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Meta-Analysis of Ionic Liquid Literature and Toxicology

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Abstract

A meta-analysis was conducted to compare the total amount of ionic liquid (IL) literature (*n* = 39,036) to the body of publications dealing with IL toxicity (*n* = 213) with the goal of establishing the state of knowledge and existing information gaps. Additionally, patent literature pertaining to issued patents utilizing ILs (*n* = 3,358) or dealing with IL toxicity (*n* =112) were analyzed. Total publishing activity and patent count served to gauge research activity, industrial usage and toxicology knowledge of ILs. Five of the most commonly studied IL cations were identified and used to establish a relationship between toxicity data and potential of commercial use: imidazolium, ammonium, phosphonium, pyridinium, and pyrrolidinium. Toxicology publications for all IL cations represented 0.55% ± 0.27% of the total publishing activity; compared with other industrial chemicals, these numbers indicate that there is still a paucity of studies on the adverse effects of this class of chemical. Toxicity studies on ILs were dominated by the use of *in vitro* models (18%) and marine bacteria (15%) as studied biological systems. Whole animal studies (*n* = 87) comprised 31% of IL toxicity studies, with a subset of *in vivo* mammalian models consisting of 8%. Human toxicology data were found to be limited to *in vitro* analyses, indicating substantial knowledge gaps. Risks from long-term and chronic low-level exposure to ILs have not been established yet for any model organisms, reemphasizing the need to fill crucial knowledge gaps concerning human health effects and the environmental safety of ILs. Adding to the existing knowledge of the molecular toxicity characteristics of ILs can help inform the design of greener, less toxic and more benign IL technologies.

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Keywords

Ionic Liquids; Toxicity; Green Chemistry; Sustainability; Environmental Health; Meta-Analysis

1. Introduction

Interest in ionic liquids has risen sharply in the last fifteen years as emerging technologies have begun to focus more deliberately on environmentally friendly processes, and as existing technologies have been adapted to reduce the output of harmful chemicals. Ionic liquids (ILs) are celebrated for their low volatility and ability to reduce the use of volatile organic compounds (VOCs) as solvents in industry, and also for their numerous other physical properties, including low melting point, low flammability, high thermal and electrochemical stability, interesting phase behavior, and high electrical and ionic conductivity [1].

As a result of the push to replace volatile organic solvents and seek greener process chemistries, ILs have been investigated and implemented as solvents, phase transfer catalysts, surfactants, and liquid electrolytes [2]. Compared with traditional solvents, ILs offer many benefits to the reactions they support, including (i) greater stability of intermediate species; (ii) higher product yields; (iii) flexibility to be used and recycled multiple times in syntheses; (iv) tailored solubility characteristics, and (v) reduced processing and/or reaction temperatures [3]. The extensive versatility of cation and anion arrangements enables ILs to be custom designed for specific needs, thereby positioning them as ideal candidates in applications including dissolution of biomass [4], refrigeration [5], CO_2 capture from coal plants [6], liquid separations [7], aliphatic/aromatic separations [8], dye sensitized solar cells [9], batteries [10], fuel cells [11], supercapacitors [12], electroplating [13], and pharmacology [14].

As with many chemicals of future, current, or past use, ILs are at risk of entering into commercial mass production before in-depth toxicity analyses are conducted and pertinent adverse effects are fully understood [15, 16]. With the effects of dichlorodiphenyltrichloroethane (DDT) [17], polychlorinated biphenyls (PCBs) [18], chlordane [19], and many other toxic and persistent chemicals lingering on long after implementation of bans and throttling down of environmental releases [20], it would be desirable and prudent to screen new chemicals judiciously and thoroughly prior to commercial mass production and large-scale environmental release [21]. However, toxicity studies are lengthy and expensive, and the desire to take advantage of and produce novel chemicals may outpace the process of fully characterizing their risk profiles. To gauge the importance of such an analysis, ILs are already being manufactured (e.g., IoLiTec, Cytec, Sigma-Aldrich, and Acros; >350 ILs in total) and sold in quantities up to five kg for “in stock ILs,” custom syntheses can scale as high as 10 kg, pilot scale syntheses can reach 100 kg, and staple ILs are manufactured on the metric ton scale [22, 23]. Additionally, large-scale chemical companies are using ILs in various processes (e.g., BASF, Degussa, and IoLiTec/Wandres have commercial-scale processes using ILs) [24], which would indicate that production volumes and demand would continue to increase.

The present analysis of the scientific literature was designed to identify trends in publishing activity for the purpose of determining whether and to what degree toxicity studies are keeping pace with the utilization of IL technologies. Specifically, IL toxicity data were compared to the total body of IL literature to determine if the ratio was consistent with the publishing activity of comparable chemical classes. Relevant IL toxicity data were analyzed to understand the representation of model organisms in IL toxicity studies and to determine whether the range of IL compounds tested for toxicity was consistent with industrial usage. Patent literature pertaining to IL usage was utilized to form an understanding of the industrial attitude toward IL toxicity.

2. Materials and Methods

2.1 Literature search

Peer-reviewed scientific literature was searched for up until March 2015 using SciFinder online database software (v2014). The initial screening was performed by one author of the team and later replicated by a non-author collaborator to confirm validity. The term '*ionic liquid*' was used to eliminate non-ionic liquid compounds from the search. These search results were then queried for the term '*toxic*' to target IL literature pertaining to toxicity. Importantly, SciFinder searches for words containing the search terms, such that, for example, terms like "ionic liquids," "toxicity," or "immunotoxicity" were included in the search results. We included journal articles focusing on ionic liquid toxicity, with abstracts published in English, and excluded commentaries, news articles, reviews, letters, opinion pieces, and studies whose entire data had been reported previously in works already included in the search results. Studies were excluded if the sole method of data collection was through qualitative, quantitative, or spectral structure-activity relationship determination or other mathematical or computer-simulated modeling. Pharmacological and drug delivery toxicity studies were excluded; specifically, ruthenium compounds were eliminated from the results to limit unwanted reporting bias resulting from such medical uses. Additionally, we confirmed the validity of our search criteria by performing equivalent searches in PubMed, Web of Science, and Scopus. Resultant data are presented online in the supplementary information.

