luminescence, $EC_{50}$ | 10 | imidazolium | alkyl | $Cl^-$, $Br^-$, $BF_4^-$, $PF_6^-$ | 7 organic solvents, 7 cationic surfactants |
| Couling et al., 2006[133] | *Vibrio fischeri* | luminescence, $EC_{50}$ | 25 | imidazolium, pyridinium, ammoinium, phosphonium, choline | alkyl | $Cl^-$, $Br^•$- bistriflamide, diethylphosphate, dicyanamide | 6 organic solvents, 7 compounds used to synthesize ILs |
| Ranke et al., 2006[54] | IPC-81 cells | WST-1 reduction, $EC_{50}$ | 74 | imidazolium, quinolinium, phosphonium, ammonium | alkyl, hydroxyl alkyl, carboxy alkyl, phenylalkyl | $Cl^-$, $Br^-$, $BF_4^-$, $PF_6^-$ | benzalkonium chloride constituents |
| Stolte et al., 2006[35] | IPC-81 cells | WST-1 reduction, $EC_{50}$ | 35 | imidazolium | alkyl | 27 | 18 compounds used to synthesize ILs, 4 organic solvents |
| Stolte et al., 2006[134] | IPC-81 cells | WST-1 reduction, $EC_{50}$ | 99 | imidazolium, pyridnium, dimethylaminopyridinium, morpholinium, pyrrolidinium, alkyl, piperidinium, ammonium | alkyl, alkoxy, nitrile, hydroxyl | $Cl^-$, $Br^-$, $I^-$, bistriflamide | 3 organic solvents, 3 biocides |
| Ganske and Bornscheuer, 2006[135] | 3 bacteria | growth at 4% and 10% IL v/v | 2 | imidazolium | butyl | $BF_4^-$, $PF_6^-$ | DMSO, methanol ethanol |
| Frade et al., 2007[136] | HT-29 and CaCo-2 cells | MTT reduction | 24 | imidazolium, guanidinium, phosphonium, choline, ammonium | alkyl, hydroxyethyl, methoxyethoxyethyl | $BF_4^-$, $PF_6^-$, dicyanamide, acesulfame, saccharinate, bistriflamide | methanol, acetone, acetonitrile, ethanol, and DMSO |
| Luis et al., 2007[118] | *Vibrio fischeri* | luminescence, $EC_{50}$ | 5 | imidazolium, pyridinium, pyrrolidinium | alkyl | $Cl^-$ | |
| Matzke et al., 2007[137] | IPC-81, *Vibrio fischeri* | WST-1 reduction, luminescence, $EC_{50}$ | 11 | imidazolium | alkyl | 6 different anions | sodium bistriflamide, carbendazim, acetone, acetonitrile |

[a] MIC = minimum inhibitory concentration, MBC = minimum bactericidal/fungicidal concentration, CFU = colony forming units

**Table 5. Aquatic Toxicity Studies on Ionic Liquids**

| reference | test systems | end point | no. of tested ILs | head groups | side chains | anions | reference compds |
|---|---|---|---|---|---|---|---|
| Bernot et al., 2005[119] | *Daphnia magna* | acute toxicity, chronic reproductive tox. | 4 | imidazolium | alkyl | $Cl^-$, $Br^-$, $BF_4^-$, $PF_6^-$ | $NaBF_4$, $NaPF_6$, 7 common chemicals |
| Garcia et al., 2005[60] | *Daphnia magna* | acute toxicity | 10 | imidazolium | alkyl | $Cl^-$, $Br^-$, $BF_4^-$, $PF_6^-$ | 7 organic solvents, 4 quat ammonium surfactants |
| Couling et al., 2006[133] | *Daphnia magna* | acute toxicity | 17 | imidazolium, pyridinium, phosphonium, ammonium, dimethylaminopyridinium | alkyl | $Cl^-$, $Br^-$, $BF_4^-$, $PF_6^-$ | |
| Wells and Coombe, 2006[53] | *Daphnia magna*, *Selenastrum capricornutum* (monocellular algae) | acute toxicity | 10 | imidazolium, pyridinium, phosphonium, ammonium | alkyl, alkoxyalkyl | $Cl^-$, $PF_6^-$, bistriflamide, diethylphosphate, methylsulfate | 6 organic solvents, sodium methylsulfate, $NaPF_6$, $HN(CF_3SO_2)_2$ |
| Jastorff et al., 2005[116] | Lemna minor | growth inhibition | 2 | imidazolium | alkyl | $BF_4^-$ | |
| Latala et al., 2005[138] | two monocellular algae | growth inhibition | 4 | imidazolium | alkyl, benzyl | $BF_4^-$ | |
| Pretti et al., 2005[139] | *Danio rerio* (zebrafish) | | | imidazolium, pyridinium, ammonium, pyrrolidinium, | alkyl, fatty acid, hydroxylalkoxyalkyl | 11 anions | methanol, acetonitrile, dichloromethane, aniline, triethylamine |
| Bernot et al., 2005[120] | *Physa acuta* (freshwater snail) | acute toxicity, movement, feeding behavior | 9 | imidazolium, pyridinium, ammonium, phosphonium | alkyl | $Br^-$, $PF_6^-$ | pentachlorophenol, ammonia, 3 organic solvents |
| Matzke et al., 2007[137] | *Scenedesmus vacuolatus* (monocellular algae), Lemna minor | acute toxicity | 10 | imidazolium | alkyl | 5 different anions | sodium bistriflamide, triclosan, carbendazim, atrazin, acetone, acetonitrile |

