Green Chemistry

TUTORIAL REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d6gc01231k

Towards safe and sustainable ionic liquids: a critical outlook on industrial and pharmaceutical integration

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Ionic liquids (ILs) have emerged over the past three decades as highly versatile and tunable solvents whose physicochemical properties can be precisely adjusted by selecting appropriate combinations of cations and anions. In pharmaceuticals, ILs serve as solvents, excipients, and active pharmaceutical ingredients (API-ILs), addressing challenges such as poor solubility, limited bioavailability, and polymorphism. Despite rapid scientific progress, the transition of ILs from laboratory research to industrial application remains slow. Significant knowledge gaps persist in toxicity, biocompatibility, biodegradability, scalability, and long-term safety, while life-cycle assessment (LCA), techno-economic analysis (TEA), and social LCA remain limited. These gaps are further exacerbated by the structural diversity of ILs, which hinders standardised testing and predictive modelling. Addressing these challenges requires early integration of Safe and Sustainable by Design (SSbD) principles, improved computational and screening tools, and the development of protocols tailored to IL diversity. Incorporating green chemistry and circular economy approaches can streamline the identification of safer and more sustainable ILs while reducing experimental and economic burdens. This review therefore brings together environmental, economic, social, and industrial considerations, including LCA, TEA, toxicity, scalability, and current pharmaceutical applications, to provide a unified perspective on the opportunities and barriers associated with IL development. By consolidating these aspects, it aims to guide more responsible, efficient, and sustainable implementation of ILs, with relevance to API-ILs and their potential future in the pharmaceutical industry.

Received 27th February 2026,
Accepted 4th May 2026

DOI: 10.1039/d6gc01231k

rsc.li/greenchem

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1. This tutorial review highlights advances in the development of tunable ionic liquids (ILs) as greener solvents and active pharmaceutical ingredient ionic liquids (API-ILs), together with emerging Safe and Sustainable by Design (SSbD) strategies and the use of computational screening to reduce experimental burden and support informed molecular design.
2. Although ILs are frequently presented as green chemistry solutions, their true sustainability depends on the integrated evaluation of toxicity, life-cycle impacts, scalability, and techno economic feasibility, emphasizing the need for robust, systems-level assessment frameworks.
3. Future progress will rely on standardized evaluation methods, predictive modelling, and circular economy thinking to translate ILs from promising concepts into responsible industrial implementation. By unifying environmental, economic, social, and industrial perspectives, this review provides a clear framework to support evidence-based decisions and help shape the next generation of green chemistry research.

Introduction

The global demand for sustainability has spread across all sectors, including the pharmaceutical sciences and industry, driven by the urgent need to reduce the environmental impact. Interestingly, the carbon footprint of the pharmaceutical industry exceeds that of the automotive industry by around 55%.[1] In 2023 alone, the total emissions of the public and private pharmaceutical sector amounted to 397 million tonnes of CO_2.[2] These emissions fall under Scope 3 of the Paris Climate Agreement,[3] and represent a major challenge not only for the pharmaceutical industry, but for many industries worldwide. To address this, many companies in the pharmaceutical industry are focusing their efforts on common sustainability goals. One innovative approach to setting new sustainability targets is to move from a linear to a circular economy model.[4] This transition is encouraged to follow a Safe and

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Sustainable by Design (SSbD) approach, which incorporates life cycle assessment (LCA), social life cycle assessment (S-LCA), life cycle costing/techno-economic analysis (LCC/TEA), water footprint and eco-design principles. Toxicity and sustainability considerations are also integrated throughout all stages of a product's life cycle, from process design to end-of-life, with a focus on recycling potential, hence ensuring intrinsic safety, functionality, and circularity throughout the product's life cycle. These methods highlight the environmental benefits and play a critical role in moving towards a low- or zero-waste future.[5] By adopting such strategies, the pharmaceutical industry can make an important contribution to global sustainability efforts. These include reducing carbon emissions, minimising water consumption, limiting hazardous and toxic materials and substances, disposing of toxic waste responsibly, minimising energy consumption, and reducing packaging waste.[6,7] Another important aspect of this goal is the implementation of efficient systems and processes through the principles of green chemistry, such as the development of safer chemicals.[8] Promising alternatives to conventional solvents used in industrial and scientific fields include ionic liquids (ILs). ILs are salts composed of large organic cations and (in)organic anions, frequently smaller than their cations. These are valued for their general very low volatility and low flammability, and high thermal and chemical stability.[9] A prominent feature of ILs is their tunability: by varying the structure of specific cations and anions, as well as their combination, their physicochemical properties can be tailored for different applications. With an estimated 10^6–10^{15} possible combinations of anions and cations, ILs have earned the title of "designer solvents".[10,11] The tunability and customizability make them an attractive replacement for volatile organic solvents, which significantly reduces the environmental impact. The earliest mention of ILs dates back to 1914, when Paul Walden discovered that ethylammonium nitrate, $[EtNH_3][NO_3]$, had a melting point of 12 °C.[12] This discovery marked the beginning of the first generation of ILs, which – some decades later – were characterised by bulky imidazolium and pyridinium cations with halides and halometallates as anions. Yet, these ILs are reactive with both water and air, as well as corrosive to metallic materials, limiting their practical applications.[13] The second generation of ILs consists of ammonium, pyridinium, imidazolium and phosphonium cations with hexafluorophosphate and tetrafluorophosphate as anions.[14,15] They were one of the main topics in the field due to the improved properties compared to the first generation, such as low viscosity, high solubility of target compounds and low melting point. However, it was found that, like the first, this generation is highly toxic to aquatic life and poorly biodegradable, prompting the development of a third generation. Cholinium is the main cation used in this generation, along with amino acids, alkyl sulphates, sugars, *etc*. as anions. In this case, environmentally friendly cations and anions were combined, resulting in task-specific ILs. This led to another advantage of ILs, namely selectivity.[16–18] They were also recognised for their biological activity, including bacteriostatic, herbicidal and fungicidal properties. In this context, the third generation can be referred to as "bio-based" or "greener" ILs.[19] These ILs are designed to minimise the environmental impact and promote sustainability by containing cations and anions derived from renewable natural sources compared to the first and second generation. The most widely used and best-studied cation in bio-based ILs is cholinium.[20–27] Betaine[28–30] and carnitine[31–33] also appear frequently, reflecting their benign character. Amino-acid-derived cations have been reported as well though remain relatively less investigated compared to cholinium-based ILs.[24,34,35] Among amino-acid-derived cations, proline-based[36–38] cations are attracting increasing interest, although experimental data remain limited. Moreover, alkaloid-based cations are discussed largely at a conceptual level and have recently begun to be explored experimentally, with examples based on quinine,[39–41] nicotine,[42,43] and caffeine.[44–47]

The concept of "greener" ILs aims to align with the principles of green chemistry, such as using renewable raw materials and minimising hazardous waste. It also seeks to reduce the environmental impact of the products and materials throughout their life cycle, enable sustainable practices without compromising performance and offer biocompatibility and biodegradability.[48] Although these ILs are often more expensive to produce, and proving their safe impact on human health remains a long-term challenge, they hold the promise of developing more sustainable, efficient and environmentally friendly technologies in various industries, particularly in the pharmacological field. More specifically, in the form of active pharmaceutical ingredients (APIs). The incorporation of ILs significantly improves drug solubility, biological activity, polymorphism and drug delivery efficiency.[49] Due to their numerous advantages, ILs are used in drug synthesis and delivery as solvents, catalysts and reaction media, as well as in biomedical analysis, and in the formation of API-ILs.[50] Interest in ILs continues to grow, and studies are increasingly being conducted in the fields of medicine, pharmaceutical sciences, drug delivery systems and the development of novel therapeutic formulations that improve the efficacy, bioavailability and stability of drugs.[50] The growing volume of research underlines the increasing interest in ILs in the pharmaceutical sector and the numerous studies being conducted on them (Fig. 1). However, there is still a considerable gap in studies on the toxicity and biocompatibility of API-ILs, which further hinders their industrial production and application.

While articles discussing the toxicity of ILs,[51–55] their industrialisation,[56–60] and API-ILs[61–66] individually are available, to our knowledge, none combine all these topics. This fragmentation limits the ability to evaluate ILs from a holistic sustainability perspective, particularly in application-driven contexts. Therefore, this review addresses the integration of the three pillars of sustainability, *i.e.* environmental, economic, and social into the development of ILs, particularly within the pharmaceutical sector, compared to other industrial areas. Rather than providing an exhaustive analysis of every aspect of IL research, which has already been extensively covered in previous literature, this work focuses on their joint

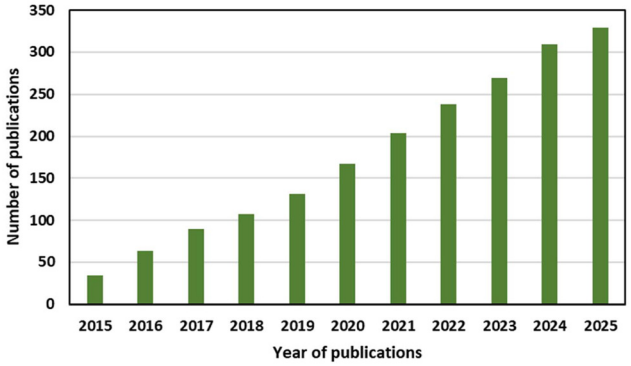

Fig. 1 Cumulative number of publications over the last ten years related to ILs and APIs (based on the SCOPUS database search on 30.09.2025 using "ionic liquids" and "active pharmaceutical ingredients" as keywords).

consideration within a use-oriented framework. Specifically, we link key assessments such as LCA, TEA, and toxicity with scale-up, industrialisation, and application requirements, demonstrating how decisions in one area directly affect the others. In this context, sustainability, safety, economic feasibility, and performance are not treated separately, but considered together when selecting or designing (API) ILs. By aligning this approach with the SSbD framework, the review highlights relevant trade-offs and knowledge gaps that are often overlooked when these aspects are evaluated independently. Thus, this review aims to serve as a conceptual guide for researchers and to support more informed and comprehensive decision-making in the development and implementation of IL technologies. For clarity, the structures of the cations and anions throughout the review are summarised in Tables S1 and S2 in the SI, respectively.

An overview of health and *in vitro* cytotoxicity assessments of ILs

ILs have gained significant attention as potential alternatives to conventional solvents due to their unique properties, such as general low volatility, high thermal and chemical stability and selectivity, as well as their designer solvent character. However, their widespread application raises concerns regarding their impact on both human health and the environment. These concerns include issues of cytotoxicity, genotoxicity and bioaccumulation, in addition to environmental persistence, ecotoxicity, and limited biodegradability. Therefore, understanding the relationships between IL structure, biodegradability, and (eco)toxicity is crucial for the rational design of biocompatible, safe, and sustainable ILs (Fig. 2). At the very beginning, ILs were considered green solvents, as they were generally regarded as non-volatile. This supports the conclusion that ILs would not contaminate the atmosphere in the way organic solvents do. Still, due to the more hydrophobic nature of the first generation of ILs, these could – and did – contaminate

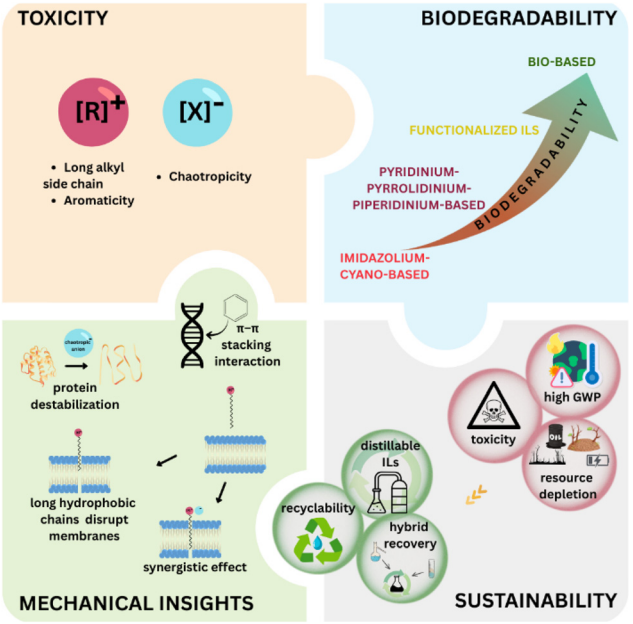

Fig. 2 Illustration on toxicity, biodegradability, mechanical insights and sustainability of ILs.

the aqueous streams. As a result, the first studies focused on aquatic bacteria, leading to the use of Microtox studies to analyse the ecotoxicity of ILs. The Microtox assay relies on testing bioluminescent bacteria, *Allivibrio fischeri*, using their natural luminescence to detect toxic substances. Within this assay, toxicity is determined from the decrease in light emission of the bacteria after exposure to a chemical, where reduced luminescence reflects disruption of cellular metabolism and membrane integrity. It is a simple, fast, and cost-effective method, sensitive to over 2700 chemicals, thus being a widely accepted technique for toxicity screening for all kinds of toxicants. It serves as a standard for acute toxicity testing in water. As much of the foundational toxicity work on ILs is now dated, we highlight only the principal outcomes here and refer readers to recent reviews for comprehensive discussion.