Toxicity literature for phthalates, polybrominated diphenyl ethers (PBDEs), perfluorinated compounds (PFCs), linear alkyl sulfonates (LASs), and alkylphenol ethoxylates (AEs) were searched for and sorted in SciFinder database to provide comparative results to ILs with other toxic industrial chemical families. First, the chemical family (e.g., "phthalate") was searched, duplicates were removed, and the results were restricted to journal articles. Subsequently, 'toxic' was searched within this field to target literature pertaining to the toxicity of the chemical family. The toxicity literature pertaining to ILs also was searched using these criteria, and head-to-head comparisons were performed utilizing identical search and exclusion criteria.

Additionally, patent literature from the United Stated Patent and Trademark Office online US Patent Collection database was collected and examined through October 2015. The terms '*ionic liquid*' and '*toxic*' were used in tandem to target patents from 2000 to present relating to ILs and toxicity consideration. Patents in which the keywords appeared only in

reference citations or in which the term '*non-ionic liquid*' appeared were omitted. Patents for which the toxicity discussion was unrelated to ionic liquids were omitted.

2.2 Data Extraction

Publication literature on ILs meeting the eligibility criteria were extracted from SciFinder database and compiled into EndNote citation manager (vX7.2, Thomson Reuters, New York, USA). The final sample (n = 213) were reviewed for the purpose of establishing relevance to industrial IL usage and for information concerning effects of ILs on living organisms or relevant biological materials. One team member conducted the initial data collection. A second team member checked the collected data, and any discrepancies were resolved by re-referral to the study and consensus decision.

Additional chemicals that share a comparable potential relative to ILs to contaminate water systems through industrial run-off were selected to establish a baseline ratio of the amount of toxicity literature generally found for chemicals exhibiting toxicity to aquatic organisms. Inclusion criteria for these chemicals required that they be manufactured and used in industry for the purpose of producing or assisting other technologies, and must also be recognized as water contaminants that cause toxicity to aquatic ecosystems and organisms.

Patent literature on ILs meeting the inclusion criteria were compiled into EndNote citation manager (vX7.4, Thomas Reuters, New York, USA). The final sample of patents that addressed IL toxicity (n = 112) was sorted by the context in which the IL toxicity discussion appeared. For instance, the most frequent context for the discussion of IL toxicity was the mentioning of the low toxicity profile or the reduced toxic nature of ILs compared to organic solvents that are commonly used.

3. Results

3.1 History and emergence of ILs

The first publication on ILs appeared in 1888 as a paper written by the German chemists Gabriel and Weiner, after observing a low melting point for the salt ethanolammonium nitrate (melting point of 52–55 °C) [25]. In 1914, a publication emerged on the physical properties of fused salts, wherein Paul Walden characterized five ammonium-based salts with low melting points, the lowest of which was approximately 12 °C [26]. The term *fused salt* has been in use since at least the early 1800s and was used simply to mean a melted and often re-solidified mass of salt [27] [28]. Fused salts differ from ILs in their melting points. For more than a century, salts in the liquid state have been referred to by various names: ionic melts and glasses [29], ionic fluids, molten salts [30], and liquid electrolytes. The term *ionic liquid* did not fully appear until the 1940s [31].

In 1929, the first IL toxicity study was conducted when Hunt and Renshaw tested the physiological effects of multiple pyridinium and piperidinium chemicals on cats and mice [32]. At least two of the chemicals tested then were consistent with the present definition of ILs. Then, over seven decades later, the interest in ILs started to soar in the early 2000s and a corresponding increase in toxicity studies emerged.

3.2 IL toxicity literature volume relative to total publishing activity

Annual IL publishing activity has steadily risen from the year 2000 to the present day, as interest in green chemistry continues to grow and ILs are being promoted as low-viscosity, non-volatile and environmentally-benign chemicals with seemingly limitless potential for widespread commercial applications. The number of toxicity studies that have been performed on ILs is just a sliver of the total annual IL publishing activity (Fig. 1). More than 5,000 peer-reviewed IL publications were found in the SciFinder database in 2014 alone; just 35 of those publications included toxicity studies. The total body of IL literature (n = 39,036) contains only 213 toxicity studies or 0.55% ± 0.27 over the span of years from 2000 and 2014.

Chemical families having a comparable number of publications to ILs, such as phthalates, have a much higher number of toxicity publications. Phthalates are one class of chemicals that, like ILs, consist of hundreds of compounds and have roughly the same amount of peer-reviewed literature. Phthalates are being monitored keenly by toxicologists, with a 12% subset of publications pertaining to research on adverse effects; however, the sheer number of structural variations precludes regulation. In contrast, the corresponding subset of literature dealing with IL toxicity represented only 2.9% (Fig. 2), determined using the SciFinder database and the same methodology employed for identifying toxicity publications for phthalates. This percentage is still low but larger than the calculated value of 0.55 ± 0.27% arrived at by applying the exclusion criteria outlined above. Although phthalates and ILs have the same amount of publishing activity, phthalates have over four times the amount of toxicity literature relative to ILs (12% vs. 2.9%). Among other compound classes considered, PBDEs were found to undergo more frequent testing for toxicity, as evidenced by their higher percentage of 16.7% of search results for toxicity-related publications. Perfluorinated compounds (PFCs) have a small amount of literature in comparison to ILs and phthalates, yet still a sizable subset (7.3%) of their literature focuses on toxicity. Both linear alkyl sulfonates (LASs) and alkylphenol ethoxylates (AEs) have very small amounts of publishing activity, but have larger relative percentages of toxicity publications of 23.8% and 17.8%, respectively. In each of the above cases, the chemical compounds have applications that promote consumer exposure (e.g., phthalates: packaging; PBDEs: building materials, automobiles and aircraft, electronics, etc.; PFCs: fabric and cookware coatings; LASs and AEs: detergents).

