# Ionic Liquids

## 1-Butyl-3-methylimidazolium Chloride (CAS No. 79917-90-1)
## 1-Butyl-1-methylpyrrolidinium Chloride (CAS No. 479500-35-1)
## *N*-Butylpyridinium Chloride (CAS No. 1124-64-7)

# Review of Toxicological Literature

**May 2004**

# Ionic Liquids

## 1-Butyl-3-methylimidazolium Chloride (CAS No. 79917-90-1)
## 1-Butyl-1-methylpyrrolidinium Chloride (CAS No. 479500-35-1)
## *N*-Butylpyridinium Chloride (CAS No. 1124-64-7)

# Review of Toxicological Literature

*Prepared for*
National Toxicology Program (NTP)
National Institute of Environmental Health Sciences (NIEHS)
National Institutes of Health
U.S Department of Health and Human Services
Contract No. N01-ES-35515

Project Officer:
Scott A. Masten, Ph.D.
NTP/NIEHS
Research Triangle Park, North Carolina

*Prepared by*
Integrated Laboratory Systems, Inc.
Research Triangle Park, North Carolina

**May 2004**

## Abstract

Ionic liquids are salts of organic cations with melting points generally below 100 °C and are being widely investigated as replacements for volatile organic solvents in industrial and laboratory processes because they are thought to be "environmentally benign." Although some efforts have begun to study their potential for ecotoxicity, limited vertebrate or genetic toxicity testing has been done. Three ionic liquids, 1-butyl-3-methylimidazolium chloride ([bmim]Cl), 1-butyl-1-methylpyrrolidinium chloride ([bmpy]Cl), and *N*-butylpyridinium chloride ([NBuPy]Cl), were nominated to the National Toxicology Program (NTP) for toxicological testing based on their widespread interest as possible alternatives to organic solvents. These chlorides are representative of the three most common cation classes of ionic liquids being investigated: imidazolium, pyridinium, and pyrrolidinium. The chlorides, soluble in water and polar organic liquids, are generally prepared from approximately equimolar amounts of the appropriately substituted heterocyclic compound and butyl chloride, often under both heat and pressure. [Bmim]Cl is widely used in metathesis (anion exchange) reactions with compounds containing metal cations and the desired anion to produce ionic liquids with melting points near or below room temperature, many of which are hydrophobic. The chlorides are also used as catalysts or catalyst components, solvents, electrolytes (batteries and metal recovery), other electrochemical applications, and stationary or mobile phases in chromatographic separations. Specific information on environmental occurrence and persistence, human exposure, or regulatory status was not available for the nominated compounds. Their low volatility makes significant air releases unlikely, however, discharges to water are possible from industrial releases. Thermal decomposition may release hazardous hydrogen halides and halogenated organic compounds. Future consumer products that may contain ionic liquids include batteries, fuel cells, solar cells and electrochromic devices, plastics plasticized with ionic liquids, and surgical implants. Information regarding acute, short-term/subchronic, or chronic exposure, synergistic/antagonistic effects, reproductive or teratological effects, carcinogenicity, genotoxicity, or immunotoxicity were not available. Exposure to [bmim]Cl and other compounds structurally similar to ionic liquids has been reported to cause irritation to the eyes, skin, and respiratory system.

# Executive Summary

## Basis for Nomination

Ionic liquids, salts of organic cations with melting points below 100 ºC, are being widely investigated as replacements for volatile organic solvents in industrial and laboratory processes because they are thought to be "environmentally benign." Although some efforts have begun to study their potential for ecotoxicity to confirm this label scarcely any vertebrate or genetic toxicity testing has been done. Early toxicity testing on these materials is vital to avoid delays in developing true "green" applications of these new solvent classes. Three ionic liquids, 1-butyl-3-methylimidazolium chloride ([bmim]Cl), 1-butyl-1-methylpyrrolidinium chloride ([bmpy]Cl), and *N*-butylpyridinium chloride ([NBuPy]Cl), were nominated by the Center for Green Manufacturing, University of Alabama for toxicological testing based on "their widespread interest as possible solvent alternatives to volatile organic compounds." The compounds recommended for review represent the three most common cation classes being investigated for use in various applications such as catalysis, separations, sensors, and electrochemistry: imidazolium, pyridinium, and pyrrolidinium cations.

## Nontoxicological Data

Chemical Identification: The melting point of [bmim]Cl has been reported between 55 and 69 ºC. It is soluble in acetone, acetonitrile, ethyl acetate, isopropyl alcohol, methylene chloride, and water. It exists in two polymorphic forms, monoclinic and orthorhombic, whose structures have been investigated by X-ray crystallography. [NBuPy]Cl can also be found as orthorhombic crystals. [Bmim]Cl, [bmpy]Cl, and [NBuPy]Cl are all soluble in water and polar organic solvents.

Commercial Availability: Several suppliers in the United States (e.g., Fischer Scientific and Sigma-Aldrich Company) and Europe (e.g., Merck KGaA and Solvent Innovation) offer individual ionic liquids in amounts of 5 g up to 1 kg. SACHEM, Inc. offers custom synthesis of bulk quantities.

Production Processes: No large-scale production processes were identified for the nominated compounds. Small-scale preparations have used approximately equimolar amounts of the organic cation and *n*-butyl chloride with conventional heating for several hours or brief microwave heating in closed vessels. The potential for tonnage production of [bmim]Cl may be tied to its use as a precursor for other ionic liquids based on the $[bmim]^+$ cation such as [bmim] octyl sulfate and [bmim] diethylene glycol monomethyl ether sulfate. In these uses, it may be produced only as a site-limited intermediate. Ionic liquids without halogen atoms are thought more likely to attain multi-ton industrial production in the near future.

Production and Import Volumes: No data were available.

Uses: Numerous recent books, journal reviews, and symposium proceedings show the broad spectrum of research and potential industrial applications for ionic liquids. This review focused on searches for specific applications of [bmim]Cl and [NBuPy]Cl. Only one literature reference was found for [bmpy]Cl. The most important uses of [bmim]Cl were as a reactant, catalyst or catalyst component, and solvent. Important uses of [NBuPy]Cl were in catalysts, battery electrolytes, syntheses (excluding the catalysts group), and electrochemical uses other than batteries.

