Prior to initiating the testing of a substance, an NIEHS/NTP staff scientist develops a research concept document. This research concept outlines the general elements for a program of study of the substance to address specific research needs raised in its nomination to the testing program. Additional information about the nomination, review, and selection of substances for study by the NTP is provided from ***Nominations to the NTP Testing Program*** (**http://ntp.niehs.nih.gov/go/nom**).

NTP Concept Document: Ionic Liquids

Ionic liquids (ILs) are salts of organic cations with melting points generally below 100°C. They typically consist of nitrogen-containing organic cations and inorganic anions. ILs are being widely investigated in industrial and laboratory processes as "green" replacements for volatile organic solvents in catalysis, synthesis, and separation processes, in addition to their role in electrochemistry and nanotechnology. Three ILs, 1-butyl-3-methylimidazolium chloride, 1-butyl-1-methylpyrrolidinium chloride, and N-butylpyridinium chloride, were nominated to the NTP by the Center for Green Manufacturing, University of Alabama for toxicological testing based on their widespread interest as possible alternative to organic solvents. Limited toxicity, ADME, and environmental fate data is available for this class of compounds.

The project leader recommended a tiered research approach in prioritizing the study needs for ILs. The first tier of proposed studies tests the hypothesis that the toxicity of the ILs is determined mainly by the cation. The studies will evaluate the *in vivo* mammalian toxicity of 3 different cations with similar alkyl chain lengths and a similar anion. The 3 compounds nominated are representative of the three most common cation classes of ILs being investigated. They are the starting materials for many other ILs and are being produced commercially. They are also free from intellectual property. ADME studies were proposed to characterize the *in vivo* absorption, disposition, and elimination of the 3 ILs following administration of a single oral, intravenous, and topical dose and to identify the major metabolites of the 3 ILs. Based on the data from the ADME studies, general toxicity studies will be designed. Genotoxicity, immunotoxicity, and reproductive/developmental toxicity studies were also recommended.

The second tier of studies proposed the use of *in vitro* assays, alternative animal model systems (i.e. *C. elegans*) or other high-throughput approaches to evaluate the toxicity of a large number of compounds in this chemical class. These studies will be designed to more systematically test the hypothesis that specific structural variations, for example increased alkyl chain length, result in increased toxicity. The studies will be designed to evaluate the relative effect of the cation, anion, alkyl chain length, and decomposition products to the toxicity of ILs and to make predictions about which compounds are most likely to produce toxicity *in vivo*. The *in vivo* toxicity studies described above will provide the benchmark of exposure related toxic effects needed to compare and anchor the data collected from high-throughput assays.

The concept review team felt that the proposed studies were consistent with the NTP Vision and Roadmap and approved the concept.

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