Values of the median lethal dose (LD_{50}) in rats for commonly used ILs (1-ethyl-1methylpyrrolidium bromide, 1-butyl-3-methylimidazolium hexafluorosphosphate ([BMIm][PF_6]), benzyltriethylammonium chloride, and 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm][BF_4])) range from 300 ppm to 980 ppm [36–38]. These values are quite low, indicating significant toxicity of this group of compounds. By comparison, problematic industrial compounds of lesser toxicity that are nevertheless under review for tighter regulations or have already been banned in many countries include phthalates, PBDEs AEs, and bisphenols (Fig. 3). Indeed, the only group including compounds significantly more toxic than ILs is that of perfluorinated compounds (PFCs), with the low LD_{50} value of PFDA signifying the greatest toxicity among the substances considered here [52]. For the ILs included in Fig. 3, the ionic liquid [BMIm][PF_6] is the most toxic with an

LD_{50} value in rats as low as 300 ppm [36]. LASs, which have the largest percentage of toxicity publishing activity compared to their total amount of publications at 23.8%, have toxicities comparable to those established for the selected ILs examined here.

3.3 IL toxicity data

The exclusion criteria utilized here resulted in a pool of only 213 relevant toxicity studies examining the effects of IL chemicals *in vivo* and *in vitro*, encompassing many groups of eukaryotic and prokaryotic organisms. Many of the studies evaluated the effects of multiple ILs and test subjects. The IL literature showed a correlation between the most commonly studied cations in the overall literature and the frequency of the cation being examined in toxicity studies. The five most common cations used to synthesize ILs in academia – imidazolium, ammonium, phosphonium, pyridinium and pyrrolidinium – were the five most frequently studied in IL toxicology (Fig. 4A). The 213 toxicity publications extracted from IL literature detail toxicity evaluations of 279 biological test systems (Fig. 4B).

When the relevant toxicology data is reduced to whole animals, the frequency of cations studied is largely retained with the exception of phosphonium (Fig. 5B). Whole mammal studies are of particular interest because they are representative of the test chemical's effects on a complete organism, which arguably are more indicative of human effects than information derived from isolated cells of an organism only. Additionally, these studies enable a more reliable differentiation of the effects caused by chronic and acute exposure to the test compound. Toxicity data on whole animals comes from many ecosystems, with much focus having been given to soil-dwelling and aquatic organisms (Fig 5B). Freshwater lake, stream, and river ecosystems have been studied extensively; in contrast, marine animal studies are lacking almost completely. The only saltwater animals assessed for toxicity were the brine shrimp *Artemia salina*, which lives in saltwater lakes [57] [58].

The number of whole animal studies can be further reduced to focus on whole mammals only, for which five cation classes of ILs have been studied thus far (Fig. 6A). Notably, phosphonium-based ILs are absent from this subset. Whole mammals having been tested for IL toxicity include mice, rats, and cats (Fig. 6B).

The commercial sale of ILs and their implementation into industrial technology (e.g., separation processes, etc.) was highlighted earlier. Since recent decades have witnessed a decline in the number of peer-reviewed publications from industrial research laboratories, the analysis of IL toxicity was expanded to the patent literature to better understand the commercialization and implementation of ILs in industrial processes (Fig. 7). The exclusion criteria applied to the total patent literature pertaining to ILs (*n=3358*) resulted in 112 patents that addressed the toxicity of ILs. Toxicity was most frequently discussed (*n=69*) to highlight the low toxicity or less toxic nature of ILs compared to the organic solvents they were replacing. Some patents address IL toxicity under multiple contexts, for example realizing that some forms of ILs are toxic while others are apparently non-toxic, and that toxicity of other ILs are not yet ascertained [59]. Notably, few (*n=17*) patents defined ILs as toxic, representing only 0.51% of the evaluated body of work on intellectual property claims.

4. Discussion

IL technology follows a not uncommon pattern of interest and decline therein, as human ideas and awareness peak and fall [15] After Gabriel and Weiner [25] discovered their low-melting salt, more than a quarter of a century passed before Walden [26] found his 12 °C melting salt. It took another fifteen years before IL compounds were first tested for their physiological effects in mammalian models [32]. Early ILs were not air-stable, which contributed to their intermittent research and testing. Today, as interest in IL technology grows, so too does interest in toxicity profiles. However, the question posed here was: *Is the body of knowledge on the adverse effects of ILs sufficient and consistent with that of other mass produced chemicals?*

Studies have demonstrated that ILs are substantially toxic to organisms of many phyla. Exposure to ILs has been shown to cause DNA damage in seaweed [60], loach [61, 62], zebrafish [63], and PC12 (rat adrenal medulla) cells; oxidative stress in plants (barley, duckweed, seaweed [60], wheat), animals (mice, snails, water fleas, and zebrafish [63]), and embryos (frog [64] and goldfish [65]); organ damage in carp, goldfish, and mice [66]; and *in vitro* mitochondrial dysfunction in PC12 and HeLa (human) cells. Toxicity effects in large mammals and whole humans have not been thoroughly analyzed and can only be projected based on preliminary protein [67], mammalian organ [66] and cell line studies [68], [69]. Further toxicity testing is needed to establish the chronic and acute exposure profiles of ILs.