This review provides specific examples of the preparation and uses of [bmim]Cl-$AlCl_3$ and/or [NBuPy]Cl-$AlCl_3$ complexes in the electrowinning, electrorefining, and recycling of aluminum, other light metals, and heavy metals such as cobalt alloys; in battery electrolytes; in catalysts; and in separations/solvents. These systems may be used as solvents for many clean syntheses and catalytic processes. Examples include cracking hydrocarbons, the Fischer indole process, preparation of ion-conductive polymers, and halogenation (substitution for chlorinated solvents). Examples are provided of anion-exchange (metathesis) reactions with [bmim]Cl to produce several other ionic liquids including

[bmim][$PF_6$] and [bmim][$BF_4$]. [Bmim]Cl, [bmim][$PF_6$], and [bmim][$BF_4$] may be used as a solvent in nuclear fuel reprocessing to separate ionic species from the metal salt in molten salt reprocessing wastes. [Bmim]Cl has been studied as the stationary phase in gas chromatographic separations and as the mobile phase in high performance liquid chromatography.

Environmental Occurrence and Persistence: No specific information about the nominated compounds or other ionic liquids was found. Although volatility is not a problem, discharges to water are possible from industrial releases. In the United States, companies involved in ionic liquids research for industrial applications have facilities located near the east, west, and Gulf coasts and the Great Lakes. Ionic liquid halides in wastes may be oxidized to biodegradable substances. Thermal decomposition of ionic liquids containing halogen atoms may release hydrogen halides and halogenated organic compounds to the environment. Safer anions without halide atoms may be the prevailing ionic liquids by the time commercial use becomes widespread.

Human Exposure: Probably the greatest potential for occupational contact to [bmim]Cl and [NBuPy]Cl would occur during bulk drumming and bagging operations of the powdered solids. Future consumer products that may contain ionic liquids include batteries, fuel cells, solar cells and electrochromic devices, plastics plasticized with ionic liquids, and surgical implants. One cosmetic patent mentioned [bmim]Cl as a suitable ingredient for skin and hair conditioning lotions.

Regulatory Status: No regulations on ionic liquids in general or the three nominated compounds in particular were found.

**Toxicological Data**

No information regarding acute, short-term/subchronic, or chronic exposure, synergistic/antagonistic effects, reproductive or teratological effects, carcinogenicity, genotoxicity, or immunotoxicity were available.

Human Studies: [Bmim]Cl causes irritation to the eyes, skin, and respiratory system (specifically, the mucous membranes in the mouth, pharynx, esophagus, and gastrointestinal tract following swallowing). Inhalation of the compound may result in irritation of the mucous membranes, coughing, and dyspnea.

Chemical Disposition, Metabolism, and Toxicokinetics: A theoretical metabolism scheme for $[bmim]^+$ has been reported where the cation undergoes cytochrome P450-dependent oxidation in different positions of the alkyl side chain and produces metabolites that can be broken down further to biocompatible fatty acids and imidazole.

Cytotoxicity: In J774A.1 macrophage cells, cultures were incubated with [bmim]Cl (0.05-1.0 mg/mL) for up to 72 hours. Cellular viabilities were reduced in a time- and dose-dependent manner. The approximate levels causing 50% cellular death were 0.75, 0.50, and 0.20 mg/mL at 24, 48, and 72 hours (incubation times), respectively.

Other Data: Ionic liquids, unlike organic solvents of similar polarity, often do not inactivate enzymes. In addition to greater enzyme stability, higher selectivity and faster rates were seen in biocatalytic reactions in the liquids.

**Structure-Activity Relationships**

Alkylpyridinium Cations

In multi-drug resistant cells (MDR+), $[NBuPy]^+$ had a partition coefficient (log P) of -1.00. At chain lengths >4, the toxicity of aromatic alkylpyridiniums in MDR- and MDR+ cells increased with increasing chain length and log P; however, toxicity for MDR+ cells was significantly less than that for MDR- cells.

Alkylpyridinium cations (1-methylpyridinium [NMePy] and dimethylpyridinium) have been identified in roasted and ground coffee as products of thermal decomposition of trigonelline. The highest concentration of NMePy, 0.25%, was found in dark roasted arabica coffee beans, while coffee extracts contained dimethylpyridiniums at concentrations of 5 to 25 mg/kg. When fed coffee beverage and an NMePy-containing diet, plasma total antioxidant capacity and plasma tocopherol were increased in rats. It also induced CYP1A1 activity (ethoxyresorufin *O*-deethylase), protein levels, and mRNA level in the lung, kidney, and liver.

1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim]$PF_6$) [CASRN 174501-64-5]
In the rat, an oral $LD_{50}$ ranging from 300 to 500 mg/kg and a dermal $LD_{50}$ of >2000 mg/kg for [bmim]$PF_6$ were reported. In the rabbit, minimal irritation was seen when the compound was tested in the eye, while no irritation was observed when applied dermally. It was not a skin sensitizer when tested on guinea pigs. Additionally, [bmim]$PF_6$ was not mutagenic in the Ames test.

Paraquat (1,1´-Dimethyl-4,4´-bipyridinium) [CASRN 4685-14-7]
Paraquat was an herbicide used to destroy green plant tissue and control broad-leaved and grassy weeds. Its use in registered pesticide products, however, has been cancelled. During the period 1971-1985, of pesticide-related illnesses in California, 231 paraquat-related cases (26% skin, 32% eye, 3.5% respiratory, and 38.5% systemic) were reported. This report briefly presents toxicity data reported in the Hazardous Substances Data Bank (HSDB) and Integrated Risk Information System (IRIS) profiles.

## Table of Contents

**Tables:**



**Figures:**

## 1.0 Basis for Nomination

Ionic liquids—specifically, 1-butyl-3-methylimidazolium chloride ([bmim]Cl), 1-butyl-1-methylpyrrolidinium chloride ([bmpy]Cl), and *N*-butylpyridinium chloride ([NBuPy]Cl)—were nominated by the Center for Green Manufacturing, University of Alabama for toxicological testing based on "their widespread interest as possible solvent alternatives to volatile organic compounds (VOCs)." The three compounds recommended for review represent the three most common cation classes being investigated for use in various applications such as catalysis, separations, sensors, and electrochemistry: imidazolium, pyridinium, and pyrrolidinium cations.

