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Review

Meta-analysis of ionic liquid literature and toxicology

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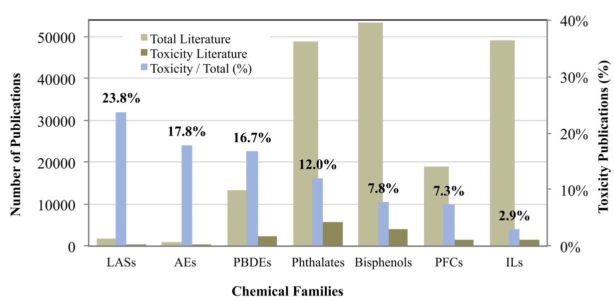
HIGHLIGHTS

- 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.

GRAPHICAL ABSTRACT



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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 ($n = 3358$) 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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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 (Tietze et al., 2012).

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 (Swatloski et al., 2003). 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 (Mattrey and Mayville, 2001). 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 (Muhammad et al., 2011), refrigeration (Kim et al., 2012), CO_2 capture from coal plants (Eljack et al., 2014), liquid separations (Yu et al., 2005), aliphatic/aromatic separations (Kim et al., 2010), dye sensitized solar cells (Brennecke, 2014), batteries (Zhang et al., 2011a), fuel cells (Fox et al., 2012), supercapacitors (Pak et al., 2013), electroplating (Stenger-Smith and Jennifer, 2009), and pharmacology (Ferraz et al., 2011).

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 (Halden, 2015; Venkatesan and Halden, 2015). With the effects of dichlorodiphenyltrichloroethane (DDT) (Neta et al., 2010), polychlorinated biphenyls (PCBs) (Herbstman et al., 2008), chlordane (Neta et al., 2011), and many other toxic and persistent chemicals lingering on long after implementation of bans and throttling down of environmental releases (Apelberg et al., 2007), it would be desirable and prudent to screen new chemicals judiciously and thoroughly prior to commercial mass production and large-scale environmental release (Novak et al., 2011). 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 (Production scale, 2015; IoLiTec, 2015). Additionally, large-scale chemical companies are using ILs in various processes (e.g., BASF, Degussa, and IoLiTec/Wandres have commercial-scale processes using ILs) (Maase and Wasserscheid, 2008), which indicate that production volumes and demand 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 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-