The number of IL toxicity publications that populate scientific databases is largely misleading because much of the literature mentions toxicity as a commendation to its role in green chemistry [70–80]. Approximately 1,430 results for peer-reviewed publications on IL toxicity are listed in SciFinder as of March 2015. Upon closer examination, less than 20% of these publications contain toxicity studies pertaining to environmental exposure. That the actual amount of IL toxicity studies, after applying relevant exclusion criteria, is just 0.55% ± 0.27% of the total literature could be an indication that scientific literature to date is focused more on applications and new discoveries than on the thorough analysis of toxicity and environmental impact. Furthermore, this trend is seen in patent literature: while 112 out of 3,358 patents from 2000–2015 address toxicity of ILs, 61.6% of this subset do so in regards to how ILs have lower toxicity compared to commonly used organic solvents or catalysts. Only 15.2% of the 112 toxicity patents explicitly recognize that ILs are in fact toxic [59, 81–95]. Thus, only 0.51% of the total patent literature specifically addresses the toxic nature of ILs, which is remarkably consistent with published literature. As described in the introduction, current production estimates for the many variations of ILs are many metric tons, and these materials are being used in academic labs and companies around the world. Therefore, the need to develop a thorough understanding of the potential human health risks and environmental concerns is crucial.

The “green” label that ILs are given as solvents [96–98], catalysts [99–108], and in products of chemical syntheses in general [109–117] is likely a result of the non-volatile and favorable reaction properties of ILs. Non-volatility addresses only a couple of the criteria manifested in the 12 Principles of Green Chemistry, the seminal framework for recognizing environmentally safe, sustainable chemicals and chemical practices [118]. Criteria met by

ILs include (1) using safer solvents compared to traditional, more hazardous alternatives (e.g., PFCs) [33, 50–52], (2) implementing inherently safer chemistry for accident prevention by reducing the risk of inhalation exposure and by virtually eliminating fire hazard from lack of ignitable vapors [1], and (3) highly selective catalysis, another favorable criteria of the principles of green chemistry [2]. These characteristics make ILs appear at the outset to be relatively benign in synthesis with little consideration to the remaining criteria. Importantly, many of the "green" judgments passed on ILs are based on physical properties rather than biological safety data [119–126]. Though ILs may be good replacements for some toxic chemicals and processes [3, 127], the need to utilize them with care cannot be overlooked and their label as a green class of chemicals is being widely oversold.

One of the very best qualities of ILs is that they have seemingly unlimited possibilities for arrangements of cations, anions, and carbon substituents that can be effectively altered to produce compounds for many processes (i.e., designer molecules). Avoidance of adverse effects and environmental contamination must become a central parameter for their design. A vast body of IL literature focuses on the identification of specific structural properties responsible for their toxicity. This knowledge ideally should be recognized and considered every time a new chemical is conceptualized. Unfortunately, many publications are conflicted on the specific structural arrangements that impart toxicity to ILs. Recent studies point to elevated toxicity as being primarily affected by cation size or branching [128], specific cation species [129], increased lengths or branching of cation alkyl chains [130], cation aromaticity [130, 131], lipophilicity, surfactant behavior [132], or anion species [131]. Clearly, an improved knowledge of the molecular toxicity characteristics of ILs can help inform the design of greener, less toxic and more benign IL technologies. In the meantime, the uncertainty about the safety profiles of ILs needs to be communicated to industries and personnel, and stringent disposal guidelines for IL chemicals need to be implemented to prevent current and future contamination of ecosystems. Despite the fact that ILs offer the potential to make many industrial processes "greener", the repeated referral to ILs as '*green*' may lead to careless handling and unnecessary harmful exposures and effects among occupational users and consumers.

Conclusions

Ionic liquids are poised to alter a variety of industrial production processes with direct impact on and benefit for consumers. Their adaptation to various applications has earned them the nickname '*designer solvents'* and '*designer chemicals*.' However, as noted herein, the lack of attention to their environmental impact and potential health risks is of concern. Based on the flexibility in structure and function inherent to ILs, the future discovery of entirely safe and benign ILs is conceivable. However, today's ILs do not yet live up to this aspirational goal. To get there, preliminary toxicity studies that eliminate certain structures or identify benign functionalities are needed to ensure that the commercialization of ILs proceeds safely to protect consumers and industrial workers, and to prevent delayed restrictions or regulations that are unnecessary if the studies are performed in advance. In this context it is important to note that the literature and knowledge on the toxicity of industrial compounds generally becomes substantial and robust only after commercialization of these materials has advanced to a scale sufficiently large for health and safety concerns to

become apparent. Continuing efforts are needed to fill data gaps and address uncertainties in the safety profile of chemicals prior to their commercialization and widespread use, with ILs serving as just one illustrative example for this general requirement of responsible chemical design, production, consumption and recycling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A meta-analysis comparing IL literature to IL toxicity established information gaps
- Toxicology publications for ILs represented 0.55% of the total publishing activity
- Most toxicity studies used *in vitro* models (18%) or marine bacteria (15%)
- *In vivo* toxicity studies on whole mammals comprised only 8% of all tests
- Chronic low-level exposure to ILs has not been studied for any model organism