## 2.0 Introduction

Ionic liquids are organic salts that generally have melting points below 100 °C, unlike conventional salts; and the melts are liquid over a wide temperature range. Ionic liquids with melting points below or near room temperature (RTILs) are especially interesting. For example, reactions and extractions may be performed under mild conditions, promoting lower likelihood of product thermal degradation and reducing energy costs. The types of organic cations used in ionic liquids include:

1. mono-, di-, and trisubstituted imidazoliums, and substituted pyridiniums and pyrrolidiniums [the free electron pairs of one of the two nitrogen atoms in the five-membered imidazoline ring and of the sole nitrogen atom in the five-membered pyrrolidine or six-membered pyridine ring have been donated to univalent alkyl groups to produce an $N^+$ cation]
2. tetraalkylammoniums ($R_4N^+$)
3. guanidiniums [$(NH_2)_3C^+$ and derivatives]
4. isouroniums and thioisouroniums [urea and thiourea derivatives of general formula $(NH_2)_2(RX)C^+$ where X = O or S and R = alkyl]
5. tetraalkylphosphoniums ($R_4P^+$)

The nitrogen cation with four organic substituents in types 1 and 2 is called a quaternary ammonium ion. In types 3 and 4, the positively charged carbon atoms are electron-deficient.

The anions used in ionic liquids include alkyl sulfates and sulfonates, halides, amides, imides, tosylates [toluenesulfonates], borates (e.g., tetrafluoroborate, $BF_4^-$), phosphates (e.g., hexafluorophosphate, $PF_6^-$), antimonates, and carboxylates (Merck KGaA, 2004c). Ionic liquids are nonvolatile and nonflammable, have high thermal stability, and show remarkable dissolution capabilities for both organic and inorganic compounds. They are being increasingly examined as replacements for volatile organic solvents in a wide range of industrial and laboratory chemical processes such as synthesis, catalysis and enzymatic biocatalysis, electrolysis, and extraction (Merck KGaA, 2004d). Ionic liquids can improve industrial processes by minimizing wastes and allowing efficient product extraction (Holbrey and Seddon, 1999). Because of their negligible vapor pressure, products may often be readily separated from the reaction media simply by distillation (Merck KGaA, 2004c). Solubility and other physical-chemical properties suitable for a particular application can be designed by appropriate combinations of the cations and anions. For example, in general, chlorides are water-soluble while hexafluorophosphates are water-insoluble. As reaction solvents, ionic liquids have been shown to increase reaction rates, selectivities, and yields (Merck KGaA, 2004d). By changing substitution patterns on the organic cation and changing anions, researchers can fine-tune reaction rates and selectivities for a

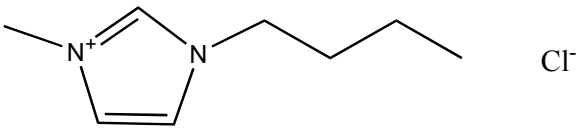
particular catalyzed synthetic reaction (Holbrey and Seddon, 1999). Because of their resistance to oxidation and reduction, they are suitable for electrochemical applications such as batteries, capacitors, electrochemical sensors, and photovoltaic devices (Merck KGaA, 2004c).

Ionic liquids are suitable for replacing organic solvents in two-phase system separation processes because partitioning of organic molecules in ionic liquid/water systems follow traditional octanol/water distributions. Ionic liquid mixtures with secondary solvents are not simple combinations. An appropriate co-solvent can solubilize hydrophobic ionic liquids. Another unique feature of ionic liquids is that they generally form liquid clathrates (inclusion compounds) in combinations with aromatic compounds (Rogers, 2003).

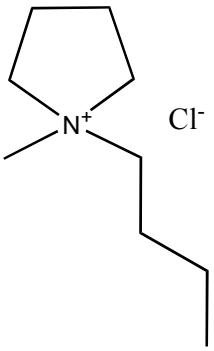
The ionic liquids reviewed in this report are chlorides of 1-butyl-3-methylimidazolium, 1-butyl-1-methylpyrrolidinum, and 1-butylpyridinium cations. All are solids at room temperature with relatively low melting points, but may be used in anion exchange reactions to prepare salts that are liquid at room temperature. Although some efforts have begun to study their potential for ecotoxicity to confirm the often-used appellation of environmentally benign, scarcely any vertebrate or genetic toxicity testing has been done. However, quaternary ammonium compounds in general are known to have antimicrobial and anticholinesterase activities. For example, biological activities of some pyridinium compounds in *The Merck Index* (Budavari, 1996) include the following:

- cholinergic (benzpyridinium bromide),
- cholinesterase inhibitor (distigmine bromide, pyridostigmine bromide),
- cholinesterase reactivator (asoxime chloride, obidoxime chloride, pralidoxime chloride),
- CNS stimulant (comphotamide), and
- disinfectant (cetylpyridinium chloride).

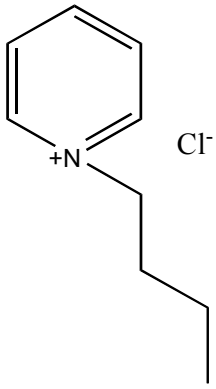
1-Butyl-3-methylimidazolium Chloride
[79917-90-1]




1-Butyl-1-methylpyrrolidinium Chloride
[479500-35-1]




*N*-Butylpyridinium Chloride
[1124-64-7]



## 2.1 Chemical Identification and Analysis

[Bmim]Cl ([$C_8H_{15}ClN_2$]; mol. wt. = 174.68 g/mol) is also called:

1-Methyl-3-butylimidazolium chloride
1-*n*-Butyl-3-methylimidazolium chloride
3-Butyl-1-methylimidazolium chloride
1*H*-Imidazolium, 1-butyl-3-methyl-, chloride (9CI)

[Bmpy]Cl ([$C_9H_{20}ClN$]; mol. wt. = 177.72 g/mol) is also called:

Pyrrolidinium, 1-butyl-1-methyl-, chloride (9CI)
*N*-Butyl-*N*-methylpyrrolidinium chloride

[NBuPy]Cl ([$C_9H_{14}ClN$]; mol. wt. = 171.67 g/mol) is also called:

1-Butylpyridinium chloride (7CI)
Butylpyridinium chloride
*N*-(*n*-Butyl)pyridinium chloride
*N*-1-Butylpyridinium chloride
Pyridinium, 1-butyl-, chloride (8CI, 9CI)

Source: Registry (2003)