In one study, Microtox toxicity data were determined for 16 ILs of different cationic and anionic compositions.[67] The ILs 1-butyl-1-methylpyrrolidinium trifluoromethanesulfonate, [BMPyr][TFO], 1-butyl-1-methylpyrrolidinium chloride, [BMPyr][Cl], hydroxypropylmethylimidazolium fluoroacetate, [HOPmim][FAc], and hydroxypropylmethylimidazolium glycolate, [HOPmim][glycolate], were found to be less toxic than conventional organic solvents such as chloroform or toluene. The toxicity of pyrrolidinium cation was lower than the imidazolium and pyridinium ones. It was found that the inclusion of a hydroxyl group in the alkyl chain length of the cation also reduced the toxicity of the IL. In the study by Ranke *et al.*,[68] effective concentrations in these test systems were generally some orders of magnitude lower than effective concentrations of the conventional solvents acetone, acetonitrile, methanol, and methyl *t*-butyl ether. Toxicity increased with alkyl chain length of the imidazolium cations from C3 to C10, and no general influence of the anionic com-

pound on toxicity could be found, although it seemed to modulate toxicity in some cases. For *V. fischeri*, toxicity varied widely among the tested ILs, while for IPC-81 cells (a type of rat promyelocytic leukaemia cell line that is commonly used in toxicology and pharmacology studies), a clear trend showed increasing toxicity with longer R2 alkyl chains. A similar pattern was observed, where longer alkyl chains led to greater toxicity.[69,70] Considering Microtox studies, toxicity generally increases with hydrophobicity, particularly with elongation of the alkyl side chain or when highly hydrophobic anions such as [NTf_2] are present, as shown for several imidazolium, phosphonium, and guanidinium ILs.[71,72] More aromatic cation structures likewise tend to enhance luminescence inhibition, whereas simpler ammonium-based ILs show notably weaker effects. This overall pattern is further reinforced by comparative analyses of mono- *versus* dicationic ILs, where monocationic ILs consistently exhibit far stronger luminescence inhibition than their dicationic counterparts, often by more than one to two orders of magnitude, and where increasing alkyl linkage length within dicationic systems again correlates with higher toxicity due to increasing hydrophobicity. In these systems, the anion plays only a minor role, confirming that cation-driven lipophilicity overwhelmingly governs Microtox responses.[73] Within cholinium-based ILs, a similar structure–toxicity relationship is evident; compounds in which the anion or substituents increase overall hydrophobicity, such as propanoate, butanoate, bitartrate, dihydrogen citrate, chloride and benzyl-cholinium chloride, show EC_{50} values characteristic of harmful acute bacterial toxicity. In contrast, more hydrophilic or oxygenated counterparts, including acetate, bicarbonate, salicylate and dihydrogen phosphate salts, exhibit substantially reduced luminescence inhibition and do not fall within acute aquatic hazard classifications.[74,75] Protic ILs show the same pattern, with increased toxicity linked to increasing structural hydrophobicity.[76]

The IL 1-butyl-3-phenylimidazolium methyl sulphate, [BPheim][$MeSO_4$], was identified as highly toxic,[77] whereas hydroxylated ILs like [HOPmim][glycolate] were much less toxic, highlighting the role of functional groups in reducing toxicity. Introduction of alkoxy groups into the cation structure lowers toxicity compared to simpler imidazolium compounds.[78] Furthermore, a comparation of the toxicity of 2 cations: 1-butyl-3-methylimidazolium, [Bmim], and 1-methyl-3-methylimidazolium, [Mmim], as well as the effect of 6 different anions: chloride, [Cl]; tetrafluoroborate, [BF_4]; octylsulphate, [OS]; bis(trifluoromethylsulfonyl)imide, [NTf_2]; bis(trifluoromethyl)imide, [BTMFI]; and bis(1,2-benzenediolato) borate, [Bphd], using an (eco)toxicological test battery, including bacterial assays, was conducted. When comparing the cations, the longer alkyl side chain showed a higher toxicity.[79] Aromatic headgroups like imidazolium showed an increased toxicity compared to saturated analogues.[68] The imidazolium-based ILs with [BF_4] and [PF_6] anions were found to be twice as toxic as their chloride counterparts, and some anions, such as trifluoromethanesulfonate, CF_3SO_3, were lethal to *Escherichia coli*, suggesting potential systemic toxicity.[80,81] An investigation of the toxicity of [Bmim] and *N*,*N*,*N*-trimethylethanolammonium, [Tmea] as cations found the latter to be significantly less toxic.[82] The same study showed that [NTf_2] drastically increased toxicity, while [Cl] and acetate [Ac] showed much lower toxicity. The toxicity of [NTf_2] can be explained by its pronounced hydrophobicity and chaotropic character. When combined with a chaotropic cation, the resulting ion pair is capable of disrupting membranes, deactivating enzymes, and denaturating proteins, *etc.*[83,84] Even though anions are considered less effective compared to cations, this study shows that certain anions can drastically affect the ILs toxicity.[85] Nevertheless, when [NTf_2] was paired with a kosmotropic cation like choline, which is also biodegradable, the resulting pair exhibited lower toxicity. This further reinforces the dominant influence of cations in determining toxicity. In particular, the fluoride-containing anions exhibit toxicity that increases with the number of fluorine atoms. The rest of the halides have minimal effects when paired with cations. Furthermore, testing the toxicity of greener ILs, such as glycine-betaine- and alkyl-glycine-betaine-based ILs, shows that toxicity increases with longer cation alkyl chains.[30] Although anion hydrophobicity influenced toxicity to some extent, the cation effects dominated, with alkyl-glycine-betaine ILs exhibiting significantly higher toxicity and confirming the influence of the alkyl side chains. When comparing the toxicity of a database of 305 ILs based on imidazolium, pyridinium, phosphonium, ammonium, cholinium, morpholinium, guanidinium, amino-acid towards *Vibrio fischeri*, the order of toxicity is: phosphonium > imidazolium > pyridinium > guanidinium > ammonium > morpholinium > amino-acid-based > cholinium.[86] Taken together, the Microtox data from all studies strongly indicate that *Vibrio* toxicity across diverse IL families is driven predominantly by molecular hydrophobicity, aromaticity, and anion character, whereas bio-inspired or functionalised structures mitigate, but do not universally eliminate, acute bacterial effects. Moreover, betainium, butylbetainium, dodecylbetainium ILs were tested on Gram-positive and Gram-negative bacteria, where most ILs were low to moderately toxic, particularly those with shorter cation chains.[29] Dodecylbetainium ILs exhibited higher antibacterial activity due to their surfactant-like character associated with longer alkyl chains. Fungal toxicity, assessed against the common yeast *Candida albicans*, and two filamentous fungus *Aspergillus niger* and *Penicillium chrysogenum*, mirrored the bacterial trends.

As toxicity studies progress to algal species such as *Chlorella vulgaris*,[87] *Scenedesmus obliquus*,[88] *Phaeodactylum tricornutum*[89] and *Chlorella pyrenoidosa*,[90] similar findings are presented. For example, EC_{50} values, *i.e.* the concentration of a substance that produces 50% of its maximum biological response, indicated increasing toxicity for *Chlorella vulgaris* with longer alkyl chains on imidazolium ILs.[87] Structural modifications such as methylation influenced the IL toxicity to *Scenedesmus obliquus*, impacting chlorophyll content, photosystem efficiency, and algal ultrastructure.[88] Interestingly, there was a significant decrease in toxicity with increasing alkyl side chain considering for *C. pyrenoidosa* when exposed to 1-butyl-3-methylimidazolium chloride, [Bmim][Cl], 1-octyl-

3-methylimidazolium chloride, [Omim][Cl], 1-octyl-3-methylimidazolium nitrate, [Omim][NO_3], 1-octyl-3-methylimidazolium tetrafluoroborate, [Omim][BF_4], and 1-dodecyl-3-methylimidazolium chloride, [Dmim][Cl].[89] The study carried out by Matzke *et al.*[79] shows that chloride and tetrafluoroborate exhibit no significant toxicity towards algae *Pseudokirchneriella subcapitata*. Cholinium- and betaine-levulinate ILs show only low to moderate toxicity toward freshwater green algae, with toxicity increasing with hydrophobicity yet remaining far below the toxicity of conventional imidazolium analogues.[91] This trend extends to betaine-based ILs paired with indole-3-butyrate, where shorter-chain homologues show minimal algal inhibition, and only the more hydrophobic derivatives induce moderate impacts on growth.[92] Cholinium amino acid ILs further illustrate the benign character of genuinely biogenic ILs, with algal EC_{50} values typically in the hundreds to thousands of mg L^{-1} range, which is several orders of magnitude less toxic than standard aromatic cation ILs.[93] Conversely, glycine-betaine-derived ILs demonstrate that "natural origin" alone does not guarantee ecological safety: in this family, algae are generally more sensitive than bacteria, and most compounds still fall within aquatic hazard classifications.[30] Similar structure–toxicity relationships appear in chlorinated and oxygenated cholinium salts, where hydrophobic anions such as propanoate, butanoate, bitartrate and dihydrogen citrate substantially increase algal sensitivity, whereas acetate, bicarbonate, salicylate and dihydrogen phosphate produce much weaker effects.[74] More recently, mixtures of cholinium ILs with inorganic salts have shown that algal toxicity remains dominated by the IL component itself and the effects follow simple concentration–addition, again highlighting hydrophobicity as the key factor of algal response.[94]

Aquatic invertebrates like *Daphnia magna*[87] are more sensitive to ILs than algae. Studies demonstrated a sharp decrease in EC_{50} values as the alkyl chain length increased, especially for imidazolium nitrate ILs. Vertebrate studies included toxicity evaluations in zebrafish and amphibians. Leitch *et al.*[95] found that [Omim] caused significant damage to liver and kidney tissues in frogs and fish, with toxicity being largely independent of the paired anion, as long as dissociated in aqueous environment. In plant models like rice seedlings,[96] IL toxicity was found to correlate with structural features. For instance, the transport and accumulation of ILs in rice decreased with longer alkyl chains, indicating possible hydrophobic barrier formation.[97] On the other hand, [NTf_2], showed high toxicity related to *Daphnia magna* alongside [Bphd]. Hydrophilic anions, such as hydrogensulphate, [HSO_4], increase toxicity, while more hydrophobic ethylsulphate, [$EtSO_4$] was found to be harmless due to its partial biodegradability when tested on *Daphnia magna*.[98]

Toxicity studies on aquatic invertebrates show that ILs designed from biogenic building blocks can exhibit markedly lower hazard than conventional aromatic ILs, although their effects remain strongly dependent on molecular structure. Cholinium- and betaine-based levulinate ILs display low to moderate toxicity toward *Daphnia magna*, with the least hydrophobic structures producing only limited immobilisation and the betaine-ester levulinate derivative emerging as both the most biodegradable and the least toxic in the series.[91] A similar pattern appears in betaine-derived ILs paired with indole-3-butyrate, where shorter-chain homologues exert minimal toxicity toward *D. magna* and *Artemia franciscana*, and toxicity increases only when the alkyl chain becomes longer and more hydrophobic, shifting EC_{50} values into the moderately toxic range.[92] In contrast, surface-active cholinium bromide ILs with long alkyl substituents show very high acute toxicity to *D. magna* despite being biodegradable, demonstrating that chain length can override the benefits of a biogenic cation.[20] Cholinium amino acid ILs further support these trends, showing only very low acute toxicity toward brine shrimp even for more hydrophobic amino acid anions, highlighting how genuinely biogenic cations paired with degradable anions can yield systems that are comparatively benign toward aquatic invertebrates.[93] Unlike assays used for *Daphnia* or *Artemia*, Mbakidi *et al.*[28] employed an *in vitro* hemocyte-based assay using immune cells isolated from the freshwater mussel *Dreissena polymorpha*. Such tests measure invertebrate cytotoxicity and immunotoxicity at the cellular level. Betaine-amide ILs were tested and compared to cholinium, ammonium, and phosphonium ILs. Results indicated the increase of toxicity with increased cation chain length. Furthermore, lactate anion produced the lowest cellular reactivity. Overall, across bio-based IL families, toxicity remains highly tunable and follows consistent hydrophobicity-driven patterns, yet many simple or oxygenated derivatives achieve low acute hazard profiles compatible with improved environmental performance.

Toxicological testing extended to human cells, specifically imidazolium-, pyridinium-, piperidinium-, and morpholinium-based ILs were tested on human cancer cell lines (HeLa, HT-29, Caco-2, and MCF-7), with imidazolium ILs being the most toxic, especially as the alkyl chain length increased. Pyridinium-based ILs were slightly less toxic, while quaternary ammonium- and phosphonium-based ILs significantly inhibited acetylcholinesterase (AChE) and adenosine monophosphate (AMP) deaminase, indicating potential neurotoxicity and metabolic disruption.[99–101] These results were confirmed by other studies where imidazolium- and pyridinium-based ILs exhibited significant cytotoxicity in human cell lines such as Caco-2, HeLa, HT29, HepG2, AGS, and A549, with toxicity increasing as the alkyl chain length increased. Pyridinium and imidazolium ILs also inhibited AChE activity, which could lead to neurological disruptions.[68,99,102] ILs with longer alkyl chains and imidazolium cations were consistently more toxic. For example, [Omim] exhibited significantly higher cytotoxicity than shorter-chain analogues, and [NTf_2] and [PF_6] enhanced cytotoxicity relative to [Cl]. Phosphonium and quaternary ammonium ILs inhibited essential enzymes such as AChE and AMP deaminase, suggesting risks of neurotoxicity and metabolic disruption. One study showed how IL toxicity was strongly influenced by the anion, with [NTf_2] and [PF_6] increasing cytotoxicity, particularly in MCF-7 cells. A set of 45 ILs

were tested for cytotoxicity and for two mechanistic toxicity endpoints; [NTf_2-ARE] oxidative stress activation in AREc32 cells and AhR activation in AhR-CALLUX cells.[103] None of the tested ILs activated these genes, but many did show high cytotoxicity. Compared to baseline toxicity predictions, some ILs were more toxic than expected. Toxicity was influenced by the structures of ILs, particularly alkyl chain length and headgroup type. More specifically, long alkyl side chain of quaternary ammonium ILs underwent oxidation in both cell lines, though this metabolism did not account for their high toxicity. Additional screening of ILs in the database suggested possible modes of action such as aromatase inhibition and disruption of mitochondrial membrane potential, but follow-up *in vitro* assays indicated these effects were non-specific and likely driven by cytotoxicity rather than interactions. The mode of toxic action could not be identified, suggesting that the current molecular descriptors may not fully capture IL interactions with cellular components.