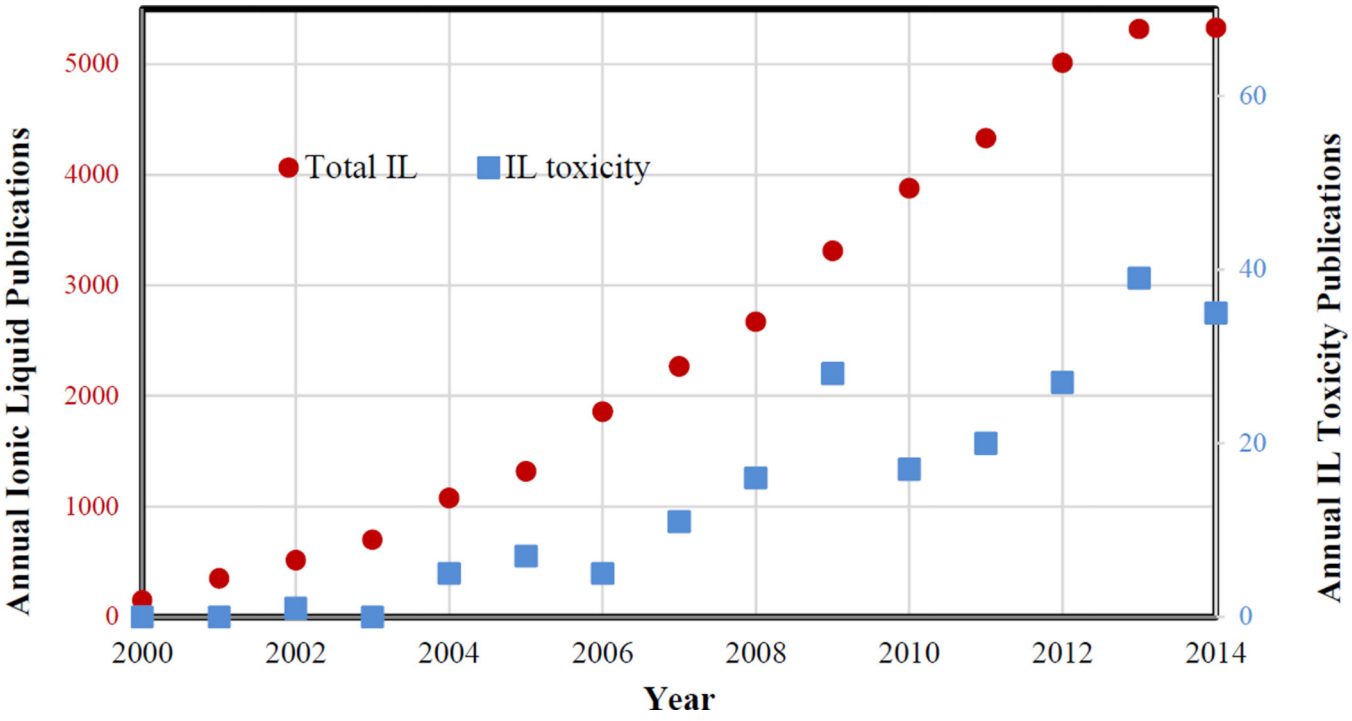

Figure 1.

Total annual publishing activity (2000–2014) of ionic liquids. Red circles represent the total annual publishing activity of ILs in the thousands of papers per year. Blue squares represent the much more limited annual number of papers studying toxic or adverse effects of ILs.

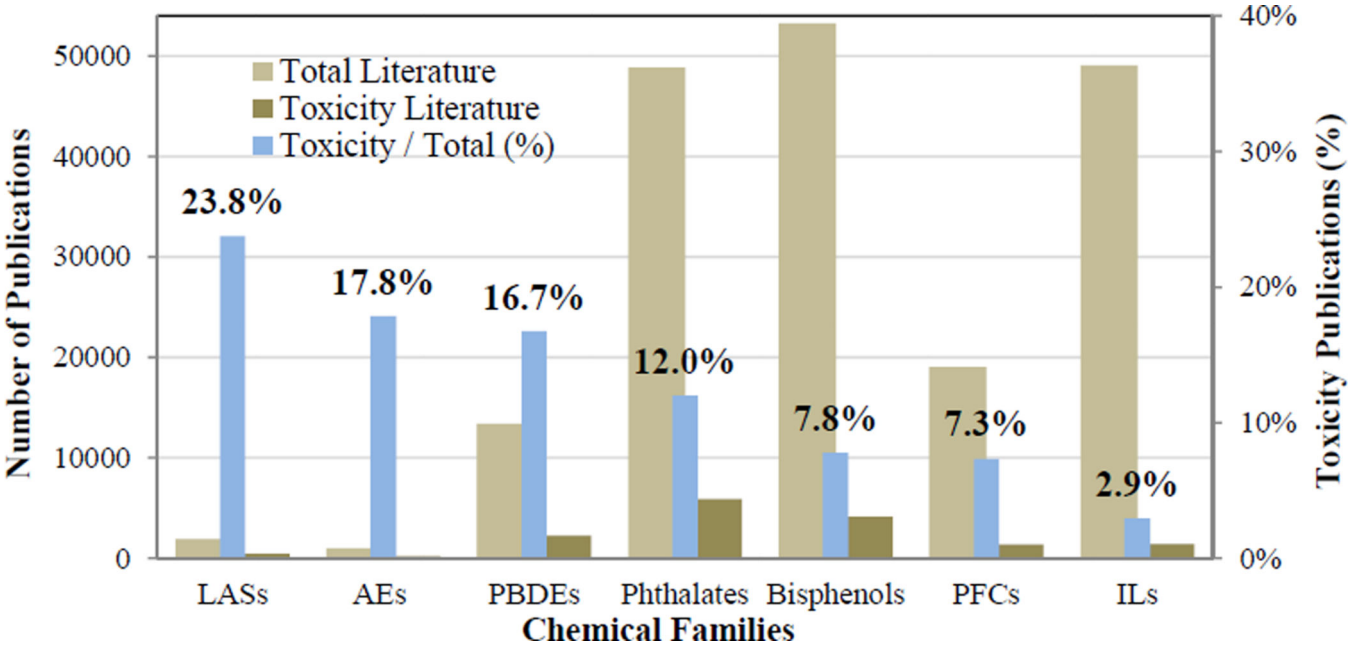

Figure 2.

Percentage of toxicity-associated literature found in SciFinder database for seven chemical groups known to exhibit toxicity in aquatic environments. Chemicals are presented in the order of descending relative fraction of toxicity studies. Total publications for each chemical are in light brown bars, with the absolute number of toxicity publications shown as dark brown bars (left hand axis). The percentage of literature related to toxicity is shown in blue for each chemical (right hand axis).