## 2.2 Physical-Chemical Properties

| Property | Information | Reference(s) |
|---|---|---|
| | ***[Bmim]Cl*** | |
| Physical State | yellowish solid | Merck KGaA (2003c) |
| | colorless orthorhombic (symmetrical space group Pna21) or monoclinic (P21/c) crystals | Holbrey et al. (2003) |
| Odor | "of solvents" | Merck KGaA (2003c) |
| pH value (20 °C) | 8 (aqueous solution) | Merck KGaA (2003c) |
| Melting Point ($^oC$) | ~55 (≥95% pure product) to 69 | Sigma-Aldrich (2003b); Merck KGaA (2003b); Koel (2000) |
| Soluble in: | acetone, acetonitrile, ethyl acetate (hot), isopropyl alcohol, methylene chloride, and water | Crowhurst et al. (2003); Ito et al. (2003 pat. appl.); Koel (2000); Merck KGaA (2003b) |
| Immiscible in: | hexane, toluene, and water (totally) | Merck KGaA (2003b); Merck Ionic Liquids Database (2004) |
| | ***[Bmpy]Cl*** | |
| Physical State | white solid | Merck KGaA (2002) |
| Odor | slightly disagreeable | Merck KGaA (2002) |
| pH value (25 °C) | 8 (aqueous solution) | Merck KGaA (2002) |
| Soluble in: | isopropyl alcohol (hot), methylene chloride, and water | Crowhurst et al. (2003) |
| | ***[NBuPy]Cl*** | |
| Physical State | white solid | Merck KGaA (2003c) |
| | orthorhombic crystals | Ward et al. (1986) |
| Odor | pyridine-like | Merck KGaA (2003c) |
| pH value (20 $^oC$) | 7 (aqueous solution) | Merck KGaA (2003c) |
| Melting Point ($^oC$) | 131-133* | Aldrich (2003) |
| Miscible in: | water (totally) | Merck Ionic Liquids Database (2004) |

*Data for 1-butylpyridinium-$d_{14}$ chloride (98 atom % D) [CASRN 312623-96-4] (Aldrich, 2003)

[Bmim]Cl, [bmpy]Cl, and [NBuPy]Cl are combustible; in fire, hydrochloric acid and nitrogen oxides may be formed. All three compounds are reactive with strong oxidizing agents. Additionally, *N*-butylpyridinium chloride should not be reacted with alkalis (Merck KGaA, 2002, 2003c,d).

Two crystal forms have been reported for [bmim]Cl, which crystallizes from mixed ionic liquids or ionic liquid-aromatic solutions and from the melt in different crystallized polymorphs (Hamaguchi et al., 2003 abstr.; Holbrey et al., 2003; Saha et al., 2003). The two forms of the $[bmim]^+$ ion, probably the "hydrogen-bonding" isomers, appear to coexist in liquid $[bmim]BF_4$ and $[bmim]PF_6$ (Hamaguchi et al., 2003 abstr.). [A drawing of the dimeric crystal structure may be seen at http://www.csj.jp/journals/chem-lett/cl-cont/GRA_03Aug/03080740PG.pdf.] Packing diagrams and crystallographic supplemental information to the *Chemical Communications* article are available on the Internet at http://www.rsc.org/suppdata/CC/ b3/b304543a/b304543a.pdf and http://www.rsc.org/suppdata/CC/b3/b304543a/b304543a.txt, respectively.

Physical-chemical properties for structurally similar compounds are presented in **Table 1**.

### 2.3 Commercial Availability

Through collaboration with Queen's University Ionic Liquids Laboratory (QUILL) in Belfast, Ireland, Acros Organics provides [bmim]Cl and [NBuPy]Cl in 25-g packs (Acros Organics, undated). The U.S. supplier of Acros Organics is Fisher Scientific (Acros Organics, 2003). [Members of QUILL are Cytec, ChemTech Research Incorporation (C-TRI), and Merck. See http://quill.qub.ac.uk/pages/manuf-set.html.] SACHEM, Inc. (Austin, TX), an associate member of QUILL, offers three classes of ionic liquids (Terrasail™, Marisail™, and Catasail™) and can provide ionic liquid systems in bulk quantity (Sachem, 2003). Sigma-Aldrich Co. (Milwaukee, WI) and Strem Chemicals, Inc. (Newburyport, MA) provide [bmim]Cl in 5- and/or 50-g quantities (Sigma-Aldrich, 2003a; Strem Chemicals, Inc., 2004). Alfa Aesar (Ward Hill, MA) and First Reaction (Hampton Falls, NH) supply [NBuPy]Cl in amounts up to 250 g (Alfa Aesar, 2003; First Reaction, 2002).

Outside of the United States, all three chemicals are available from ChemTech Research Incorporation under the following product names: CTRI-1 for [bmim]Cl, CTRI-43 for [NBuPy]Cl, and CTRI-57 for *N*-butyl-*N*-methylpyrrolidinium chloride (C-TRI Dtld. GmbH, 2003). Solvent Innovation sells [bmim]Cl with a purity of >98% in quantities up to 5 kg (Solvent Innovation, undated-a). Another German company, GeReSo mgH, provides [bmim]Cl and [NBuPy]Cl in amounts ranging from 1 to 10 kg (GeReSo mgH, 2003). ABCR GmbH KG supplies the latter compound (ABCR GmbH KG, 2003). Merck sells [bmim]Cl in quantities ranging from 10 to 1000 g and [NBuPy]Cl in 25-g quantities (Merck KGaA, 2003a,b). Merck Schuchardt OHG, an associate of Merck KGaA, also provides [bmim]Cl (Merck Schuchardt, 2002). [Bmim]Cl and [NbuPy]Cl are also available from Tokyo Kasei Kogyo Co., Ltd., headquartered in Japan; its U.S. supplier is TCI America (Portland, OR), providing up to 25 g (TCI Japan, 2000, 2003a,b).