to but are generally not lower than 100 $\mu$g $L^{-1}$.[21,48,72,113] This further indicates the importance of the data put forward by Wells and Coombe as negative examples. It should be realized however that two members of the most commonly employed ILs, namely the 1-butyl-3-methylimidazolium salts, showed only moderate aquatic toxicity values between 5 and 50 mg $L^{-1}$ in their dataset.

Recently, the first data on fish toxicity (if data on surfactants that can be regarded as ionic liquids is not counted) of 15 ILs were published by Pretti et al.[114] and were interpreted as a warning shot. Out of the 15 ILs tested, 2 exhibited 96 h fish toxicity to zebrafish lower than 100 mg/L (between about 2 and 30 mg $L^{-1}$). These two ILs share their most important structural features with common cationic surfactants, and compared with fish toxicity values for such compounds, the fish toxicity data by Pretti et al. do not look unusual, as acute toxicity values below 1 mg $L^{-1}$ have been collected earlier for cationic surfactants.[21]

Nevertheless, the potential impact of large, hydrophobic cations on aquatic organisms has to be kept in mind for a sustainable process design with ionic liquids.

## 5.3. Terrestrial and Mammalian Toxicity of Ionic Liquids

Terrestrial toxicity data for ILs published in international journals is very sparse. Therefore, we decided to include some recently presented talks and posters in our collection (Table 6). The data is in the process of being published in peer-reviewed journals. Still, the investigations are confined to 1-alkyl-3-imidazolium type ILs. However, the first conclusions can already be drawn. It can be stated that plant growth inhibition due to ionic liquid exposure does occur, with effective concentrations ranging down to 100 mg $kg^{-1}$ and lower. Matzke et al. have investigated the sorption of both 1-butyl-3-methylimidazolium and 1-octyl-3-methylimidazolium ILs to different soils, modified by addition of clay and organic substance.[115] Although they found that sorption of the 1-butyl-3-methylimidazolium cation is less than that of the 1-octyl-3-methylimidazolium cation, and therefore the bioavailability of 1-butyl-3-methylimidazolium can be said to be higher, 1-octyl-3-methylimidazolium still showed effects at lower concentrations than those for 1-butyl-3-methylimidazolium, confounding the results that were published earlier.[116]

Concerning mammalian toxicity, a series of acute toxicity tests on rats, among others on its contact sensitizing potential, have recently become available for 1-butyl-3-methylimidazolium chloride, reporting an acute oral $LD_{50}$ for female rats of 550 (381−1710) mg $kg^{-1}$. The activity in dermal application was much increased when 1-butyl-3-methylimidazolium chloride was applied in dimethylformamide, lowering the dermal LC50 at least for the female sex from >2000 mg $kg^{-1}$ to the range between 800 and 200 mg $kg^{-1}$.

1-Butyl-3-methylimidazolium was also found to be slightly irritating to the skin. The lymph node proliferative activity in the local lymph node assay indicated a behavior consistent with some sensitation potential.