Studies using human T-lymphocytes and dermal fibroblasts demonstrate that long-chain imidazolium, pyridinium, and phosphonium ILs readily disrupt membrane integrity, impair mitochondrial function, and induce both apoptosis and cell-cycle arrest, while more hydrophobic anions such as [NTf_2] or [PF_6] further enhance cytotoxic effects.[104] Similarly, investigations on normal human dermal fibroblasts demonstrate that ILs with longer alkyl substituents markedly reduce cell viability, whereas ILs containing more polar anions such as dialkyl phosphates or ethyl sulphate are substantially less toxic.[105] These trends are reinforced by large-scale cytotoxicity datasets encompassing over one thousand ILs, where lipophilicity, aromaticity, and the presence of extended alkyl chains emerge as dominant predictors of reduced cell viability.[106,107] Additional work in human keratinocytes shows that conventional ILs induce oxidative stress, membrane destabilization, and cytoskeletal disruption, with toxicity again increasing alongside hydrophobicity and aromaticity.[106] In contrast, biocompatible and bio-derived ILs exhibit much more favourable cytotoxicity profiles. Cholinium- and carnitine-based ILs incorporating naturally occurring organic acids, such as phenyllactate, show minimal toxicity toward human epithelial cells and preserve normal morphology even at relatively high concentrations, highlighting the compatibility of these cationic species with mammalian systems.[108]

Cholinium–amino-acid ILs show low cytotoxicity in mammalian cells at formulation–relevant concentrations. For example, choline-phenylalanine [Cho][Phe] and choline-glutamate [Cho][Glu] did not significantly reduce viability of MDA-MB-231 cells up to 0.2% v/v, while a broader panel of cholinium-based ILs revealed that amino-acid and acetate anions lie at the lower end of cytotoxicity compared with more hydrophobic anions such as geranate across multiple human cell lines.[109,110] Even among less benign structures, replacing long hydrophobic tails with short or oxygenated groups, and substituting aromatic cations with aliphatic, bio-based ones, substantially improves cellular tolerance. In general, anions contribute to an overall IL toxicity, but their specific effects are not as pronounced as the influence of the cation. Though, the combination of certain anions with toxic cations led to greater accumulation in human cells, raising concerns about bioaccumulation and long-term exposure risks.[68,111] Some combinations of cations and anions exhibit unexpected toxicity due to synergistic effects, such as [NTf_2], and imidazolium.[103] Overall, longer alkyl side chains generally indicate higher toxicity due to increased hydrophobicity. However, ILs can have different effects on different organisms, as demonstrated by the aforementioned studies. In general, shorter alkyl side chains are safer as they cannot penetrate cells and are therefore recommended when designing ILs.

Although numerous studies have been conducted on the toxicity of ILs,[112–116] its mechanism is still not fully understood. Considering this, structure–activity relationships (QSAR) models have been developed to predict the toxicity of ILs. In simple words, QSAR models use mathematical equations as a link between compound's chemical structure and biological activity. These models are based on the principal that the structure of a compound is directly related to its biological activity. Therefore, physicochemical properties and molecular descriptors are used as predictor variables in such models, whereas biological activity serves as a response variable. QSAR models analyse data from known compounds to identify patterns between the chemical structure and their biological activity. This allows them to predict the biological activity for unknown compounds. In this way, ILs can be safely designed, as QSAR models contribute to the prediction of cytotoxicity, microbial inhibition and enzyme inhibition. Several QSAR approaches have been developed for ILs specifically. Over 200 ILs were analysed using a tool called CORAL, which builds mathematical models based on chemical structure, to investigate their effects on the bacteria *Staphylococcus aureus*.[117] Authors considered how changes in both the cation and anion influenced the ILs toxicity. The model was very accurate in predicting the bacterial response. To be more precise, the correlation coefficients (R^2) for the different sets mostly ranged between 0.85 and 0.92, indicating a strong relationship between predicted and experimental values. Furthermore, a prediction of the toxicity of different ILs toward rat leukaemia cells was also conducted, using a mathematical approach that combines information about both the cation and the anion.[118] They applied a method called Support Vector Machine (SVM) to build a model capable of predicting ILs toxicity toward leukaemia cells. Thirteen molecular features describing the ILs' chemical structures were used. A total of 318 ILs were tested on a leukaemia rat cell line (IPC-81), including imidazolium, pyridinium, ammonium, phosphonium, and others. The model was capable of estimating how toxic a new IL might be based solely on its structure. A key finding was that the interaction between the anion and the cation plays a major role in determining toxicity and not just their individual effects. Moreover, various models were built to explain how the structure of ILs influenced their toxicity towards the algae *Scenedesmus vacuolatus* and the water flea *Daphnia magna*.[119] The authors used a statistical method called partial least squares regression to develop QSAR models for predicting how toxic different ILs would be to both species. Molecular fea-

tures, *i.e.* descriptors with clear chemical meanings were applied, such as the hydrophobicity of the IL, the ability to disrupt cell membranes, *etc*. Two major findings were reported: (i) the ILs cation breaks through cell membranes, especially with long alkyl chains, and (ii) the anion often had a "chaotropic" effect, meaning that it destabilises proteins and other cell structures. Chaotropic species, distinguished by their low charge density and hydrophobic character, weaken the hydrogen-bonding network of water and can destabilize non-covalent interactions such as hydrogen bonds and hydrophobic associations. The researchers further extended the study by applying an interspecies model, called i-QSTR, predicting toxicity in one species based on data from the other and *vice versa*. This approach is valuable when toxicity data is missing for a species, allowing estimation from known data from another species. Artificial intelligence has also been used to study the toxicity of over 300 ILs on leukaemia cells with a machine learning model – SVM, and improved it using algorithms inspired by nature, such as moth flight or wolf pack hunting strategies.[118] Their best model could predict toxicity with very high accuracy. They also identified 13 main chemical features that strongly influenced how toxic each IL was. In examining the impact of nearly 300 ILs on AChE, an enzyme essential for nerve function, the team used machine learning to find patterns between IL structures and their enzyme-blocking ability.[120] The model assists in creating ILs that are safer for humans and the environment. Using both qualitative and quantitative SAR/QSAR approaches, authors examined how the IL structure influences AChE inhibition. ILs with longer alkyl chains were generally more toxic, likely due to their interaction with biological membranes and proteins. Introducing heteroatoms like oxygen or nitrogen reduced toxicity, likely due to hydrogen bonding. Cyano groups also reduced toxicity, while certain fragments, such as R≡N and R=N-increased it. Among different cation cores, toxicity followed the order: morpholinium < imidazolium < pyrrolidinium < piperidinium, indicating that morpholinium-based ILs were the least harmful ones. The structure–activity relationship in the cytotoxicity of imidazolium and benzalkonium ILs was determined using a predictive model.[103] A linear relationship was found between toxicity and increasing alkyl side chain up to C_{14} and C_{16}, where toxicity stabilises. This phenomenon is due to the fact that very long side chains do not fit well into the cell membranes as these have a certain thickness. Instead, they "sit" close to the outer layer without causing any damage. In contrast, ILs with the side chains of medium length, *i.e.* C_{10} to C_{12}, have the ability to create gaps in the membrane, leading to instability and cell damage. Experimental evidence supports this theory, showing that ILs with C_{15} side chains at positions 4 and 5 of the imidazole ring do not disrupt membranes, whereas ILs with C_{11} side chains at the same positions disrupt and significantly alter the membrane structure.[121] Bae *et al.*[103] compared the toxicity of aromatic and non-aromatic cations, finding that aromatic head groups (imidazolium and pyridinium) were significantly more toxic than the non-aromatic head groups (piperidinium and pyrrolidinium). A possible explanation is that the aromatic rings can cause specific toxic interactions with cells. More specifically, aromatic rings reduce the overall charge density, thereby enhancing the chaotropic character of the species, which in turn promotes more interactions with membranes as well as with enzymes and proteins. In addition, dicationic ILs have been shown to be less toxic compared to monocationic ILs, as their structure makes it more difficult to penetrate cell membranes.[122] Considering more benign ILs, relatively few studies have applied QSAR or related modelling approaches. These models are typically developed for traditional ILs and only rarely include "biocompatible" systems. However, the studies that do incorporate such ILs reveal a consistent pattern. In a QSAR analysis of toxicity toward four human-pathogen bacteria (*L. monocytogenes*, *S. aureus*, *E. coli*, *A. hydrophila*), classical imidazolium ILs were the most inhibitory, whereas amino-acid-based imidazolium ILs were among the least toxic.[123] Another QSAR study using Microtox® similarly confirmed the dominant structural drivers of toxicity: hydrophobicity and aromatic cations strongly increase toxicity, while cholinium, ammonium, morpholinium and amino-acid-based ILs consistently occupy the low-toxicity end of the model's training data. The experimental validation further showed that synthetically designed morpholinium ILs displayed lower toxicity toward *Vibrio fischeri* than structurally comparable imidazolium analogues.[86] Evaluation of triethanolammonium [Teoa] amino-acid ILs, through phytotoxicity tests with *Lepidium sativum* and cytotoxicity assays using L929 fibroblasts, also demonstrated very low toxicity. Across both studies, the measured values were frequently similar to or only slightly above those of the parent [Tea] base, and orders of magnitude lower than those typically reported for imidazolium ILs.[124]

While toxicity studies offer essential insights into the potential adverse effects of ILs, they mainly focus on harmful outcomes under specific conditions and do not fully reflect the complexity of interactions within biological systems. Therefore, a broader evaluation through biocompatibility is necessary to assess how ILs interact within physiological environments and to better determine their suitability for pharmaceutical applications. In this context, initial screening can be guided by established structure–toxicity relationships, such as alkyl chain length, hydrophobicity, and the nature of the cation and anion, supported where possible by modelling studies, to pre-select candidates with lower expected toxicity. These criteria should then be complemented by application-specific thresholds and experimental validation, allowing a more targeted and efficient selection of ILs for further development.

Biocompatibility of ILs

Given the limitations of toxicity assessments, biocompatibility provides a more comprehensive evaluation of IL behaviour in biological systems, focusing on their interactions with living organisms and their suitability for safe use, particularly in pharmaceutical applications. In this regard, biodegradability has emerged as a key aspect of biocompatibility, and numer-

ous studies have investigated the degradation behaviour of ILs across different generations. For example, aerobic biodegradability tests of various pyrrolidinium, morpholinium, piperidinium, imidazolium, and pyridinium cations[125] and phosphonium-, ammonium-, and imidazolium-based ILs[126] have been conducted. Aerobic biodegradability test usually refers to any test assessing the breakdown of a substance by microbes in the presence of oxygen. The studies showed that pyridinium and pyrrolidinium ILs were the most biodegradable, followed by piperidinium and morpholinium, while imidazolium showed the lowest biodegradability. The imidazolium ring's stability makes it more resistant to degradation, while the presence of nitrogen in pyridinium and pyrrolidinium cations enhances the microbial breakdown. Additionally, phosphonium-based ILs exhibited higher biodegradability. Six ILs composed of either [Bmim] or [Ch] as the cation, and [Cl], [Ac], or [Ntf_2] as the anion were tested for biodegradability using activated sludge.[82] The study found ILs containing [Ntf_2] and/or [Bmim] to be non-biodegradable, while ILs comprised of [Ch] and/or [Ac] were readily broken down. This shows that ILs must have both components biodegradable in order to be biodegradable overall, as resistant ions remain persistent and to not degrade. Analysis of a large literature dataset, including 508 ILs took place to identify the structural features directly affecting the biodegradability of compounds.[127] The analysis confirmed that certain cation families and functional groups are far more favourable for biodegradation. For example, cholinium and related bio-derived cations stood out as biodegradable. Conversely, ILs based on imidazolium or tetraalkylphosphonium cations tended to be non-biodegradable. This study also pointed the benefits of incorporating labile bonds since ester or carboxylate groups in side chains of quaternary ammonium and pyrrolidinium cations improved their respective biodegradability. QSAR predictions can be also used in biodegradability predictions. In that sense, a study using 7 BIOWIN models that are based on QSAR, evaluated three quaternary ammonium salts based on nicotinamide, *i.e.* vitamin B3; with butyl, decyl and hexadecyl chains.[128] The QSAR results suggested all these nicotinamide-based ILs would undergo primary biodegradation fairly quickly, based on models 1 & 2. However, models 5 & 6 showed none as readily biodegradable under OECD 301C criteria. Lastly, models 3 & 4 predicted primary degradation within days and ultimate biodegradation in weeks (butyl ammonium) to months (hexadecyl). Only nicotinamide itself was rated as readily biodegradable by BIOWIN 7. Imidazolium-based ILs with hydroxyl, carboxyl and ether functional groups were tested using a manometric respiratory test, which detects pressure changes in a sealed vessel due to microbial oxygen use during aerobic biodegradation.[129] This study showed an enhanced biodegradability of hydroxyl and carboxyl functionalized ILs. Such findings indicate that functional groups increase the microbial accessibility and enzymatic degradation potential. Cyano-based ILs anions have also been studied using enzymatic hydrolysis by nitrile hydratase and *Cupriavidus spp.*[130] culture, and they have been shown not to be readily biodegradable, even though related cyanide compounds typically undergo microbial degradation *via* different metabolic pathways. Complex bonded cyano-ligands, such as $K_2[Ni(CN)_4]$, are known to be biodegradable.[131] However, the cyano-metal complexes tested were resistant to microbial attack. This was attributed to the requirement of highly specialised bacteria for degradation, which were likely absent in the wastewater inoculate used in the study. Furthermore, shortening the length of the substituted alkyl chains significantly increased biodegradability, particularly in the chloride series of 1-methylimidazole ILs.[132] Linear cholinium alkanoates were tested using fungus *Penicillium corylophilum* over 28 days.[133] It was shown that ILs with shorter chains showed no degradation, while ILs with medium-length chains completely biodegraded. Branched analogues were partially degraded or have not degraded at all, which is a known effect. The cholinium cation itself was only partly degraded. Nonetheless, all these ILs are considered environmentally preferable since their linear anions readily underwent microbial decay under the test conditions. A soil biodegradation test on the ILs 1-butyl-3-methylimidazolium tetrafluoroborate, [Bmim][BF_4], 1-butyl-3-methylimidazolium dicyanamide, [Bmim][$N(CN)_2$], 2-methoxyethyl-3-methylimidazolium tetrafluoroborate, [$MeOCH_2CH_2$mim][BF_4], 2-methoxyethyl-3-methylimidazolium dicyanamide, [$MeOCH_2CH_2$mim][$N(CN)_2$] showed the highest degradation of [Bmim][BF_4], which was attributed to its comparatively simple and accessible linear alkyl chain.[134] The presence of cyano groups in [Bmim][$N(CN)_2$] on the other hand, reduced its biodegradability. The oxygenated derivatives showed almost no degradation due to structural stability. Usually, a soil biodegradation test evaluates the breakdown of a substance in soil by monitoring CO_2 evolution or compound disappearance over time. Respirometric test, which tracks oxygen consumption by microorganisms as they aerobically degrade a test substance, was conducted on 1-butyl-3-methylimidazolium acetate ([Bmim][Ac]), showing moderate biodegradability.[135] A possible reasoning is that the imidazolium cation actually slows down the overall process even though [Ac] is likely biodegradable. Organic anions, such as carboxylates and amino acids, are more biodegradable than inorganic halide anions or perfluorinated anions.[136] Cholinium-based ILs were tested using a CO_2 headspace test, showing a readily biodegradable character with over 60% CO_2 evolution within 28 days.[137] The CO_2 headspace test quantifies the amount of CO_2 released into the headspace of a closed system in order to assess mineralisation of organic compounds. If a compound exceeds 60% CO_2 evolution within those 28 days, it is considered readily biodegradable. Such results were expected due to the natural origin of choline, making it a promising alternative to other cations. A closed-bottle test was also used for biodegradability testing of ILs derived from naturally occurring compounds, such as choline-based ILs.[82] This type of test measures the oxygen consumption in a sealed bottle over 28 days to assess if the compound in question is biodegradable in water. The study investigated bio-inspired ILs derived from natural compounds, including choline-based ILs and derivatives with func-