## 3.0 Production Processes

No large-scale production processes were identified for the assigned compounds. In general, the assigned chlorides have been prepared by mixing the heterocyclic compound 1-methylimidazole, pyridine, or 1-methylpyrrolidine with *n*-butyl chloride. Closed vessels and microwave

## Table 1. Physical-Chemical Properties of Other Similar Ionic Liquids

| Chemical Name | CASRN | Hill Formula | Molecular Weight (g/mol) | Physical Properties | Melting Point (°C) | Water Solubility |
|---|---|---|---|---|---|---|
| **1-Butyl-3-methylimidazolium compounds** | | | | | | |
| 1-Butyl-3-methylimidazolium bis(trifluoromethyl)imide ($bmim^+$ $[N(CF_3)_2]^-$) | NA | $C_{10}H_{15}F_6N_3$ | 291.24 | yellow wax-like | NA | NA |
| 1-Butyl-3-methylimidazolium bromide ($bmim^+$ $Br^-$) | 85100-77-2 | $C_8H_{15}BrN_2$ | 219.13 | weakly yellowish powder | 7.43 in acetonitrile | totally miscible in $H_2O$ |
| 1-Butyl-3-methylimidazolium dicyanamide ($bmim^+$ $[CN]_2N^-$) | 448245-52-1 | $C_{10}H_{15}N_5$ | 205.26 | yellow liquid to viscous | NA | NA |
| 1-Butyl-3-methylimidazolium hexafluorophosphate ($bmim^+$ $PF_6^-$) | 174501-64-5 | $C_8H_5F_6N_2P$ | 284.19 | colorless to yellow liquid to viscous; viscosity = 312 mPa·s at 298 K; density = 1.38 g/cm$^3$ | 6.5 | immiscible in $H_2O$<br>hydrophobicity = 22,600 ppm<br>$H_2O$ absorption = 0.083 M<br>totally miscible with aqueous EtOH (0.5-0.9 mol fraction EtOH); immiscible with 100% EtOH |
| 1-Butyl-3-methylimidazolium methylsulfate ($bmim^+$ $CH_3SO_4^-$) | 401788-98-5 | $C_9H_{18}N_2O_4S$ | 250.32 | brownish to brown liquid | NA | totally miscible in $H_2O$ |
| 1-Butyl-3-methylimidazolium octyl sulfate ($bmim^+$ $CH_3(CH_2)_7SO_4^-$) | 500214-09-5 | $C_{16}H_{32}N_2O_4S$ | 348.57 | NA | NA | NA |
| 1-Butyl-3-methylimidazolium tetrafluoroborate ($bmim^+$ $BF_4^-$) | 174501-65-6 | $C_8H_{15}BF_4N_2$ | 226.02 | yellowish liquid to viscous; viscosity = 233 mPa·s at 298 K; density = 1.21 g/cm$^3$ at room temperature | -71 | totally immiscible in $H_2O$<br>$H_2O$ absorption = 0.32 M |
| 1-Butyl-3-methylimidazolium trifluoroacetate salt ($bmim^+$ $C_2F_3O_2^-$) | 174899-94-6 | $C_{10}H_{15}F_3N_2O_2$ | 252.27 | NA | NA | NA |
| 1-Butyl-3-methylimidazolium trifluoromethanesulfonate ($bmim^+$ $F_3CSO_3^-$) | 174899-66-2 | $C_9H_{15}F_3N_2O_3S$ | 288.29 | brown liquid to viscous | 16.4 | totally miscible in $H_2O$ |
| 1-Butyl-3-methylimidazolium trifluoromethanesulfonyl imide ($bmim^+$ $[N(SO_2CF_3)]^-$) | 174899-83-3 | $C_{10}H_{15}F_6N_3O_4S_2$ | 419.42 | liquid | -4.9 | NA |

## Table 1. Physical-Chemical Properties of Other Similar Ionic Liquids (Continued)

| Chemical Name | CASRN | Formula Hill | Molecular Weight (g/mol) | Physical Form | Melting Point (°C) | Water Data |
|---|---|---|---|---|---|---|
| **1-Butyl-1-methylpyrrolidinium compounds** | | | | | | |
| 1-Butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ($bmpy^+ [N(SO_2CF_3)_2]^-$) | 223437-11-4 | $C_{11}H_{20}F_6N_2O_4S_2$ | 422.41 | yellowish liquid to viscous | NA | immiscible with $H_2O$<br>hydrophobicity = 14,800 ppm<br>$H_2O$ solubility = 6.0±0.5 g/L |
| 1-Butyl-1-methylpyrrolidinium dicyanamide ($bmpy^+ [CN]_2N^-$) | 370865-80-8 | $C_{11}H_{20}N_4$ | 208.31 | yellowish to brownish liquid; viscosity = 50 mPa·s at 298 K | NA | NA |
| 1-Butyl-1-methylpyrrolidinium hexafluorophosphate ($bmpy^+ PF_6^-$) | 330671-29-9 | $C_9H_{20}F_6NP$ | 287.23 | yellowish paste | NA | $H_2O$ solubility = 18.6±0.7 g/L |
| 1-Butyl-1-methylpyrrolidinium tetrafluoroborate ($bmpy^+ BF_4^-$) | 345984-11-4 | $C_9H_{20}BF_4N$ | 229.07 | white solid | 152 | NA |
| 1-Butyl-1-methylpyrrolidinium trifluoromethanesulfonate ($bmpy^+ F_3CSO_3^-$) | 367522-96-1 | $C_{10}H_{20}F_3NO_3S$ | 291.34 | yellowish liquid to viscous | NA | NA |
| 1-Butyl-1-methylpyrrolidinium tris(pentafluoroethyl)trifluorophosphate ($bmpy^+ [C_2F_5]_3PF_3^-$) | NA | $C_{15}H_{20}F_{18}NP$ | 587.28 | yellowish liquid to viscous | NA | immiscible with $H_2O$<br>hydrophobicity = 3500 ppm |
| ***N*-Butylpyridinium compounds** | | | | | | |
| *N*-Butylpyridinium bromide ($NBuPy^+ Br^-$) | 874-80-6 | $C_9H_{14}BrN$ | 384.51 | NA | 33 | totally miscible with $H_2O$ |
| *N*-Butylpyridinium hexafluorophosphate ($NBuPy^+ PF_6^-$) | 186088-50-6 | $C_9H_{14}F_6NP$ | 281.18 | white to grey-beige fine crystals | 76 | immiscible with $H_2O$ |
| *N*-Butylpyridinium tetrafluoroborate ($NBuPy^+ BF_4^-$) | 203389-28-0 | $C_9H_{14}BF_4N$ | 223.02 | colorless to yellowish liquid to viscous | NA | totally miscible with $H_2O$ |

Abbreviation: NA = not available

Sources: The majority of data are from the Merck KGaA MSDS (URLs are provided in Attachment B). Additional data were obtained from Alfassi et al. (2003), Merck Ionic Liquids Database (2004), Merck KGaA (2004a,b,c,d), Registry database, Solvent Innovation (undated), Swatloski et al. (2001), and Tran et al. (2003).

heating shortened reaction times. The ionic liquid quaternary ammonium halides undergo anion exchange (metathesis) with salts having inorganic cations to prepare other ionic liquids.