Tests for ionic liquid mutagenicity by Docherty et al. in a bacterial assay with ten compounds resulted in none of them meeting US EPA criteria for mutagenicity.[117]

## 5.4. Uncertainty in the Evaluation of Biological Activity

Recently, attempts have been undertaken to rationalize results from biological testing by quantitative structure−

**Table 6. Terrestrial and Mammalian Toxicity Studies on Ionic Liquids**

| reference | test systems | end point | no. of tested ILs | head groups | side chains | anions | reference compds |
|---|---|---|---|---|---|---|---|
| Jastorff et al., 2005[116] | *Lepidium sativum* | growth inhibition | 2 | imidazolium | alkyl | $BF_4^-$ | |
| Pernak et al., 2004[45] | *Hordeum vulgare* | growth inhibition | 10 | imidazolium | alkoxyalkyl | $BF_4^-$ | |
| Thiele et al., 2006[140] | *Folsomia candida* | acute toxicity, chronic reproductive tox. growth inhibition | 1 | imidazolium | alkyl | $BF_4^-$ | benzalkonium chloride |
| Swatloski et al., 2004[141] | *Caenorhabditis elegans* | acute toxicity | 3 | imidazolium | alkyl | $Cl^-$ | |
| Juffemholz and Filser, 2004[142] | *Enchytraeus albidus* | acute toxicity, chronic reproductive tox. growth inhibition | 2 | imidazolium | alkyl | $BF_4^-$ | |
| Baczewski et al., 2007[143] | *Hordeum vulgare*, *Raphanus sativus* | germination, growth, growth anomalies | 2 | imidazolium | (-)-1-(1*R*)-nopyl | $Cl^-$, $NO_3^-$ | 1-methylimidazole |
| Pernak et al., 2001[144] | rat | acute toxicity | 1 | imidazolium | alkoxyalkyl | $PF_6^-$ | |
| Swatloski et al., 2003[67] | rat | acute toxicity | 1 | imidazolium | alkyl | $PF_6^-$ | |
| Landry et al., 2005[145] | rat | acute toxicity (oral and dermal) | 1 | imidazolium | alkyl | $Cl^-$ | |
| Landry et al., 2005[145] | rabbit | dermal and eye irretation | 1 | imidazolium | alkyl | $Cl^-$ | |
| Landry et al., 2005[145] | mouse | dermal toxicity | 1 | imidazolium | alkyl | $Cl^-$ | |
| Matzke et al., 2007[137] | *Lepidium sativum*, *Triticum aestivum*, *Folsomia candida* | growth inhibition, reproduction | 4 | imidazolium | alkyl | $BF_4^-$, bistriflamide | sodium bistriflamide, carbendazim, atrazin |

activity relationships (QSARs), in order to be able to estimate the hazard potential of ILs that have not been tested yet.[112,118] While these studies are currently confined to one assay (V. fischeri luminescence), it can be expected that attempts will be made to extrapolate to other species. At the same time, there are indications that, for simple, small organisms living in aqueous media, an unspecific mode of action dominated by hydrophobicity dominates the observeable adverse effects[54] and that cations and anions act according to the principle of concentration addition.[35] As long as these hypotheses are not confirmed by independent studies and tested for applicability to a variety of organisms, a prediction of biological activity for the vast untested majority of combinations of ILs and organisms is not possible.

It also has to be noted that, with very few exceptions,[119−121] no studies on chronic toxicity or sublethal effects have been carried out.

Concerning human health risks, no mammalian mutagenicity or carcinogenicity studies have been performed, and only limited data on sensitization of skin, eyes, and respiratory tract have been published.

## 6. Evaluation Uncertainties and Data Gaps

The largest uncertainty in the evaluation of the comparative ecotoxicological risk profiles of ionic liquids as compared to functionally related conventional molecular solvents and structurally related ionic surfactants is currently the question under what circumstances and in what amounts ILs or their breakdown products will enter the environment. Without this information, their ecotoxicological risk profiles are highly underdetermined.

In our assessment of potential release scenarios, we have focused on industrial uses. However, it is also possible that ILs will be used in consumer products. To illustrate this point, hexafluorophosphate anions are a common ingredient in the popular Li ion batteries that have become almost ubiquitous in industrialized parts of the world. This analogy also illustrates that in such a case it can become quite difficult to control these substances, as recent expensive product recalls by laptop producers have shown.

Presuming a release, the next important piece of information about the potential impact of a chemical substance on the environment is its fate in the environment, which can be simplified to its environmental degradability in the environmental medium to which it has the highest affinity. Although we have shown that some information on biodegradability is already available, it must be noted that knowledge of this is of utmost importance for a chemical substance that is to be termed “green”.