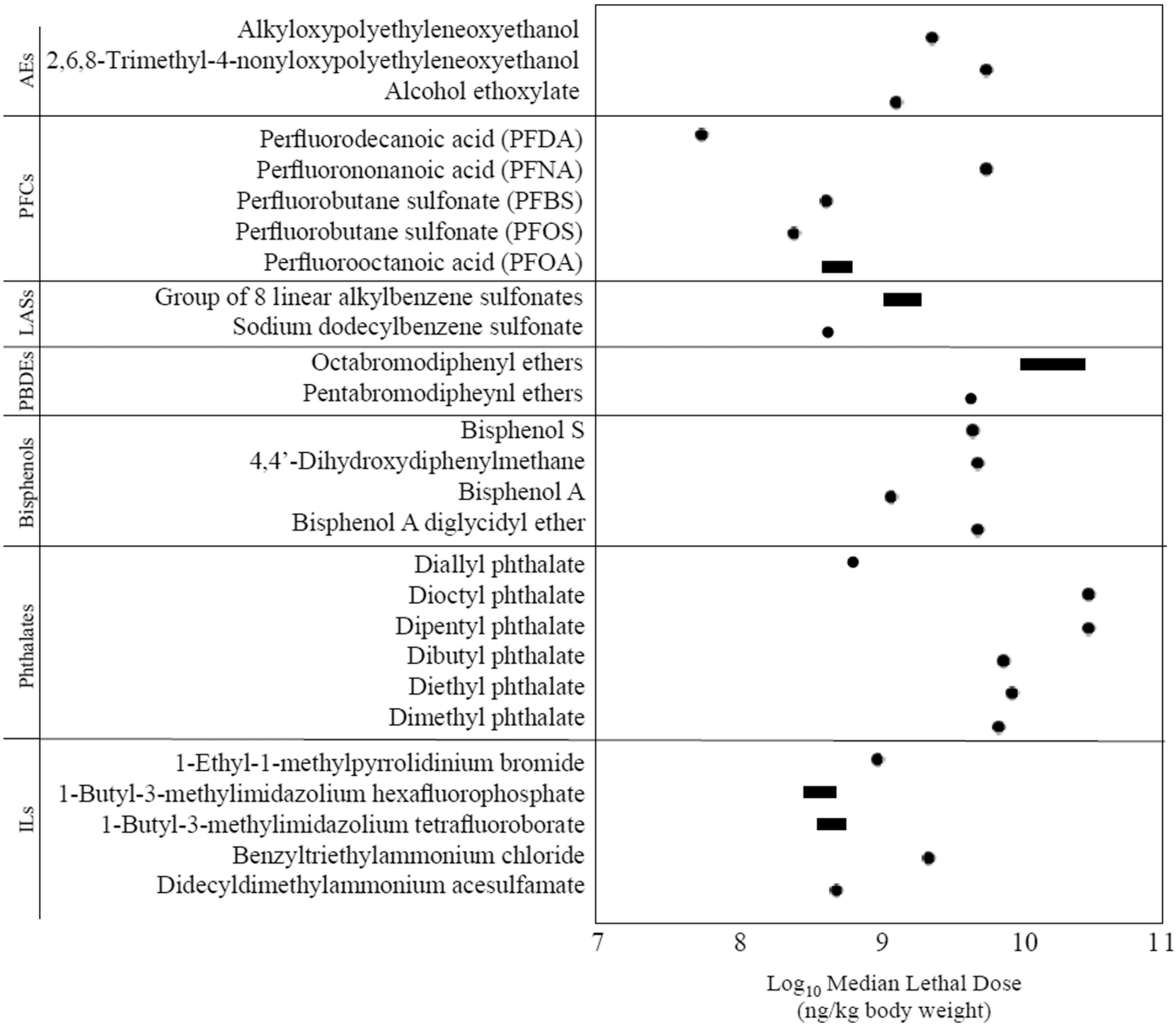

Figure 3.

LD_{50} values for a variety of chemical families administered to rats [33–56]. The bars indicate the range of reported values and dots represent only one reported value. Eight LAS compounds are grouped and their toxicity thresholds expressed as a single range.