tional groups like carboxylates and amino acids. Most of them showed biodegradability of around 60% within 28 days, which means they meet the criteria for being readily biodegradable, as noted earlier. However, some of the tested ILs had larger or more complex ring systems, which resulted in reduced biodegradability due to steric hindrance and molecular stability. A soil biodegradability test on various bio-based ILs, using anions such as lactate, tartrate, acetate, propionate, benzoate, fumarate, and succinate showed a high biodegradability, namely over 70% CO_2 evolution within 6 months.[138] The closed-bottle test and CO_2 headspace test were used for biodegradability scanning of 18 different cholinium amino acids ILs.[139] Every tested IL achieved mineralisation between 62% and 87%, qualifying as readily biodegradable by OECD criteria. Interestingly enough, this study showed that amino acid anions with extra functional groups were broken down more easily than simpler amino acids. This indicates that such functionalities increase microbial susceptibility. Likewise, 25 pyridinium ILs with dipeptide functionalization were evaluated using closed bottle test.[140] ILs with phenylalanine residues degraded more completely than those with only alanine. Phe–Ala orientation near the cation favoured faster biodegradation and fewer toxic intermediates. Furthermore, three ester-functionalized cholinium ILs were tested where all exceeded 60% degradation, qualifying as readily biodegradable.[141] Longer chains required 28 days while shorter chains degraded faster. Analogous ILs without ester groups degraded slower. ILs composed of sugar-derived quaternary ammonium cations and amino acid anions showed complete mineralization within 5–6 days when tested using activated sludge.[142] All were readily biodegradable. Performance exceeded that of standard ILs with conventional cations. Overall, these studies confirm that using compounds of natural origin in the ILs synthesis improves microbial breakdown, making bio-based ILs suitable for use.

Sustainability considerations

Another important parameter that is crucial in understanding the sustainability of a process, end product, or service is the LCA.[143] LCA is a method that has gained popularity over the years due to its ability to assess environmental impacts at all stages of the life cycle. It is a systematic approach that allows a quantitative assessment of how inputs and outputs of a system lead to environmental impacts. An expression often associated with LCA is the "cradle-to-grave" assessment,[144] as LCA starts with the raw materials, production and use, and extends to waste treatment, thus forming a complete circle. However, this is not always possible, so several studies report only *cradle-to-gate*,[145,146] which includes the environmental impact of a product from the extraction of raw materials to the point before reaching the application and/or consumer. LCA can be generally categorised into the following types:[147,148] (i) environmental LCA, which assesses environmental impacts such as carbon footprint, toxicity, energy use, water use; (ii) social LCA, which evaluates social and socio-economic impacts on stakeholders, including labour rights, community well-being, and health and safety; (iii) LCC, which estimates the costs incurred over the product's lifetime; and (iv) life cycle sustainability assessment, which integrates environmental, social and economic assessments into a comprehensive sustainability evaluation. Considering the vital insights that LCA provides, it is of the outmost importance to conduct LCA studies to better understand and potentially improve the process, technology, product or service. To comprehensively evaluate the sustainability of processes, it is essential to assess the broad range of environmental impact categories within the LCA framework. These include: (1) global warming potential (GWP), (2) stratospheric ozone depletion potential (ODP), (3) ionizing radiation (IR), (4) ozone formation – photochemical oxidant formation, (5) fine particulate matter formation (PMFP), (6) ozone formation (terrestrial ecosystems), (7) terrestrial acidification, (8) freshwater eutrophication, (9) marine eutrophication, (10) terrestrial ecotoxicity, (11) freshwater ecotoxicity, (12) marine ecotoxicity, (13) human carcinogenic toxicity, (14) human non-carcinogenic toxicity, (15) land use, (16) mineral resource scarcity, and (17) fossil resource scarcity.[149]

However, there are relatively few studies focused on the LCA of ILs-based processes. In one of these studies, [Bmim][BF_4] was tested as a solvent in the synthesis of cyclohexane *via* a Diels–Alder reaction and compared to the conventional process using organic solvents such as toluene.[150] The conclusion was that the environmental impacts of the IL-based process for the synthesis of cyclohexane was approximately five times higher than the conventional process using toluene. The reason behind this is the synthesis of the precursors used in the production of [Bmim][BF_4]. The increase of environmental impact is reflected in higher GWP, resource depletion, and human toxicity, while acidification and eutrophication may also result from emissions during production. In the dissolution of cellulose, [Bmim][Cl] was tested and compared to a solvent system made of *N*-methylmorpholine *N*-oxide and water (NMMO/H_2O), a standard solvent for this purpose.[151] It was found that the IL and the traditional solvent had a similar environmental impact, including comparable GWP, energy consumption, and human toxicity. However, aquatic ecotoxicity remains a potential concern due to solvent release, both NMMO/H_2O and the IL, in the environment. Notable differences were also observed in photochemical ozone creation, where IL shows almost double the value, and in VOCs emission, which are around 30% higher for IL. Moreover, three ILs, namely 1-allyl-3-methylimidazolium chloride, [Amim]Cl, 1-ethyl-3-methylimidazolium chloride, [Bmim]Cl, and 1-ethyl-3-methylimidazolium acetate, [Emim][Ac] were assessed using the GREENNESS framework[152] for cellulose dissolution. [Emim][Ac] and [Bmim][Cl] had the lowest and highest experimental ecotoxicity, respectively. However, when integrating these results with fate and exposure data, [Amim][Cl] emerged as the most sustainable IL, followed by [Emim][Ac] and [Bmim][Cl]. A comparison between [Bmim][Br] and toluene as a traditional solvent in the synthesis of acetylsalicylic acid also found them comparable in terms of environmental perform-

ance, with impacts covering GWP, photochemical ozone formation, and resource depletion.[153] Baaqel *et al.*[154] proposed a holistic framework, which enabled a fairer comparison between 1-hexyl-3-methylimidazolium hydrogen sulphate, [Hmim][HSO_4], and triethylammonium hydrogen sulphate [Tea][HSO_4] as ILs and conventional solvents derived from fossil (acetone) and renewable (glycerol) sources. The results indicated that the IL [Tea][HSO_4] is a better option than the bio-based solvent glycerol in terms of resource depletion and human toxicity, outperforming bio-based glycerol in overall cost and environmental footprint, though acidification and eutrophication were still relevant factors to consider. In carbon capture and storage applications,[155] [Bmim][Ac] was found to outperform a 15 wt% monoethanolamine (MEA) aqueous solution, achieving a 15% reduction in both life-cycle GWP and human toxicity, despite the higher impacts associated with IL's synthesis. Energy use and resource depletion persist as challenges due to the complex IL production. Another study comparing [Bmim][Ac] in a supercritical hard coal power plant showed that while the GWP of [Bmim][Ac] was two times higher than MEA, its CO_2 uptake capacity and lower regeneration temperatures resulted in process-level benefits. This highlights freshwater ecotoxicity and human toxicity as dominant impacts, with variations of in the GWP and resource depletion further distinguishing these ILs. Freshwater ecotoxicity characterisation factors were further developed for [Bmim][Br], [Bmim][Cl], [Bmim][BF_4], [Bmim][PF_6], and [BPy][Cl]. The study demonstrates that, from a life-cycle perspective, IL-based processes do not necessarily outperform conventional molecular-solvent-based processes.[156] It was found that [BPy][Cl], [Bmim][BF_4], and [Bmim][PF_6] show the highest environmental concern. The results identified ecotoxicity and human toxicity as critical life-cycle impact categories, emphasizing the need to consider full life-cycle impacts when evaluating the "greenness" of ILs. In a desulfurization process,[150] [Bmim][BF_4] was compared to acetonitrile and dimethylformamide using both metathesis and halide-free synthesis routes, with the latter reducing production cost by half and environmental impacts by 3–5-fold. While conventional solvents appeared better when ignoring use-phase, [Bmim][BF_4] surpassed them in sulphur extraction efficiency and recyclability, making it the most favourable when a full life cycle was considered. GWP, human toxicity and ecotoxicity emerged as the major impact categories due to significant reductions in environmental impacts and solvent differences, while resource depletion reflects cost and production differences. Additionally, photochemical ozone formation, acidification, and eutrophication may also be relevant concerns, potentially driven by solvent emissions and degradation products.

Overall, these results challenge the original assumption that all ILs are inherently "green" and demonstrate that their actual impact depends heavily on how they are managed and the specific processes involved. An important observation from the literature review is the evident lack of LCA studies on processes involving ILs in general, and especially within pharmaceutical applications. Conducting LCA in the pharmaceutical sector is crucial not only for regulatory compliance but also to identify hidden environmental impacts throughout the drug life cycle, optimise resource use and waste management. It also supports the selection of greener solvents and processes without compromising efficacy, while enhancing transparency and trust among consumers and stakeholders concerned with sustainability. Additionally, a review of current LCA studies reveals that one critical aspect remains unexplored: social LCA. As of 2026, there is no available data on social LCA studies involving any type of ILs across any industry sector, including pharmaceuticals. Furthermore, no projects investigating social LCA of ILs have been identified. Typically, LCA studies focus on environmental impacts such as toxicity, biodegradability, and energy consumption, but they lack comprehensive evaluations of social impacts. This gap is necessary to achieve a holistic understanding of the ILs sustainability. Thus, one cannot definitively confirm whether a specific IL is truly green. Social LCA is an integral part in understanding the sustainability, and without it, the assessment remains incomplete.

Given these limitations, a more integrated and structured approach to decision-making is necessary. The authors therefore advocate the use of the SSbD framework as a guiding structure for the design, selection, and prioritisation of ILs. In this context, the development and use of predictive models are increasingly crucial for guiding IL development. Modelling approaches, including quantitative structure–property relationships (QSPR), molecular simulations, and process models, enable early prediction of key physicochemical properties, performance metrics, and potential environmental and health impacts of ILs, thereby reducing reliance on trial-and-error experimentation. Integrating these tools into process design allows the application of SSbD principles from the outset, regardless of the final use, and supports more efficient and better-informed decision-making. It is important that basic assessment methods, such as LCA, TEA, toxicity and bioavailability assessments, are not treated as separate or sequential steps, but as integral parts of the SSbD framework. When considered together, these aspects provide a clearer structure for decision-making in the screening and prioritisation of IL candidates. Although the relative importance of each parameter inherently depends on the application, a structured approach can still be proposed. For example, for API-ILs, initial screening may prioritise bioavailability and therapeutic efficacy, then consider toxicity constraints, while LCA and TEA guide the feasibility of scaling up production and manufacturing. Such a layered yet interconnected framework demonstrates how SSbD can be applied in practice, enabling the systematic identification of ILs that balance functionality, safety, sustainability, and economic viability across diverse application domains.