While there is now a good amount of data on the degradabilty of IL cations, the lack of knowledge about the environmental fate of widely used anions such as bistriflamide is disturbing. This anion has already been shown to increase the toxicity of ionic liquid cations and, potentially, also of other organic cations.[35,122]

The third large uncertainty factor is the rate at which new ionic liquids and ionic liquid applications are published, in many cases in the journal *Green Chemistry*, implying that they *are* green chemistry, but with not more than a trace of consideration for the questions that have been addressed in this paper. It is impossible to foresee what kind of structures will appear next, and it seems reasonable to argue that the bar should be raised for products and processes to be considered green, in the sense that a monocriterial optimiza-

tion (low vapor pressure) cannot be considered sufficient in the presence of multicriterial optimization challenges.

While external effect concentrations for ionic liquids—for example aquatic toxicity values—are appearing at quite a fast pace recently, evaluation uncertainties regarding their large scatter can potentially be reduced by studies focusing on more general concepts such as correlations between hydrophobicity, potentially modified by more specific interaction potentials, and bioconcentration, critical body residues, but also basal cytotoxicity.[123,124]

The benchmark chemicals (conventional molecular organic solvents and surfactants, including biocidal surfactants) that we have chosen for our comparative evaluation show a much lower evaluation uncertainty, which already starts with their fairly well-known and stable use patterns. This imbalance could possibly be reverted by focusing only on the technological development of ionic liquids that are really candidates for sustainable products from a multicriterial perspective.

## 7. Conclusions

In the beginning, we have stated that the rationale for calling ionic liquids "green" consists of three arguments relating to vapor pressure, flammability, and toxicity. We have argued that this is not sufficient for a design of sustainable chemical products and have referred to the concept of ecotoxicological risk profiles, which comparatively assess substances according to the five risk indicators—release, spatiotemporal range, bioaccumulation, biological activity, and uncertainty (Figure 2).

Concerning the release of and from ionic liquids, applications and processes have to be designed to take into account the toxic potential of the substances employed. At current, this seems to be possible, especially when ILs are used under highly controlled conditions in chemical production facilities.

The biodegradability of ILs has focused on making the cation more biodegradable. Because of the need for hydrophobic ILs, it seems to be of primary importance to develop anions that introduce sufficient hydrophobicity but are at the same time biodegradable. Even if high bioaccumulation and toxicity might be observed for the parent compound, its ready degradation, starting in wastewater treatment facilities, would decrease the joint bioaccumulation of the parent compound and the transformation products, and critical body residues would not be reached. Of course, similar considerations are valid for both anions and cations, and the focus on cation biodegradability might be justified by the above-mentioned tendency of organic cations to be more toxic than anions, which could in turn be related to the negative surface charge (membrane potential) of living organisms.

In addition to current studies on wastewater treatment methods and biodegradation, the toxicity of the degradation products should be investigated, in order to make sure that they are less toxic than the original products.

The knowledge we have on IL toxicity, which has been argued to be dominated by their bioaccumulation potential, already allows for an T-SAR directed design for low toxicity. The key factor will be low anion and cation lipophilicity. If, however, lipophilicity in the form of low water solubility is a technical requirement, a design for biodegradability could resolve the conflict between safety and technical requirements.

The fact that cations and anions will generally have a separate fate in the environment leads to the conclusion that they have to be evaluated separately. A convenient strategy is to test the alkali salts of anions and the halogenides of cations, and to attempt to explain their combined effects by means of mixture toxicity.[35] Biodegradation should be evaluated separately for cations and anions, in order to avoid simple dilution of refractory ions with biodegradable ones.

Next to the obvious advantages in optimizing the breakdown of ILs in the environment from the environmental viewpoint, some direct tests of bioaccumulation of ILs should be carried out. If a sufficient body of such data should appear, these could be generalized by the help of QSAR and the proposed screening indicators for hydrophobicity.

There is also next to no knowledge on sublethal and chronic effects of ILs on biological organisms. However, we argue that this is of limited relevance as long as only small volumes of readily biodegradable ILs are released to the environment, which is what we would aim for with first priority. If large volumes of refractory ILs were to be released, the question of sublethal and chronic effects would of course quickly be relevant.

Summing up, the structural variability of ionic liquids provides substances that have a low risk regarding each of the five risk indicators. Therefore, there is a good chance that we will see a sustainable ionic liquid with an excellent risk profile for a defined technical application which is itself in line with sustainable development. However, the reverse is also possible, if no care is taken to avoid unfavorable risk profiles.

Finally, it must be noted that the type of risk analysis carried out here will be most efficient when embedded in a sustainable product design (Figure 1) or even a life-cycle design process, as indicated in the Introduction and further described in earlier contributions.[19,116] A start with analyzing the life cycle of an ionic liquid has already been made,[125] and future studies should take a more holistic view on products and processes than could be propagated in this study.

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