Several small-scale preparative methods for [bmim]Cl have been published, only one of which was reported by a commercial source (Ito et al., 2003 pat. appl.) [Kuraray Co., Ltd., Japan]. Generally, 1-methylimidazole and 1-chlorobutane (butyl chloride, BuCl), in equimolar amounts or with a slight excess of BuCl, are heated under nitrogen or under pressure at temperatures in the range 70 to 150 °C. Without high pressure, solvents may be used (acetonitrile or toluene) and reaction times are 24 to 48 hours (Dupont et al., 2002; Crowhurst et al., 2003 [supplemental material to published article]; Koel, 2000). The high-pressure syntheses are solvent-free and use microwave heating (Khadilkar and Rebeir, 2001, 2002; Varma and Namboodiri (2001a,b; Namboodiri and Varma, 2002 [U.S. EPA, Clean Processing Branch, National Risk Management Research Laboratory]).

Three preparations found for [NBuPy]Cl also appear to be small-scale. Two use equimolar amounts of pyridine (Py) and BuCl, and one uses a slight excess of pyridine. Reactions are solventless and occur under pressure at temperatures up to 350 °C. Khadilkar and Rebeiro (2001, 2002) achieved a 98% yield using a microwave digester at 200 °C and 271 psi (18.4 atm, 19.1 kg/cm$^2$) for 24 minutes. Two preparations were in patents assigned to the U.S. Department of the Air Force (Nardi et al., 1979 patent application; Nardi et al. (1978a patent) and to Wako Pure Chemical Industries, Ltd. (Sano et al., 2001 patent application).

Only one preparation was found for [bmpy]Cl. Refluxing a mixture of 1-methylpyrrolidine with a slight excess of BuCl for 24 hours gave [bmpy]Cl in 92% yield after recrystallization from isopropyl alcohol (Crowhurst et al., 2003 [supplemental material]).

Commercialization involving tonnage volumes of a few ionic liquids is in very early stages. Use of 1-methylimidazolium chloride as an ionic liquid represents the first commercial use of ionic liquids in an organic process. In the BASIL (Biphasic Acid Scavenging Utilizing Ionic Liquids) process, which has been in use for about two years, BASF heats starting materials and 1-hexylimidazolium chloride [Hmim]Cl, m.p. 75 °C, in a multi-ton batch reactor to produce alkoxyphenylphosphines. The products are used in the manufacture of photoinitiators for printing ink and coatings (Freemantle, 2003).

The potential for tonnage production of [bmim]Cl may be tied to its use as a starting material for [bmim]$^+$ salts with other anions, especially two of the compounds in Solvent Innovation GmbH's halogen free ECOENG™ family of ionic liquids. These compounds are [bmim][$OcSO_4$] (octyl sulfate) and [bmim][MDEG $SO_4$] (diethylene glycol monomethyl ether sulfate) (Solvent Innovation, undated-b; Wasserscheid et al., 2002, 2003a,b [pat. appl.]). By 2002, some ionic liquids in the ECOENG™ series were being sold in amounts up to one metric ton. Ionic liquids without halogen atoms are thought more likely to attain multi-ton industrial production in the near future (Scott, 2002).

Processes that have current or near-term industrial applications include the following according to DePaoli (2003 poster) of Oak Ridge National Laboratory:

- Ionic liquids as a catalyst support for biphasic butene dimerization in the Difasol process commercialized by the IFP (French Petroleum Institute), which replaces the Dimersol process (Holbrey and Seddon, 1999)
- Olefin polymerization using chloroaluminate(III) ionic liquids (to replace the Cosden process) (Holbrey and Seddon, 1999)
- Manufacture of fine chemicals and pharmaceuticals (Sheldon, 2001; cited by DePaoli, 2003).

Other important industrial processes that may switch to ionic liquids as solvents and/or catalysts include oligomerization of butenes and polymerization of olefins (as a modification of the Cosden process), Ziegler-Natta polymerization of ethylene to linear α-olefins, hydrodimerization of dienes, Diels-Alder additions, alkylation of olefins, hydrogenation and hydroformylation, production of conductive polymers such as poly(*p*-phenylene), and synthesis of linear alkylbenzenes (LABs) (precursors of linear alkylbenzenesulfonates, which are widely used as detergents, emulsifiers, wetting agents, dry cleaning additives, lubricants, and greases). Global production of LABs was more than 2.5 million metric tons annually in the late 1990s (Holbrey and Seddon, 1999).

The industrial interest in ionic liquids is shown by the participation in research consortiums such as QUILL and funding of research (for example, the abstract for EPA Grant No. R828257, "Investigation of Room Temperature Ionic Liquids [RTILs] as Environmentally Benign Solvents for Industrial Separations [TSE99-A])," stated the following in the Approach: "f) Toxicology SACHEM has agreed to facilitate testing for aquatic toxicity and human health affects [*sic*] for the classes of RTIL which have the most favorable characteristics for industrial use as solvents" (Rogers, 2003).

## 4.0 Production and Import Volumes

Under the Inventory Update Rule, high-volume production of cations or salts of the three assigned compounds or related compounds was not identified; no Inventory Update Rule information were available (U.S. EPA, 2004).

## 5.0 Uses

Due to the exponential growth in publications on ionic liquids, reviews could not be relied upon to indicate the level of interest for specific applications of the assigned compounds. In addition, *Chemical Abstracts* will not necessarily indicate proprietary work on prospective uses that remains unpublished.

A December 31, 2003, CAPLUS search for the CASRN of [bmim]Cl associated with the role USES gave 105 records. Combination of the CASRN with the RCT (reactant) role gave 64 records, only one of which was included in the uses group of 105 records. Combination of the CASRN with the PREP (preparation) role gave 36 records, seven of which were included in the uses group. These preparations were probably as intermediates for the syntheses of other ionic liquids containing the bmim+ cation. Similarly, only two of the six records associated with the ANST (analytical studies) role were included in the uses group. After these overlapping records

were excluded from the uses group, keywords were combined with the resulting 95 records. The 95 records were further subgrouped by combining with the keywords electroly?, cataly?, synthe?, or solvent. The total number of records considered was 172; the extent of overlap among the subgroups derived by keywords was not determined. Results are summarized in **Table 2**.