Techno-economic analysis of ILs or ILs-based processes

Beyond safety and biological performance, the economic feasibility of ILs and IL-based processes represents a critical factor

in their potential for real-world application. In this context, TEA serves an important tool for evaluating the technical and economic performance of a process, product, or service.[157] It is a technique that enables the assessment of costs, profitability, risks, and economic relevance, helping to identify bottlenecks in process configurations.[158] This method accounts for factors such as equipment, labour, construction costs, and consumables.[159] When combined with toxicity and biocompatibility data, LCA, and scale-up considerations, TEA provides a comprehensive view of a process' or product's sustainability. As such, it is an integral element in determining economic feasibility, efficiency, efficacy, and overall sustainability. At first glance, TEA appears similar to LCC, but there are some differences. While TEA shows if a technology is commercially viable, LCC considers the entire life span cost of a product or a system. For example, when buying a new washing machine, TEA would consider purchase price, energy efficiency, water usage, and maintenance costs and compare it to other models. LLC on the other hand would consider the total cost of owning that washing machine over its entire life, such as purchase price, electricity and water bills, repairs, disposal costs.

In the context of TEA, the economic feasibility of using ILs is highly dependent on the parameters and depth of the analysis performed. Usually, when considering only the production cost of ILs, they are significantly more expensive than traditional organic solvents. However, this comparison overlooks the broader context of their application. In general, ILs are economically viable in processes where (i) solvent performance creates step-change value, (ii) recycling exceeds 97–99%, and (iii) IL synthesis relies on commodity feedstocks; otherwise, conventional solvents dominate, as discussed below.

TEA, which accounts for both the technical benefits and the economic implications of their use, reveals that ILs can offer cost-efficiency over the entire process. Usually, they can improve the efficiency, reduce waste and minimise energy consumption, which offsets their initially higher production costs.[11] For example, the production costs of the [Bmim][BF_4] has been compared to two organic solvents, acetonitrile and dimethylformamide.[160] Herein, two synthesis routes for [Bmim][BF_4] have been analysed, with one being half the cost of the other. However, even the cheaper route was about four times more expensive than acetonitrile and dimethylformamide when only the production costs were considered. Once the solvents' usage in the process was factored in, the costs dropped significantly. The cheaper synthesis route for [Bmim][BF_4] became the most cost-effective option, while the more expensive route was comparable in cost to the organic solvents.

Moreover, the theoretical, model-based minimum production costs for [Tea][HSO_4] and 1-methylimidazolium hydrogen sulphate, [Mmim][HSO_4] were estimated using ASPEN process simulation to be \$1.24 and \$2.96–5.88 per kg, respectively.[59] These estimates were based on a hypothetical plant capacity designed as 144 000 tons per year, a suggested design capacity for an IL-based biomass pretreatment process. Notably, the first IL is cost-competitive with conventional solvents, acetone (\$1.32 per kg), and ethyl acetate (\$1.39 per kg). The analysis further revealed that raw material costs, particularly the amine component, dominate the total production expense for sulfuric-acid-based ILs. The study also demonstrated that process intensification can further reduce production costs, making IL manufacturing more economically attractive. In addition to synthesis efficiency, the high recyclability contributes to enhancing the benefits of using ILs, further reducing solvent replacement rates. In addition to the initial synthesis costs, the ability to recycle ILs efficiently plays a crucial role in determining their long-term economic viability as well as the recycling process.[161] However, we consider these cost estimates to be overly optimistic and likely unrealistic under practical industrial conditions. When accounting for additional costs (*e.g.* compliance, regulatory, quality control, depreciation, filling, packaging, storage, and profit margins), the estimated large-scale selling price of such an IL would likely be at least two to three times higher than the reported value, reaching approximately 3–4 USD per kg, which remains modest for an IL.

An additional example demonstrating the economic and functional potential of ILs involves protic ILs containing the hydrogen sulphate anion, [HSO_4] used for lignocellulosic biomass pretreatment. The cations studied included monoethylammonium, [Mea], diethylammonium, [Dea], triethylammonium, [Tea], monoethanolammonium, [Meoa], diethanolammonium, [Deoa], triethanolammonium, [Teoa], and diisopropylammonium, [Dipa].[162] These were compared to the widely used aprotic [Emim][Ac], which is known for its high efficiency in biomass pretreatment but suffers from high production cost, around \$50 per kg.[161,163] The goal of the comparison was to determine whether cheaper ILs synthesized from commodity feedstocks could maintain effective biomass pretreatment performance for ethanol production while significantly reducing overall process costs. Based on techno-economic modelling, the bulk (144 000 tonnes per year) production cost of [Tea][HSO_4] appears substantially lower than that of [Emim][Ac].[59,164] However, these estimates are purely theoretical and do not reflect real industrial conditions, meaning its practical relevance remains limited. This cost reduction has a significant impact on the minimum ethanol selling price (MESP). When using expensive ILs such as [C_2mim][Ac], even with high recyclability, the MESP can exceed \$6 per gallon, making the process economically unviable.[163] In contrast, with low-cost ILs like [Tea][HSO_4], the MESP is reduced to a level comparable with conventional dilute acid pretreatment, estimated around \$1.40–2.00 per gallon.[165] Thus, the use of low-cost ILs not only retains effective pretreatment capability but also enables economically competitive bioethanol production, aligning with the techno-economic thresholds for commercial viability. Furthermore, these studies confirm that high IL recycling rates of over 99% are essential for economic feasibility.[161,163]

Another comparative case study examined four different solvents for lignocellulosic biomass pretreatment, including 1-methylimidazolium hydrogen sulphate [Hmim][HSO_4], [Tea][HSO_4], acetone, and glycerol from renewable sources.

[Tea][HSO_4] has the lowest direct costs, while [Hmim][HSO_4] has the highest. Although [Hmim][HSO_4] has a higher total monetised cost than acetone and glycerol, its high recyclability makes it a more sustainable and cost-effective alternative. Considering the total monetised cost, glycerol is the most expensive, while [Tea][HSO_4]has the lowest cost of all four solvents.[154,160]

Large-scale production of 4-methyl-*N*-butylpyridinium tetrafluoroborate, [4MBPy][BF_4] has been estimated at around $22 *per* kg, for a total investment of $61 million in the aromatics extraction process. Compared to sulfolane-based processes, this results in savings of around $22 million *per* year, as energy costs are lower. This makes the IL process far more efficient and cost effective, making it a desirable alternative.[166] Another good example is the cost of synthesising 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [Bmim][NTf_2] on a laboratory-scale which is used as a solvent in nanoparticle synthesis. It costs approximately $4000 *per* kg, making it a very expensive solvent in comparison with the commonly used conventional solvent, 1-octadecene (~$169 *per* kg). However, when the total costs of the process are taken into account, recycling the IL significantly reduces its cost to $529 *per* kg at 80% recovery, and $212 *per* kg at 94% recovery, making it cost-competitive with the traditional solvent.[167] Nonetheless, it is important to highlight that these prices were based on catalogue prices for laboratory-scale quantities. In contrast, Proionic, a company that manufactures ILs at ton scale, sells [Bmim][NTf_2] for around $910 *per* kg, which is significantly lower. The listed price is $420 for 250 g, with significantly lower pricing available for larger quantities upon request. This discrepancy suggests that while the TEA highlights the cost issues of using "virgin" [Bmim][NTf_2], it probably overestimates the solvent costs in mass production, as the lab-scale prices do not reflect the process optimisations or economies of scale that are possible in industrial production.

Given the desirability of high-purity compounds in industrial applications, it is essential to evaluate the cost implications associated with ILs. For instance, the minimum selling price for high-purity [Bmim][BF_4] was estimated at $12 *per* kg.[168] The market price for high-purity ILs is typically $20–50 *per* kg. The raw materials have a significant impact on the overall price, as switching from $LiBF_4$ to $NaBF_4$ could reduce the IL costs by over 50%. This further lowers the price to $5.7 *per* kg. If the raw materials would be optimised, [Bmim][BF_4] obtained in this way would be cost-competitive with the standard solvents used in industry. Moreover, various ILs were tested for their economic feasibility for CO_2 capture and compared the conventional MEA absorption process. Based on the cost *per* kg of CO_2 captured, the ILs rank as follows: 1-ethyl-3-methylimidazolium bis-(trifluoromethylsulfonyl)imide, [Emim][NTf_2] at $0.083 *per* kg, followed by 1-ethyl-3-methylimidazolium dicyanamide, [Emim][$N(CN)_2$] at $0.09 *per* kg, and [Bmim][Ac] as the most expensive at $0.14 *per* kg.[169] The most cost-effective option is mixing ILs with MEA, more specifically using 1-butylpyridinium tetrafluoroborate, [BPy][BF_4], in a mixed solution with MEA ($0.025 *per* kg CO_2).[170] The use of ILs improves CO_2 absorption efficiency and reduces energy costs, unlike MEA, which has a high energy cost for regeneration. The conventional method is also more expensive than IL-MEA mixtures at $0.07 *per* kg CO_2, but still cheaper than using pure ILs. Nonetheless, pure ILs are still competitive with the conventional method.[171] Biogas upgrading with [Emim][NTf_2], has also been tested and is far less economical than other methods at $0.271 *per* kg CO_2.[172]

Based on the aforementioned, the ability to effectively recover and reuse ILs is a critical factor for enabling the efficient scale-up of IL-based processes and ensuring their economic and environmental competitiveness. When it comes to traditional IL recycling, multiple techniques can be used. For example, liquid–liquid extraction is a flexible method that works for both hydrophilic and hydrophobic systems, but it often requires large volumes of solvent and may result in phase contamination.[173,174] Adsorption offers a cost-effective and non-destructive approach to IL recovery, especially from wastewater. Nonetheless, its efficiency strongly depends on the IL structure and compatibility, on adsorbent properties, and desorption can be challenging.[175,176] Membrane-based technology appears promising for IL recovery, with commercial membranes demonstrating adequate separation and purification. It enables continuous, energy-efficient processing, although issues such as membrane fouling, limited selectivity, and incompatibility with viscous ILs can delay wider application.[177,178] Aqueous biphasic systems (ABS) are environmentally friendly and particularly suitable for mild bio-separations; however, their effectiveness is highly dependent on the specific IL–salt or IL–polymer system used.[179,180] Depending on the objective, these systems can be quite tricky. For example, if an inorganic salt is used to form an ABS with an IL, unwanted ion exchange can occur, making the system difficult to control. Nevertheless, ABS offers advantages over conventional extraction, as the polarity of the aqueous phase can be adjusted by adding different components to form the ABS. This allows selective isolation of the target, which can later be recovered by simple dissolution once the ABS counterphase has been removed. In addition, ABS processes can be scaled-up, making them a promising approach for the future. Crystallisation provides high-purity recovery with low solvent input, but it is typically slow, requires precise control, and is not suitable for amorphous or thermally unstable ILs.[181] Moreover, many ILs cannot be crystallized as they often form glasses and are highly sensitive to contaminants. A typical contaminant example is water: even small amounts can strongly affect their behaviour. [Emim][Ac] for instance, can be crystallized and purified, but only under extremely dry conditions. In its pure form, it has a melting point of around 20 °C. However, with just a few hundred ppm of water present, crystallization becomes impossible. Thus, crystallization remains one of the major challenges, as many ILs cannot be crystallized at all.[182] Another technique used is distillation of contaminants, a widely used and uncomplicated method, but it is unsuitable for thermally sensitive ILs due to the risk of degradation or hydrolysis during prolonged heating. Nonetheless, prolonged heating can be minimized by using alternative distillation

devices, such as short path thin film devices.[183] These increase the vapor throughput by orders of magnitude and reduce the time needed to distil a given volume from hours to minutes, or even seconds. As a result, prolonged heating can be avoided so that even thermally sensitive ILs can withstand the process due to the very short contact time. Despite its simplicity, the cost of IL distillation is significantly higher than that of common solvent distillation. Furthermore, one the initial and main benefits of ILs that attracted researchers was their low volatility. Yet, over time, this very characteristic became a disadvantage during recycling studies, since conventional ILs cannot be evaporated, hence hindering their reuse. Nevertheless, they are already employed on an industrial scale[184] so the development of distillable ILs could present an attractive option for many applications.[185,186] This fact brings us full circle to the current interest in distillable ILs, a new category that is described in the literature as combining low boiling points with high thermal stability, breaking the norm of traditional ILs.[187] However, strictly speaking, referring to distillable ILs as "thermally stable" is not entirely correct. The distillation process proceeds *via* a deliberate thermal decomposition into two neutral molecular species, which are then volatilized and recombined on the condenser surface to form again the IL. Thus, the process is better described as a controlled, reversible thermal decomposition followed by recombination. If one considers the thermal stability of the two molecular precursors, the description in the literature holds true. Nonetheless, for the IL itself, the apparent thermal stability is a consequence of a controlled thermal decomposition. This ability combined with their recyclability directly impacts process costs by enabling multiple reuse cycles, which also facilitates easier scale-up and industrialisation. In summary, to overcome the limitations of individual methods, hybrid technologies, such as combining ABS, membrane separation, and distillation, have shown potential to significantly reduce both energy consumption and total operational costs.[188]