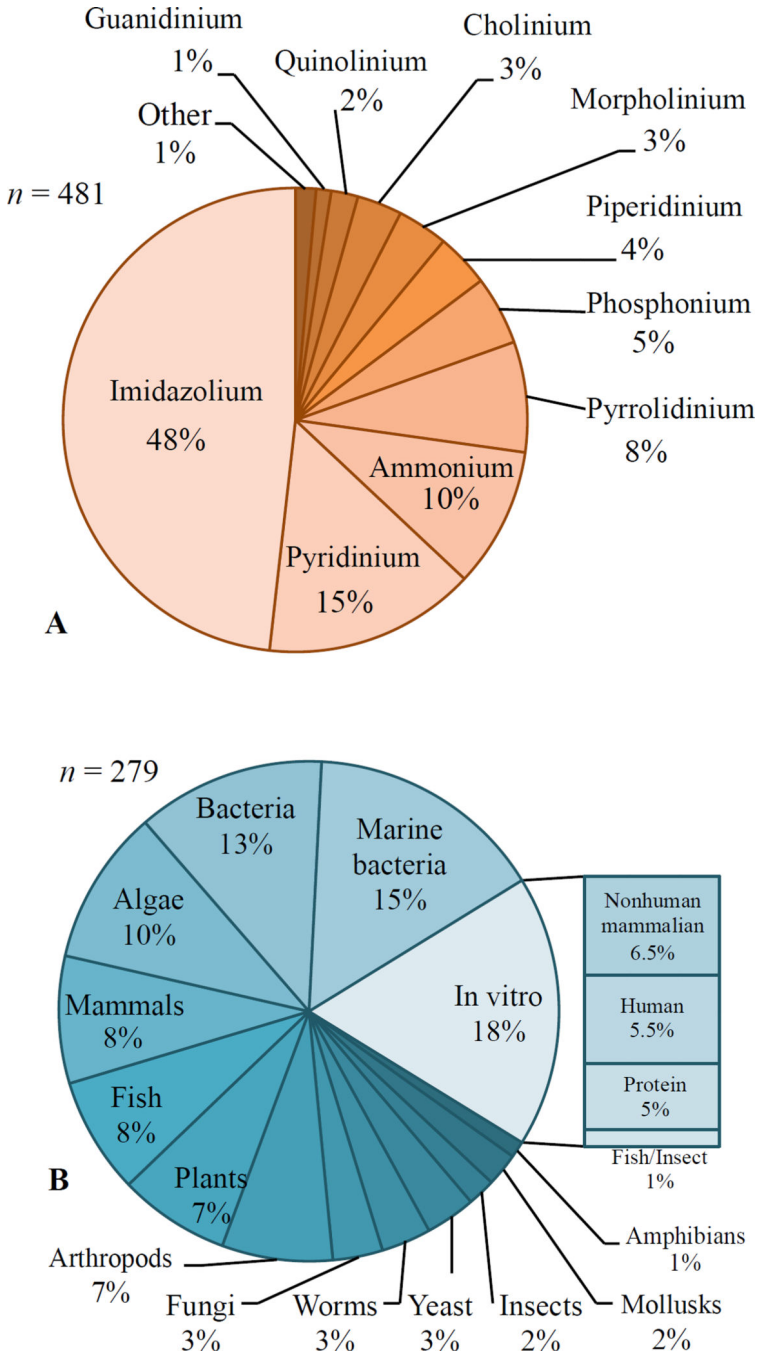

Figure 4.

Classification of 213 IL toxicity publications based on (**A**) the number of cations (*n* = 481) and (**B**) model organisms (*n* = 279) studied. Many papers tested multiple ILs and organisms. The "other" category includes caprolactam, quiniclidium, sulfonium, thiophenium, and tropinium-based ILs.

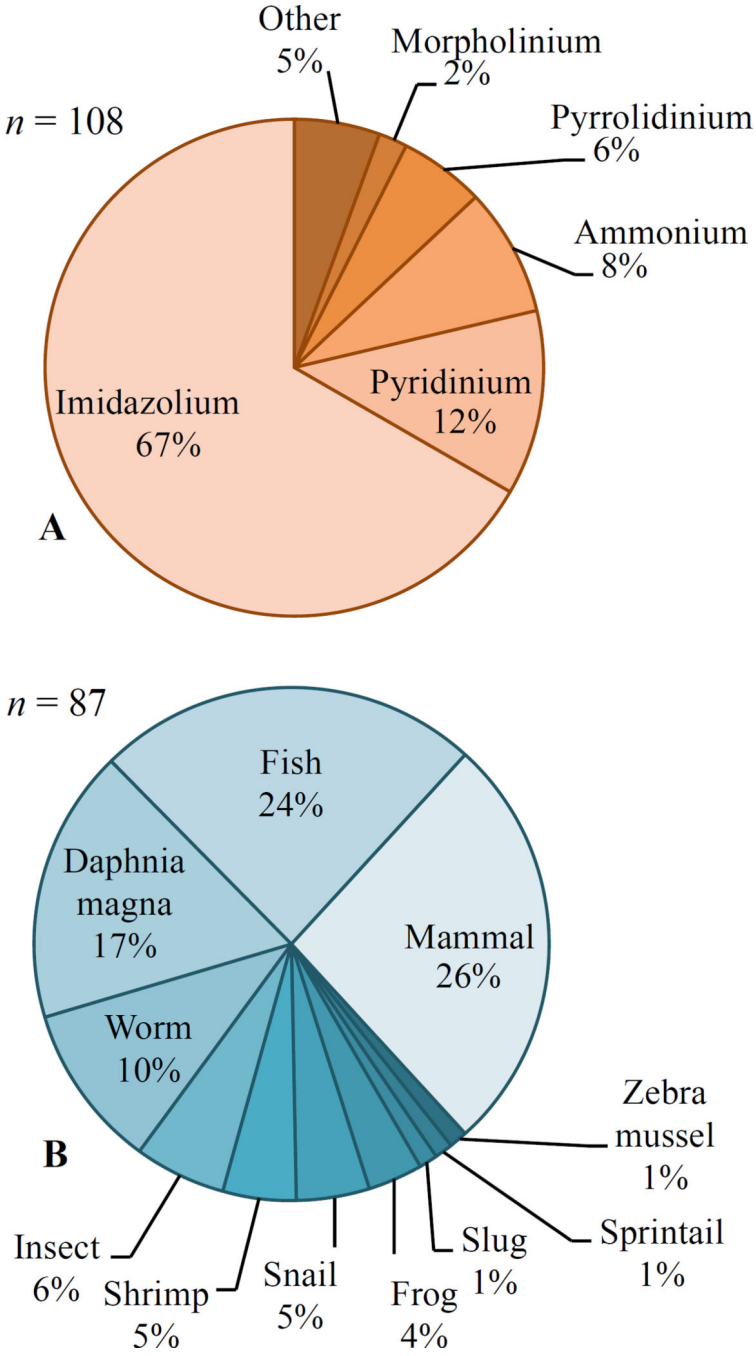

Figure 5.

Whole animal toxicity publications based on (**A**) the number of cations (*n* = 108) studied and (**B**) the number of whole animals (*n* = 87) studied. The “other” category describes caprolactam, cholinium, morpholinium, phosphonium, piperidinium, and thiophenium cations.