**Table 2. Use Categories for 1-Butyl-3-methylimidazolium Chloride Based on Indexing Roles and Keywords in CAPLUS Records**

| Uses | Record Tally | Percent of 172 Records |
|---|---|---|
| Reactant total | 64 | 37 |
| Analytical studies (not analyte) total | 6 | 3 |
| Preparation as an intermediate (prep + uses roles) | 7 | 4 |
| Electr? (electrolytic baths for electroplating, other electrodeposition, etc.; battery electrolytes) | 19 | 11 |
| Cataly? (catalyst, catalytic) | 64 | 37 |
| Synthe? (synthesis, synthetic) | 13 | 8 |
| Solvent | 38 | 22 |
| None of the above | 8 | 5 |

A December 31, 2003, search of CAPLUS retrieved 163 records that associated the indexing role USES with the CASRN of *N*-butylpyridinium chloride. (Unlike the analysis above, which included reactant and other indexer-assigned roles, the following analysis was based on terminology in the record titles.) The records were then divided almost equally into patent and nonpatent groups. Examination and analysis of the record titles indicated the relative interest in prospective uses of the compound. No assumptions were made for presence of aluminum chloride or catalytic use unless some forms of the terms were present in the title. Results of the analysis are presented in **Table 3**.

**Table 3. Use Categories for *N*-Butylpyridinium Chloride Based on Terms in CAPLUS Record Titles**

| Uses | Nonpatent (82) | Patent (81) | Total | Percent of 163 Records |
|---|---|---|---|---|
| Uses in association with aluminum chloride (also tallied with other categories below) | 35 | 25 | 60 | 37 |
| Catalysts | 5 | 15 | 20 | 12 |
| Batteries (total includes primary cells) | 15 | 17 | 32 | 20 |
| Photoelectrochemical devices | 5 | ≥1 | ~6 | 4 |
| Separations | 0 | 2 | 2 | 2 |
| Syntheses excluding the catalysts group | 17 | 5 | 22 | 13 |
| Electrolytic baths for electrodeposition, etc. (includes electroplating and electrorefining; excludes electrolytes for batteries) | 21 | 25 | 46 | 28 |
| Subtotal excluding the aluminum group | 63 | 65 | 128 | 79 |
| Miscellaneous other uses not tallied | 19 | 16 | 35 | 21 |

**Table 4** is based on examination of full database records or other source material. They were chosen as examples of some of the use categories noted during the analyses above and mentioned in the reviews examined. In these analyses, the use of ionic liquids in catalysis and separation may be under-represented because the ionic liquid may have been used as a catalyst or in a separation process as well as used as a solvent. DePaoli (2003 poster) estimated the number of publications on "ionic liquids" and "catalysis" or "separation" as approximately 330 and 110, respectively in the period 1999-2003.

## 6.0 Environmental Occurrence and Persistence

No specific information about the nominated compounds or other ionic liquids was found. However, because of the wide variety of potential commercial applications, some ecotoxicity studies are in progress. For example, Juffernholz (2003) presented a paper at SETAC 2003 on toxicity of ionic liquids to the soil organisms *Collembolen* and *Enchytraeiden*. Lamberti et al. (undated) reported $LC_{50}$ data for [bmim][$PF_6$] and [bmim][$BF_4$] to *Daphnia magna*. Mölter et al. (2003 abstr.) reported results from screening imidazolium ionic liquids with the luminescent bacteria acute toxicity test and tests with two rat cell lines.

In a grant proposal to the National Oceanic and Atmospheric Administration (NOAA) to conduct ecotoxicological research, the University of Notre Dame (ca. 2001) pointed out that U.S. companies that produce or that are considering the use of ionic liquids in their processes include Sachem, Lithchem, Ozark Fluorine Specialty, Reilly Industries, BP, DuPont, Exxon, Chevron, UOP, Merck, SmithKline Beecham, and Schering Plough, which have facilities in the Great Lakes region as well as on the east, west, and gulf coasts. The proposal authors stated that although the problems of volatile organic chemical emissions will be reduced by their replacement with ionic liquids in industrial processes, "water pollution may increase because these solvents have varying degrees of solubility in water and will inevitably escape into the aquatic environment. The overall objective of the proposed project was "to perform a proactive risk assessment of the ecological impact of ionic liquids in aquatic environments before widespread adoption by industry."

Methods to treat industrial wastes containing ionic liquids are being explored. For example, Suzuki et al. (1993 pat. appl.) described the oxidation of onium halides to biodegradable substances in wastewater from aluminum electroplating. The process used hydrogen peroxide in the presence of iron. Ionic liquids used in manufacturing processes may be recycled by supercritical carbon dioxide regeneration (Atkins et al., 2004).

The complex halide anions in some ionic liquids represent some environmental and safety risks. For example, Swatloski et al. (2003) pointed out that during purification of the commonly used [bmim]$PF_6$, a simple fluoride hydrate is formed by decomposition. Thermal decomposition may release hazardous hydrogen halides and halogenated organic compounds. Safer anions such as octyl sulfate and diethylene glycol methyl ether methanesulfonate may be the prevailing ionic liquids by the time commercial use becomes widespread.