Overall, the economic analyses of various processes in which ILs have been used indicate a potential cost-competitiveness of ILs compared to conventional solvents for mature industrial processes. However, this is highly dependent on the raw materials needed to synthesise the ILs and how many steps are required to obtain the ILs in question. Further optimisation is required in this area for IL processes to overtake conventional methods. Nonetheless, the studies carried out so far suggest that the shortcomings of conventional solvents can be overcome by using different ILs. At the same time, it is important to note that ILs are not simply general replacements for traditional solvents, these are niche enablers. ILs have many advantages, starting with their designer solvent status (although in reality this can be challenging, as developing, scaling up, and ensuring REACH compliance for each newly designed IL is rarely feasible or economically viable), high thermal stability, wide liquid temperature range, selectivity and low energy costs. While their cost has decreased over time, ILs remain relatively expensive. Consequently, the ability to recover and reuse ILs, and thus develop effective recycling strategies, is essential for improving their cost competitiveness relative to conventional solvents. The potential and cost competitiveness of ILs compared to conventional solvents should be emphasised, although this competitiveness varies significantly depending on the application. In applications such as extraction and separation processes, *i.e.* downstream processes, ILs may not yet be cost-competitive. ILs have been used to pretreat lignocellulosic biomass for fermentable sugar production.[164] This pretreatment is technically effective, achieving more than 90% glucose recovery (compared to 82% of Ammonia Fiber Expansion, *i.e.* AFEX) and offering environmental benefits such as a lower ecological footprint compared to conventional methods. However, the economics remain unfavourable: the cost of sugar production was \$2.7–3.2 *per* kg, compared to \$0.26 *per* kg for dilute sulfuric acid. The main cost drivers are the high price and large volumes of ILs, as well as the energy required for solvent recovery. To be competitive, over 97% IL would need to be recovered, IL cost $\leq$ \$1 *per* kg, and >90% of heat recovered. These targets are optimistic given the current technology. Another study on IL-based ethanol biorefineries confirmed the technical advantages, such as high sugar yield, strong delignification and wide feedstock applicability, but pointed out the same economic barriers.[163] Reducing IL loading and developing markets for by-products (especially lignin) were identified as key strategies. Overall, IL pretreatment is technically promising but not yet cost-competitive with traditional methods unless solvent costs are reduced and the valorisation of by-products is achieved. Nonetheless, pharmaceutical industry likely offers one of the greatest potential due to the performance advantages and life-saving possibilities associated with API-ILs. Additionally, pharmaceuticals is an industry where high costs are common, making the adoption of ILs more feasible. These are vital pieces of information that will be valuable for the further development of API-ILs and the broader application of ILs in pharmaceutical sector. However, the lack of economic analysis in this area highlights that API-ILs are still at a stage far from being ready for the industrialisation. This gap between technical potential and economic feasibility underscores the need to consider industrialisation and commercialisation aspects more closely.

Industrialisation and commercialisation of ILs

The transition from laboratory-scale research to industrial implementation is a critical step in determining the practical viability of IL-based systems. While TEA provides insight onto potential feasibility, scale-up and industrial application ultimately determine whether these systems can be realised in practice. However, prior to discussing the scale-up and industrial applications, a crucial question should be addressed: why scale-up matters and why are industrial applications important? Scale-up presents a bridge between small laboratory-scale and larger, commercially viable production. This is a critical step to demonstrate and prove the technology in ques-

tion is reliable, safe, and economically feasible under real-world industrial conditions. It confirms whether the stability, recyclability, cost-efficiency and integration into industrial infrastructure hold when applied at hundreds of litres or tonnes. Scale-up proves the technology does not remain academic and unused in practice. Here is where the large-scale industrial applications come in. These allow for those scientific discoveries and novel technologies to be translated into real-world, practical solutions. Furthermore, applying these measures leads to economic growth, as industry is the backbone of the world economy. Many of the current challenges that we face on a global level, for instance climate change, sustainable agriculture, and energy storage, require technologies that operate at large scale. This way, industrial applications allow innovations to reach people around the globe and make a meaningful impact. Therefore, addressing the industrial applicability of certain type of compounds is crucial in understanding its potential in contributing to a more sustainable environment. It is well known that ILs have emerged as a transformative class of solvents with applications across various industries. Their unique properties have led to their adoption in fields ranging from catalysis and energy storage to advanced cooling systems and engineering solutions. As research continues to advance, these innovative chemicals are finding their way into large-scale industrial applications, improving efficiency, sustainability, and safety. Herein, a couple of processes where ILs are implemented on industrial scale will be presented.

Mari Signum Mid-Atlantic, LLC, a subsidiary of Ross Group Plc, played a significant role in scaling up IL-based chitin extraction, particularly using [Emim][Ac].[189,190] They were known for scaling up IL-based chitin extraction, focusing primarily on [Emim][Ac]. The process evolved from gram- and kilogram-scale tests to semi-continuous processing of 5–50 kg batches, eventually reaching multi-tonne production levels. To ensure purity and consistency, the company primarily synthesised ILs in-house, supplementing with commercial ILs when cost-effective. Despite promising progress, Ross Group's 2021 report indicated that in 2020 "pilot production trials did not reach a point to allow consideration of commercial mass production of chitin".[191] By 2021, operations were restructured into RGP525 Solutions LLC in collaboration with 525 Solutions. In 2022, the company's report added that "the commercial confluence of COVID and the consequential cashflow constraints, caused by the lack of the pre-agreed financing from the seller of the AAG business were both exceptionally unique and unpredictable", suggesting trial suspensions due to the pandemic.[192]

The BASIL™ process (Biphasic Acid Scavenging utilizing Ionic Liquids), developed by BASF in the early 2000s, was one of the first large-scale industrial applications of ILs. Introduced at BASF's Ludwigshafen site in Germany,[193] it facilitates the production of alkoxyphenylphosphines by eliminating problematic solid by-products, thereby improving efficiency and product purity. Operated on a large scale in a jet reactor,[194] the process uses 1-methylimidazolium chloride ([Hmim][Cl]), formed *in situ*, which separates into its own liquid phase, enabling efficient HCl removal and a cleaner reaction.[195] BASF also created the Basionics® brand to market its ILs, with [Hmim][Cl] among the first in the line. The BASIL process itself, however, remains a proprietary in-house technology used exclusively by BASF.[11]

Another IL technology worth mentioning is ILTEC technology (Ionic Liquid Cooling Technology). Together with Proionic, a company under the name Mettop developed this technology, a patented cooling system for high-temperature and high-risk environments, especially for metallurgical furnaces. Instead of water or conventional liquids, ILTEC uses ILs as a heat transfer medium, eliminating the risk of explosive water leaks and allowing safer cooling in the vicinity of molten metal and slag.[196] This technology is protected by several patents (508292, WO2013113461A1, WO2008052863A2, WO05021484A2, WO2008052860A1, WO2010122150A1)[197] and uses IL-B2001. This salt is stable at high operating temperatures, shows no reactivity with slag or liquid metal and avoids problems such as hydration of the refractory material and cooler corrosion.[198] Applications include hydraulic devices, measuring lances, purging nozzles, nozzle areas, furnace bottoms and side walls.[199] Toxicity and decomposition safety have been tested at Proionic and at the University of Leoben, while the production route has been patented by Proionic.[200] The ILTEC system was first introduced on an industrial scale in 2014, four plants were manufactured and put into operation in 2023.[201,202]

Overall, ILs are already being used in larger scale in catalysis and chemical processing, including hydroformylation, fluorination, alkylation, hydrogenation, and hydrosilylation reactions, where they improve selectivity, efficiency, and catalyst recovery. They also find applications in energy storage, separations, and advanced materials, serving as electrolytes in batteries and supercapacitors, solvents for polymer recycling, agents for rare earth recovery, heat-transfer fluids, and functional fluids in compressors and hydraulic systems.[203–210] Most industrial applications still rely on first- and second-generation ILs, although industrialisation is increasing as the challenges of scalability and regulation are addressed. Their versatility emphasises their great potential for sustainable innovation in various sectors. In contrast, large-scale biological applications remain limited: laboratory studies show promising results in the extraction of bioactive substances, but pilot and industrial applications are still lacking. This disparity is particularly evident in the case of API-ILs, where the transition from laboratory-scale research to pharmaceutical application remains a key challenge.

Do API-based ILs have a real future?

API-ILs represent one of the most promising yet least industrially realised applications of ILs, highlighting the challenges associated with translating laboratory-scale advances into pharmaceutical practice. To better understand their potential

and limitations, it is first necessary to consider the fundamental components and principles underlying their design. APIs are compounds with pharmacological activity that enable the therapeutic effect of drugs. Usually, APIs are combined with various compounds, also known as excipients, with different functions to form a medication. It is important to note that excipients do not have a therapeutic effect but rather help to ensure that the APIs enter the body safely. APIs can be solid, liquid or even gas. However, solid forms of APIs are highly preferred in the pharmaceutical industry due to their advantages, such as easy scaling, high purity, easy handling and thermal stability. Nevertheless, these solid forms also pose significant challenges such as problems with bioavailability, solubility and polymorphism. While conventional organic solvents dissolve a wide range of active ingredients, they are often subject to regulatory restrictions due to safety concerns, particularly from health and drug authorities. In this context, ILs have proven to be a promising alternative. Their versatility and efficacy make ILs a transformative tool for overcoming challenges in drug development.[63,211,212] The liquid state of API-ILs can significantly improve the physicochemical properties of APIs, including solubility and stability. In particular, biocompatible ILs offer several key advantages: they improve formulation stability, increase solubility and are suitable for different routes of administration. Importantly, biocompatible ILs also ensure safety in the human body.[83]

Drug-based ILs can be categorised into three main groups based on their formation mechanisms. The most common approach is ionic bond formation, where the drug acts as either a cation or an anion, leading to ionic bond formation. The second group involves the chemical modification of neutral agents by covalent bonding to introduce charged groups that enable their conversion to ILs when paired with suitable counterions. The third category combines both strategies, resulting in dual-active API-ILs. To further improve the properties and efficiency of API-ILs, different strategies can be applied depending on the desired outcome.[213,214] For example, readily ionisable APIs are selected for ionisation and salt formation, and the properties of the counterions are carefully considered to optimise characteristics such as charge distribution and symmetry.[215] To improve properties that are important for IL formation, for example lowering the melting point or improving thermal stability, strategies may include reducing intermolecular interactions, selecting ions with low symmetry and low charge density, high charge delocalisation, or altering the hydrophilic/hydrophobic balance through functional group substitutions.[216] In addition, hydrophilic counterions or long alkyl side chains can be incorporated to improve solubility, bioavailability and delivery.[217] On the other hand, dual-active API-ILs can be designed to combine complementary biological activities. These approaches improve the efficacy, stability and safety of API-ILs, which ideally remain liquid and have properties that prevent polymorph formation while maintaining the biomedical activity of the parent API.[218,219] Ibuprofen paired with a benzylammonium cation exhibited improved stability due to charge delocalisation,[220] while interactions between benzethonium proline[221] and imidazolium salicylate[222] ILs and biomolecules influenced their solubility and thermodynamic properties.

Other examples include carvedilol, which doubled in solubility when formulated with citric acid, tartaric acid or saccharin anions;[223] a cholinium-based methotrexate IL, which increased solubility in 5000-fold while exhibiting enhanced anticancer activity;[224] a diclofenac imidazolium IL, which improved water solubility in 100-fold due to hydrogen transfer mechanisms;[225] mefenamic acid ammonium IL, which also showed improved solubility.[226] In addition to their physicochemical advantages, API-ILs have shown promising biomedical applications. For example, alendronic acid ILs showed potent anticancer activity with minimal toxicity to healthy cells.[227] A series of alendronic acid ILs were tested against healthy human gingival fibroblasts and three cancer cell lines (T47D, A549, MG63). The results showed that monoanionic species were generally less cytotoxic than their dianionic counterparts, while choline-based ILs displayed minimal toxicity comparable to the parent drug. Amino acid salicylate ILs improved skin transport in nine-fold,[228] and imidazolium salicylate ILs were incorporated into an acne patch for effective treatment.[229] Furthermore, salicylate ILs were evaluated on L929 fibroblast and HeLa cancer cells.[228] Toxicity increased with cation hydrophobicity, following the order L-phenylalanine ethyl ester > L-methionine ethyl ester cation > L-leucine ethyl ester cation > L-aspartic acid ethyl ester cation > L-proline ethyl ester cation, indicating that hydrophobic and π–π interactions drive membrane disruptions. Nonetheless, cytotoxicity remains within acceptable ranges. The cytotoxicity study on methotrexate ILs confirm a similar dependence on cation structure with tetrabutylphosphonium, [Bmim], and L-phenylalanine ethyl ester more toxic, whereas tetramethylammonium [TMA] and choline [Ch] were the least cytotoxic.[224]

Lidocaine-ibuprofen and lidocaine docusate ILs were investigated for topical applications, with lidocaine-ibuprofen demonstrating better systemic absorption.[230] Furthermore, incorporation of lidocaine-ibuprofen into zein threads allowed sustained drug release over two weeks, far exceeding the release profile of non-extruded formulations.[231] Oral bioavailability studies suggest that API-ILs exhibit slower and prolonged absorption at higher doses, likely due to reduced distribution in the stomach, underscoring the importance of detailed pharmacokinetic profiling.[232] Lidocaine ibuprofenate combines both anesthetic and anti-inflammatory properties as a dual API-IL, providing therapeutic benefits in a single formulation.[233] Prodrug-ILs further improve solubility while maintaining the efficacy of the original drug.

Combining non-steroidal anti-inflammatory drugs (NSAIDs), specifically ibuprofen, ketoprofen, naproxen and salicylic acid, with ILs resulted in better penetration of said drugs through the skin.[234] Biocompatible IL counterparts were synthesized as L-amino acid alkyl esters, which further enhanced bioavailability by increasing the solubility. Additionally, these compounds exhibited enhanced transport across membranes compared to the parent drugs. The best results were observed

with L-threonine alkyl esters, indicating potential for use in topical formulations.