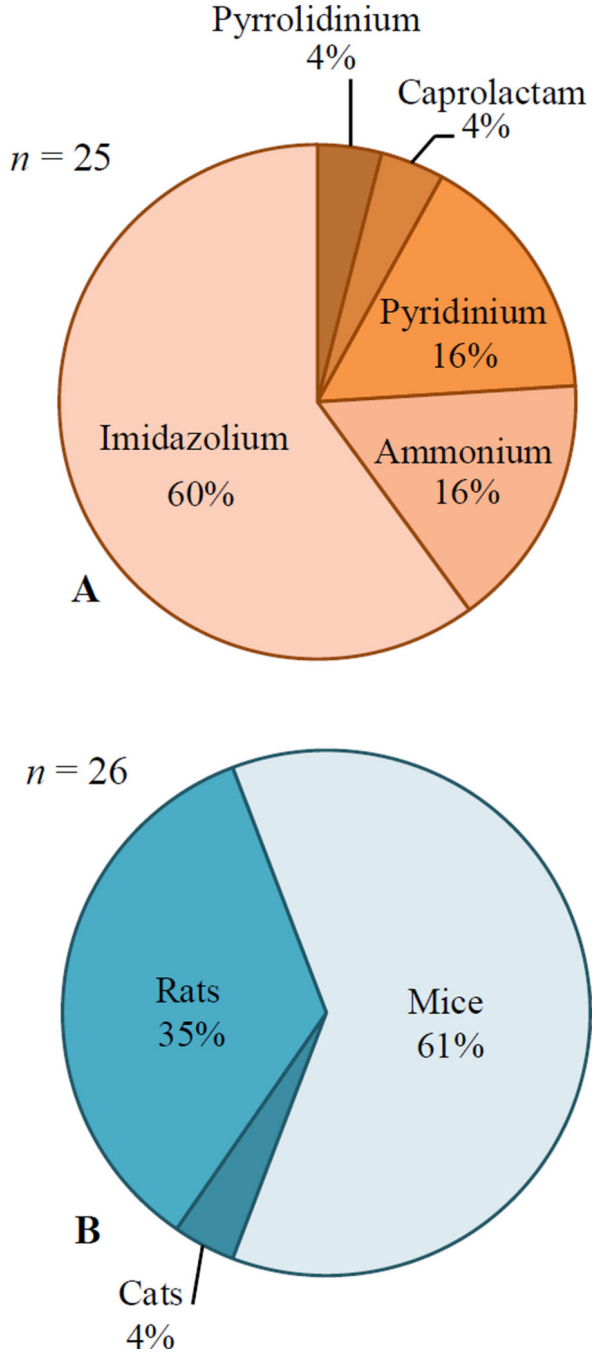

Figure 6.

Classification of 23 whole mammal IL toxicity publications based on (**A**) the number of cations (n = 25) studied and (**B**) model organisms (n = 26) studied. Twelve papers tested multiple ILs and organisms.

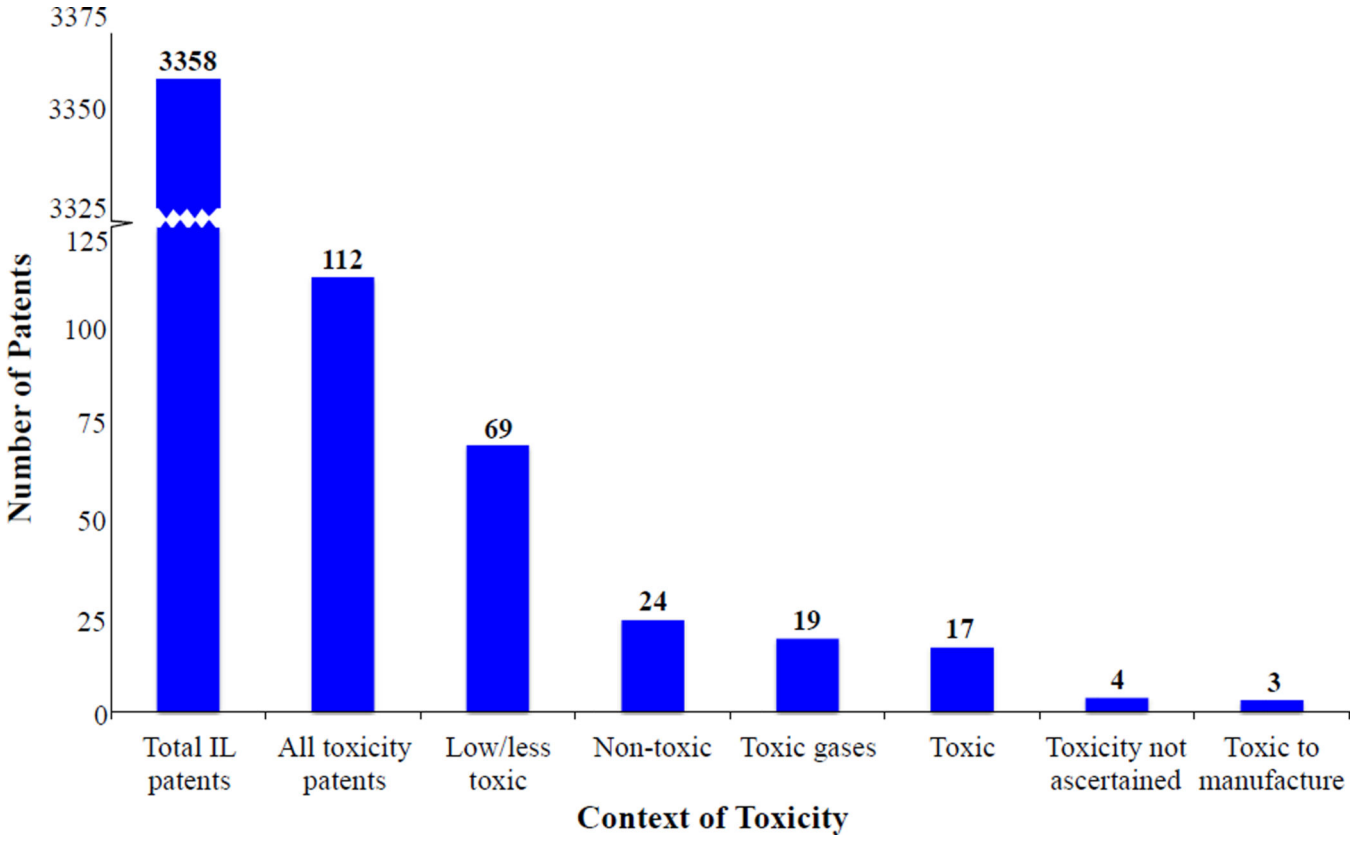

Figure 7.

Patents from 2000 to 2015 in which ionic liquid toxicity was addressed. The context of toxicity varies from patent to patent, in which some patents addressed IL toxicity under two or more considerations.