Ketoprofen was combined with piperine to form KI-PI IL for transdermal application.[235] The physical mixture of these compounds did not produce such effects, demonstrating that IL formation is directly related to the physicochemical properties of the drug. *In vivo* tests showed a superior anti-inflammatory response from KP-PI IL, highlighting the significant potential of API-IL technology to enhance therapeutic performance. Similarly, matrine and NSAIDs were prepared as API-ILs, resulting in increased solubility of loxoprofen and diclofenac, by 282 and 220 times compared to the bulk drugs, respectively. For these two NSAIDs, the API-IL form increased transdermal penetration, while for ibuprofen, ketoprofen, and naproxen, the API-IL form reduced overall penetration but increased skin accumulation. These differences arise from the specific structure of each NSAID anion and the way IL formation alters solubility, diffusion coefficient, and interactions with the stratum corneum, the outermost layer of the skin. Choline-ketoprofen API-IL significantly enhanced ketoprofen's skin permeation and systemic absorption, showing a 1.4-to 2.2-fold increase in transdermal flux and a nearly five-fold increase in peak plasma concentration compared to conventional ketoprofen formulations.[236] These improvements were attributed to stronger interactions with skin phospholipids, leading to temporary widening of intercellular spaces and improved bioavailability *in vivo*.

These advances highlight the transformative potential of IL-based drugs, particularly in delivery systems such as transdermal patches,[50] where improved absorption and prolonged action have shown great promise. The versatility and efficacy of drug ILs make them a powerful tool to address long-standing challenges in drug development. Their potential has been demonstrated by significant improvements in the solubility and performance of various drugs. For example, acyclovir-based ILs showed a 400-fold improvement in aqueous and simulated liquids.[233] Extensive literature searches have shown the broad applicability of API-ILs in various medical conditions, including osteoporosis drugs,[227] antiviral,[237–239] gastrointestinal disorders,[240] antibiotics,[241–243] NSAIDs,[244–246] antibacterial medication,[247] beta blockers,[223] antimalarial and antifungal,[248,249] arthritis,[250] and neurodegenerative diseases such as Alzheimer's[49,251,252] and Parkinson's.[253] These findings underscore the potential of API-ILs to revolutionize drug formulation and pave the way for advances in a variety of therapeutic applications.

Nonetheless, one important question remains: *Do API-ILs have a real future?* Although a definitive answer is still lacking, the growing interest in API-ILs is undeniable. However, many API-ILs developed to date are not biocompatible and therefore cannot be considered as candidates for therapeutic treatments. Such systems are mainly used to understand the fundamental mechanisms, including structure–property relationships, the influence of ion pairing on solubility and log *P*, and how ionic interactions affect permeability and membrane dynamics. In addition, such API-ILs are often easier to synthesize and more stable, making them useful model systems for developing and testing analytical and formulation methodologies. Their study also supports progress in process engineering, such as extraction techniques, separation of APIs from wastewater, purification strategies, enhanced solubility and improved process handling in industry. Overall, these studies deepen our understanding of API-IL behaviour, thus contributing to better predictions and design of future API-IL based on more biocompatible ILs. In line with this, our review indicates that only a very small number of API-ILs reported in the literature are genuinely biocompatible, while most systems involving ILs and APIs fall into other categories, such as IL-based delivery systems rather than API-ILs.

Moreover, several research projects and patents have explored their pharmaceutical potential. For instance, the EcoCosmePharm project specifically addressed the toxicity[254] of products in pharmaceutical industry, mainly APIs and solvents such as ILs and deep eutectic solvents (DES), using AI/QSAR tools and models. Other efforts include the development of models[255] enabling computer-aided design of API-ILs, which would ideally lead to extensive exploration of the API-ILs chemical space, thereby addressing the issue of bioavailability. This project, scheduled to begin in December 2025 with a duration of two years, aims to develop advanced models and software to revolutionize drug formulations through optimization of thermodynamic and physicochemical properties. Another research centres on quantum-chemical investigation of molecular interactions between ILs or DES and APIs.[256] The aim is to establish a fundamental understanding of (hydrogen) bonding and charge distribution in API-ILs and API-DES. Moreover, experimental and computational designing of biodegradable silica or polymer matrices are in focus for the controlled release of API-ILs.[257] The project studies how molecular interactions between ILs and the material influence the drug release kinetics. Research also explores ILs as alternatives to traditional solvents in drug crystallization.[258] Furthermore, notable patents include:

- WO2022232282A1/EP4329732A1,[259] which focuses on IL-salts of APIs with enhanced stability.
- WO2022037982A1[260] focuses on formulations combining polymers and ILs as APIs.
- US11786597[261] demonstrates how tailoring ILs can enhance skin permeability and irritation in transdermal delivery of drugs.
- US11464738B2[262] describes nanoemulsions incorporating ILs for effective delivery of both hydrophilic and hydrophobic drugs.
- US8232265B2[247] presents ILs compositions designed to overcome polymorphism and poor solubility of APIs.
- US20150071922A1[263] investigates the use of ILs for stabilising protein-based drugs.

These developments demonstrate that ILs are gradually becoming a subject of attention within the pharmaceutical sector, with significant innovation and progress expected in the near future. While there is extensive research available at the laboratory-scale concerning API-ILs and the broader incor-

poration of ILs in the pharmaceutical sector, this is not fully matched by the number of projects and patents, which remains limited. There are still very few investigations beyond the laboratory-scale on the use of ILs as APIs, despite many industrial applications of ILs in other sectors. The widespread adoption of API-ILs technologies requires testing of their toxicity, biocompatibility and biodegradability. Ensuring their safety and environmental friendliness will cement their status as biocompatible and green solvents and pave the way for their integration into future pharmaceutical applications (Fig. 3).

Nonetheless, ongoing clinical trials using ILs in the pharmaceutical industry provide encouraging signs for the future of API-ILs. One notable example is the development of CGB-500, a topical treatment for atopic dermatitis. In a 2023 phase 2a clinical trial, patients treated with CGB-500 exhibited a 98% improvement in the severity index, compared to a 28% improvement in the placebo group. Following these promising results, an Investigational New Drug application was filed with the FDA, and a larger phase 2b study has been initiated, with findings expected by the end of 2025.[264] Additionally, a study evaluated the efficacy and safety of ILs containing ketoconazole (KCZ-ILs) in patients with tinea pedis, also known as athlete's foot. The research described the clinical translation of KCZ-ILs from laboratory settings into clinical applications, assessing their effectiveness and safety profile in treating this condition.[265]

To gain a complete understanding, the patenting and intellectual property (IP) aspects of API-ILs must be considered. Patenting API-ILs is challenging because they lie between pharmaceuticals and chemical formulations.[266] Many APIs used in API-ILs are already known, so simply converting an existing API into an ionic liquid may not always meet the requirements of novelty or non-obviousness. Under both US and European patent law, an invention must be novel, non-obvious, and useful or industrially applicable, with the last requirement usually straightforward in the pharmaceutical sector.[267] To establish novelty, it must be demonstrated that the specific ion pair has not been disclosed in prior literature or patents. Even if the API and the counter-ion are known separately, their exact combination can still be novel if it has not previously been described. For non-obviousness, it is necessary to show an unexpected technical effect, such as improved solubility or bioavailability, as these are outcomes that a skilled person could not readily predict.[268,269] Otherwise, the preparation of an API-IL may be considered obvious. Patents on API-ILs are sometimes challenged as covering mere formulations rather than genuinely new chemical entities. Protection can also be relatively narrow, as competitors may "design around" patents by altering the cation or anion.[270] Additionally, some counter-ions used in API-ILs may themselves be covered by earlier patents, leading to overlapping intellectual property and the need for licensing or cross-licensing. This creates the risk of blocking patents: while a patent gives the right to exclude others from using an invention, it does not guarantee the right to commercialise it. If a broader, earlier patent covers part of the invention, it can effectively prevent its use, which is a common issue in pharmaceuticals where multiple layers of patents often coexist on APIs, salt forms, formulations, and processes.

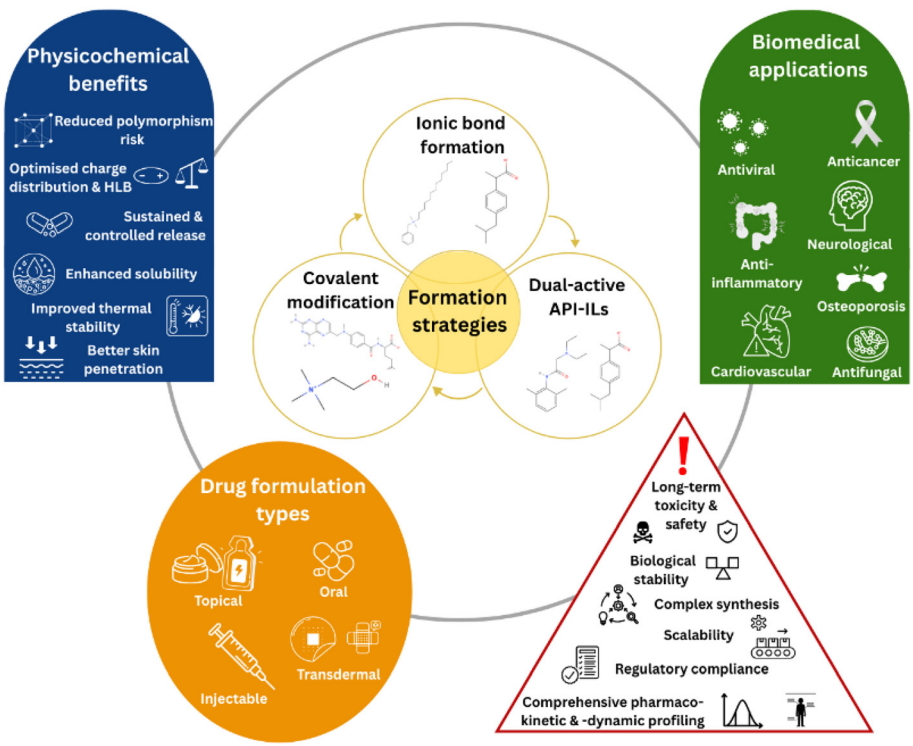

Fig. 3 Schematic representation of advantages and disadvantages of API-ILs.

From a regulatory perspective, the Food and Drug Administration (FDA) has not issued guidance specific to API-ILs.[271] New ionic or salt forms of an approved active moiety are not treated as the same drug for approval purposes; they are typically reviewed as new drugs *via* a New Drug Application (NDA) with appropriate nonclinical or clinical bridging, rather than as generics under an Abbreviated New Drug Application (ANDA).[272] A similar situation exists in Europe, where regulators apply the existing framework for different forms of active substances to determine whether an API-IL should be filed as a generic, a hybrid, or a full new active substance dossier.[273–275] This is an issue regulatory bodies should address, as patents are crucial in the pharmaceutical sector because they provide market exclusivity. If patent protection is weak, narrow, or uncertain, companies are far less motivated to invest, making patenting a critical aspect of API-IL development. Since both the FDA and European Medicines Agency (EMA) treat API-ILs as new chemical forms without specific guidance, the regulatory burden is heavy, and the additional cost is harder to justify.

These challenges highlight systemic constraints rather than limitations of the technology itself. In this sense, a balanced assessment of API-ILs is therefore best approached with a Strength, Weaknesses, Opportunities, and Threats (SWOT) analysis (Fig. 4), which captures both their advantages and practical limitations. API-ILs offer several clear benefits over conventional solid-state APIs. By eliminating polymorphism, they remove a major source of variability in drug performance and manufacturing.[211] They can also improve solubility, dissolution, and bioavailability, which is important for many new drug candidates that are poorly water-soluble. A key feature of the API-IL approach is the tunability, given that physicochemical properties can be modulated through cation–anion selection without changing the pharmacophore, preserving the drug's established activity while altering its delivery characteristics. In some cases, API-ILs can also support multifunctional formulations, including dual-active systems in which both ions are pharmacologically active, and they may be adapted for oral, topical, or transdermal delivery. Their efficacy has been demonstrated across multiple therapeutic areas in extensive laboratory-scale studies.[218] However, these strengths are counterbalanced by several significant weaknesses. Only a small proportion of studied IL systems appear sufficiently biocompatible for therapeutic use, and long-term safety data remain limited, especially for counterion toxicity, biodegradability, and bioaccumulation. The structural complexity of API-ILs also makes standardisation difficult, which in turn slows the development of a shared regulatory framework. Their liquid form creates handling and manufacturing challenges in an industry built around solid dosage forms. In addition, the field still lacks robust TEA and broader sustainability assessment, including S-LCA. Despite these weaknesses, multiple emerging opportunities could accelerate the field. Predictive approaches such as QSAR, machine learning, and other data-driven methods may make it easier to design safer and more effective API-ILs. SSbD framework could bring safety and sustainability into development earlier, while standardised protocols for toxicity, environmental impact, and manufacturability would help close a major gap in the literature. Market demand for formulations that improve poorly soluble drugs remains strong, and early clinical studies of IL-based delivery systems suggest translational potential.[276,277] In the longer term, API-ILs may also

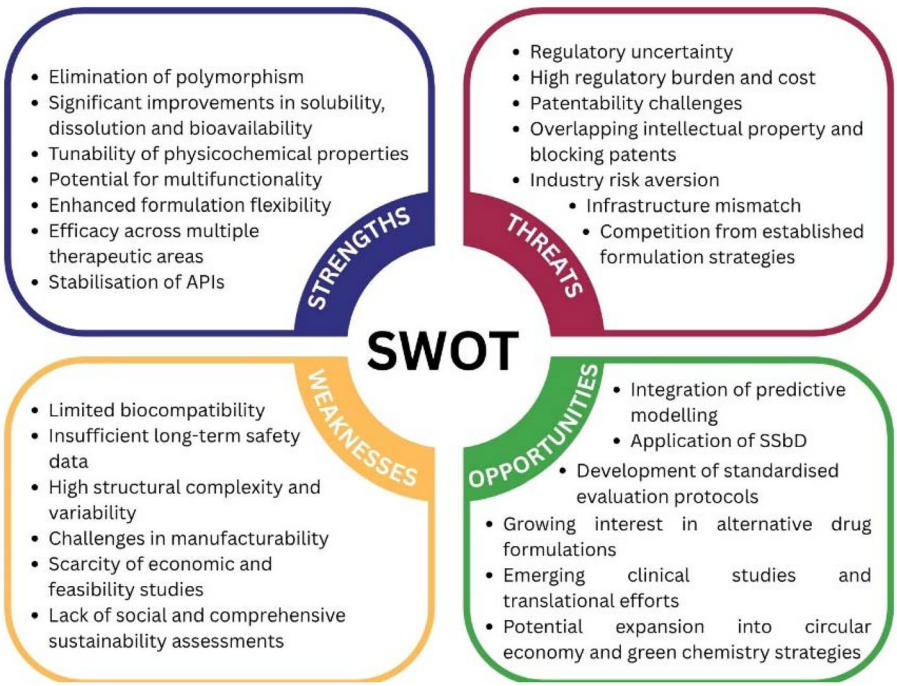

Fig. 4 SWOT analysis of API-ILs in pharmaceutical development.

fit well with green chemistry and circular economy goals. The main threats are external: (i) regulatory uncertainty, (ii) unresolved intellectual property issues, and (iii) the need for new manufacturing infrastructure. API-ILs do not fit neatly into existing regulatory categories, and patent protection may be complicated by overlapping claims and blocking patents.[278] Industry adoption may also be slow because these systems require investment in processes that differ from established solid-dose manufacturing. For now, the main obstacles to adoption are less about intrinsic performance than about regulation, economics, and infrastructure. Although no API-IL has yet reached full regulatory approval or commercialisation, the growing number of clinical studies suggests that the field remains promising, even if it is still at an early stage.[218]

Critical perspective and future outlook

ILs have indeed become a highly interesting topic over the last three decades due to their remarkable and now well-known characteristics. These properties can be tuned to specific needs by selecting appropriate cations and anions, leading to millions of possible combinations. As a result, ILs have found applications across a wide range of industries and fields. Particularly, since 2010, research on IL has shifted towards more application-driven and sustainability-conscious directions, especially in biomass processing, energy storage, advanced materials, and pharmaceuticals. In the pharmaceutical sector specifically, ILs have been utilised not only as solvents but also as APIs and agents that improve challenging properties such as low bioavailability, poor solubility, and polymorphism. Consequently, this review aimed to gather the available information on the health and environmental concerns associated with ILs use in industry. It also covers aspects such as LCA, TEA, scale-up potential, commercialisation, and current industrial applications. Together, these considerations highlight the need for a unified, application-oriented framework in which sustainability, safety, and economic feasibility are treated as interdependent criteria rather than as separate evaluation steps. Only by assessing ILs from such a holistic perspective, guided by their intended use and associated constraints, can more realistic and feasible decisions be made regarding their development and implementation. In this context, the most commonly used cation and anion families in ILs are presented in Fig. 5. This figure highlights a recurring, though not universal, trade off between performance, environmental profile, and synthesis cost. Imidazolium and phosphonium systems often offer high thermal and chemical stability together with favourable solvation properties, however, many widely used representatives remain difficult to justify from an environmental perspective. Toxicity is influenced by both the cation and the anion, with cation alkyl chain length playing a particularly significant role, while biodegradability is often reduced in more highly substituted or more hydrophobic systems. Pyridinium based ILs are not consistently more problematic and can display promising biodegradation behaviour, with shorter chain derivatives generally associated with improved biodegradability, although the relationship remains strongly structure dependent. Saturated cations such as piperidinium, pyrrolidinium, and morpholinium can be designed to exhibit lower toxicity and, in some cases, improved biodegradability relative to aromatic systems, nevertheless, outcomes remain highly structure dependent, and representatives of all major head groups have been reported to show partial biodegradability under standard test conditions. Cholinium and related bio-based cations are among the more promising

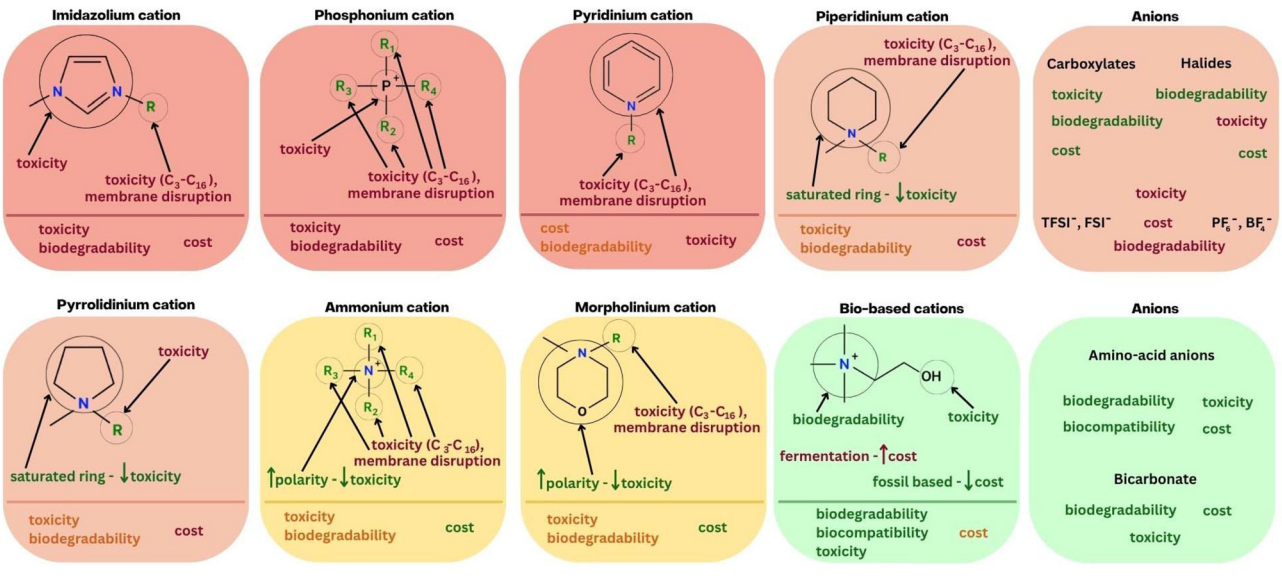

Fig. 5 Environmental and economic aspects of cations and anions. Red, orange, and green colours represent high, intermediate, and low toxicity, biodegradability, and cost, respectively.

options from a sustainability perspective, with examples such as choline and methoxy choline showing ready biodegradability in combination with suitable anions. However, their relatively low hydrophobicity can limit applicability in nonpolar or strongly interacting systems. It is also important to note that the designation "bio-based" depends not only on molecular structure but also on feedstock origin and synthesis route. For example, cholinium salts derived from fermentation based processes can be considered genuinely bio based, although this route is typically more expensive. In contrast, production *via* conventional petrochemical pathways (*e.g.*, from trimethylamine and ethylene oxide) yields structurally identical but lower cost materials that are more appropriately classified as conventional quaternary ammonium salts rather than truly bio-based compounds. On the anion side, simpler anions such as carboxylates and amino acid derived anions are generally cheaper and more environmentally benign, whereas fluorinated anions often enhance electrochemical or thermal performance at the expense of environmental persistence and associated concerns. Halide anions are typically inexpensive and readily available, but can contribute to higher toxicity and limited biodegradability, depending on the overall ionic liquid structure. The main point is that there is no universally "good" or "bad" IL family; rather, suitability depends on how effectively the combined properties of a given cation–anion pair align with the requirements of the intended application.

Given the momentum in IL-related research, the natural progression from laboratory-scale investigations would be to evaluate feasibility factors, such as toxicity, biocompatibility, scalability, and sustainability, before these systems can be adopted at an industrial level. Nevertheless, a critical look reveals that such studies are still lacking. While fundamental research continues to expand, there is a notable lack of practical assessments. Data on economic analysis and LCA studies of ILs remain scarce. Furthermore, social LCA data for ILs are virtually non-existent. Despite the extensive work done on ILs' physicochemical properties and bioactivity, very few to no studies explore their cost-effectiveness, long-term safety, or viability in large-scale pharmaceutical manufacturing. This disconnect raises the question of whether ILs really have a future within pharmaceutical development.

On the other hand, this gap is not entirely unexpected. In early phases of innovation, research typically centres on synthesis, characterisation, and possible applications. But ILs pose a unique complication: their structural variability and tunability make it difficult to draw general conclusions. Standardised testing frameworks and predictive models struggle to accommodate such diversity, meaning that nearly every IL system may require tailored analysis. As a result, drawing clear conclusions remains challenging, and collecting reliable data on toxicity, environmental fate, and economic viability is both resource- and time-consuming. Although technological advancements continue to support the field, they have not yet reached standardised, efficient, and simplified processes to design and use ILs to the extent one might expect. Computational screening and QSAR models are limited by the complexity of IL behaviour in both biological and environmental systems. Ultimately, while the scientific progress around ILs is substantial, the lack of practical data and scalability insights still presents a critical obstacle. Systematically closing these fundamental gaps, especially in terms of sustainability and regulation, will be the key to industrial adoption.

While these challenges present significant barriers, they also present clear directions for future work. First and foremost, applying SSbD principles as a guiding framework for designing safer ILs could save researchers considerable time and resources, while promoting the development of sustainable compounds. A deeper and broader development of computational tools is essential to accurately predict the properties, toxicity, and environmental impacts of ILs before synthesis. Herein, artificial intelligence and machine learning can significantly enhance traditional computational methods by enabling high-throughput screening, accurate structure–property predictions, and early-stage safety assessments, particularly when integrated into SSbD frameworks. This approach would help prevent loss of money, time, and resources, ultimately paying off in the long run. Incorporating green chemistry principles and circular economy business models alongside SSbD offers a powerful strategy to bridge existing knowledge gaps. This holistic and integrated approach enables the prediction of toxicity, biodegradability, and bioaccumulation without the need to physically produce the compounds. By doing so, it helps tailor the design of safer and more sustainable ILs while significantly reducing experimental effort and cost.

Equally important is the development of protocols and assessment methods tailored to the structural diversity of ILs, which would facilitate more comprehensive and accessible toxicity and biocompatibility studies. Ultimately, this would lead to the early incorporation of LCA in IL development, assisting in the evaluation of sustainability and feasibility. Another crucial parameter is economic studies, which are essential to better understand market potential and tap into unexplored opportunities. Additionally, social LCA, which assesses societal acceptance and impacts, represents an important but often overlooked piece of the puzzle. Together, these efforts could greatly ease and accelerate the transition of ILs from the laboratory to industrial applications. Finally, to support this process, effective communication and collaboration between academia, research institutes, and regulatory bodies are crucial. These broader needs are exemplified by the pharmaceutical sector, where API-ILs illustrate both the promise and complexity of IL implementation. This particular case emphasises the broader trends observed in IL research.

Overall, API-ILs have shown great potential. To realize their full potential, this integrated approach, which combines SSbD principles, advanced computational tools and circular economy models, must accelerate development while ensuring safety, sustainability and economic feasibility. Only through continued collaboration and commitment can these innovative compounds successfully transition from the lab to industrial scale and make a significant impact in the world. This per-

spective is further supported by the SWOT analysis which highlights the imbalance between the innovative potential of API-IL systems and their practical limitations. It emphasizes the urgency of implementing an integrated approach that combines the SSbD framework, namely TEA, LCA, s-LCA, toxicity, and biodegradability, supported by computational tools, to address the challenges arising from regulatory, clinical trial, and industry requirements. The pharmaceutical industry is one of the world's leading sectors, with substantial financial resources. Furthermore, it addresses some of the most pressing global challenges: finding cures for diseases and saving lives. This makes the introduction and eventual commercialisation of ILs worthwhile, especially if they can contribute to improved therapeutic solutions. However, a major challenge lies in the clinical trial phase, where unexpected adverse effects, formulation instabilities, or pharmacokinetic issues may arise, potentially leading to significant risks for patient safety. This presents a moral dilemma that the pharmaceutical industry must navigate. This may partly explain why progress in IL development and scale-up for pharmaceuticals has been slower compared to other industries.

Conclusion

This review consolidates current knowledge on ILs across toxicity, biodegradability, LCA, TEA, scalability, and pharmaceutical applications, providing a unified, use-oriented perspective on their development. Rather than supporting uncritical optimism, this integration highlights a clear imbalance between the strong scientific potential of ILs, particularly API-ILs, and the limitations of the existing evidence base required for their industrial and pharmaceutical translation. While API-ILs demonstrate clear advantages at the laboratory scale, including improved solubility, bioavailability, and elimination of polymorphism, their development remains largely preclinical, with a substantial gap between *in vitro* performance and validated real-world applications. This gap is driven not by a lack of functionality, but by fragmented toxicity data, insufficient sustainability assessments, and limited techno-economic and scale-up studies. Addressing these challenges requires a shift from isolated evaluations towards integrated assessment frameworks. In this context, the SSbD approach provides a critical foundation by enabling the simultaneous consideration of safety, environmental and social impact, economic feasibility, and performance from the earliest stages of development. Ultimately, advancing the field will depend not on demonstrating what ILs can achieve in principle, but on establishing, with rigour and consistency, which ILs are viable in practice and under what conditions they offer a meaningful advantage over existing technologies.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data supporting this study are available within the article.

Supplementary Information contains the chemical structures of the cations and anions constituting the ionic liquids discussed in this article. Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d6gc01231k.

Acknowledgements

The authors acknowledge the financial support from the from the Slovenian Research Agency under the research core funding No. P2-0152; J2-70079; J2-70093; J2-70080 and PhD grant 139012.

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