## Table 4. Uses of the Assigned Compounds or Their Derivatives

| Use | Comment | Patent Assignee or Other Affiliation | Author |
|---|---|---|---|
| **Catalyst:** Both [bmim]Cl and [NBuPy]Cl were claimed as components of suitable ionic liquids with $AlCl_3$, $CoCl_2$, $CuCl_2$, or $H_2PtCl_6$ for cracking hydrocarbons. | | The Secretary of State for Defence, UK | Green et al. (2000 pat. appl.) |
| **Cosmetic ingredient:** [bmim]Cl was one of the components listed for formulations for cleaning skin and hair. The compositions contained quaternary ammonium compounds selected from imidazolium, pyridinium, pyrimidinium, and tetraalkylphosphonium compounds with melting points below 60 °C. | In the example given in the CAPLUS record, [bmim]$BF_4$ was combined in an aqueous solution with preservative, perfume, and Dow Corning®-5225C, a silicone formulation aid. This was the only example found for use of organic ionic liquids in personal care products in CAPLUS. [A TOXLINE record for McCarthy (1974) mentions " non-ionic and ionic liquid make-up lotion," but there is no indication of chemical composition in the record.] | L'Oreal France | Giroud (2003 pat. appl.) |
| **Electrolyte component:** [bmim]Cl-$AlCl_3$ electrolytes were studied for their applicability for electrorefining of aluminum alloys. | | Department of Metallurgy and Materials Engineering, University of Alabama, Tuscaloosa, Alabama | Kamavaram et al. (2003 abstr.) |
| **Electrolyte component:** [bmim]Cl-$AlCl_3$ may be used in the electrowinning, electrorefining, and recycling of aluminum at 100-150 °C. The aluminum recovered at the cathode is 80-99.9% pure. | | University of Alabama | Wu et al. (2001 abstr.) |
| **Electrolyte component:** [bmim]Cl-$AlCl_3$ was used as the electrolyte in the electrorefining of light metals such as Al, Li, Mg, Nd, Ti, and Zr) from ore, alloy, and metal matrix composites. | | University of Alabama | Wu et al. (2002 pat. appl.) |
| **Electrolyte component:** [NBupy]Cl-$AlCl_3$ was the electrolyte for a new low-temperature electroplating process announced by Nisshin Steel Co., Ltd., Japan, in 1987. | [NBupy]Cl can be recovered from the electrolyte by precipitating $AlCl_3$ by addition of a secondary alcohol. | Nisshin Steel Co., Ltd., Japan | Comline Chem. Mater. (12-18-1987); Mori and Takahashi (1990 pat. appl.) |
| **Electrolyte component:** $AlCl_3$-[NBupy]Cl; $AlCl_3$-NaCl-[NBupy]Cl, and $AlCl_3$-LiCl-[NBupy]Cl have been studied as electrolytes for Al/polyaniline (ref. 1) and Al/$FeS_2$ (ref. 2) secondary cells and an Al/chloranil battery (ref. 3). | | (3) U.S. Department of the Air Force, USA | (1) Koura et al. (1993); (2) Takami and Koura (1993); (3) Nardi et al. (1978b pat.) |
| **Electrolyte component:** Metals other than Al may be electrodeposited from ionic liquids. For example, $CoCl_2$-$ZnCl_2$-[NBupy]Cl was used as the electrolyte in the deposition of Co-Zn alloys. | Adding an organic solvent reduced the bath temperature from 130 °C to 25 °C. | | Koura et al. (1996) |
| **Electrolyte:** [NBupy]Cl was patented for use as the electrolyte in thermal primary batteries | | (1) U.S. Dept. of the Air Force, USA; (2) USA | (1) Nardi et al. (1979 pat. appl.); (2) Nardi et al. (1978a pat.) |

## Table 4. Uses of the Assigned Compounds or Their Derivatives (Continued)

| Use | Comment | Patent Assignee or Other Affiliation | Author |
|---|---|---|---|
| **Reactant:** [bmim]Cl "is a precursor for a multitude of other ionic liquids..." | | Dept. of Chem. and Center for Green Manufacturing, University of Alabama, Tuscaloosa, Alabama | Rogers and Reichert (2002 abstr.) |
| **Reactant:** [bmim]Cl, [NBupy]Cl, and other quaternary ammonium compounds such as 1-methyl-1-propylpyrrolidinium chloride (a close structural analog of 1-butyl-1-methylpyrrolidinium chloride) were used with organic and mineral acids in an electrochemical process to produce ionic liquids. | The esters formed included the nitrates of $[bmim]^+$ and $[NBupy]^+$; the tetrafluoroborate of 1-methyl-1-propylpyrrolidinium cation; and the acetate, dihydrogen phosphate, and formate of $[bmim]^+$. | USA | Moulton (2003 pat. appl.) |
| **Reactant:** 0.29 mol [bmim]Cl in dichloromethane was stirred with 0.32 mol $NaPF_6$, $NaBF_4$, $Li(CF_3SO_2)_2N$, $NaCF_3SO_3$, and $NaSbF_6$ for 24 hr to give the corresponding bmim salts. | Polarity measurements and solvent-solute interactions were studied in the series of ionic liquids prepared. | | Crowhurst et al. (2003) [Supplemental material] |
| **Reactant:** Stirring equimolar amounts of [bmim]Cl and potassium tetrafluoroborate ($KBF_4$) or potassium hexafluorophosphate ($KPF_6$) for 2 hr at room temperature gave [bmim]Cl in 81% yield or $[bmim]BF_4$ in 91% yield after isolating and drying the product. | $[bmim]BF_4$ and $[bmim]PF_6$ are used in organic synthesis, extraction technologies, electrochemistry, biphasic organometallic catalysis, and as stationary phases for gas chromatography. | | Dupont et al. (2002) in *Organic Syntheses*, vol. 79, p. 236 |
| **Reactant:** Anion exchange of [bmim]Cl with $LiN(SO_2CF_3)_2$ gave $[bmim]^+$ bis(trifluoromethylsulfonyl)imide, also called $[bmpy][N(Tf)_2]$. | This French patent relates to manufacture of nitriles used in the production of adiponitrile, which is a precursor for synthesis of hexamethylenediamine, ε-caprolactam, and nylon 6,6. [The ionic liquid is used as a solvent in a process for nitrile manufacture by hydrocyanation of unsaturated compounds and hydrocyanation of unsaturated nitriles to give dinitriles. The hydrocyanation catalyst system comprised Ni, Pt, or Pd and an organophosphorus ligand.] | Rhodia Polyamide Intermediates, France | Basset et al. (2003 pat. appl.); Crowhurst et al. (2003) [Supplemental material] |
| **Reactant:** Anion exchange of [bmim]Cl with Na octyl sulfate in aqueous solution at 60 °C followed by drying *in vacuo* and purification gave [bmim] octyl sulfate in 76% yield. | [bmim] octyl sulfate ($[bmim][OcSO_4]$) may be used as a solvent additive, an extracting agent, and a heat-transfer agent. The relatively hydrolysis stable compound was used in the rhodium-catalyzed hydroformylation of 1-octene. Solvent Innovation offers this ionic liquid as ECOENG™ 418. | Institute for Technical Chemistry and Macromolecular Chemistry; Solvent Innovation, GmbH, Germany | Wasserscheid et al. (2002, 2003a pat. appl.); Solvent Innovation (undated-b) |
| **Reactant:** Anion exchange of $BF_4^-$ or $PF_6^-$ with [bmim]Cl, [NBupy]Cl, and other chlorides to give ionic liquid solvents that are air- and moisture-stable at low temperatures and noncorrosive (ref. 1). | Producers of petroleum products and natural gas are interested in processes for removing mercaptans from hydrocarbon streams. For example, a gaseous or liquid mercaptan-containing hydrocarbon stream may be passed over the ionic liquid by countercurrent or other extraction procedure. Basic metal salts dissolved in the ionic liquids form mercaptides that are separated from the hydrocarbon stream and oxidized to disulfides, which are insoluble in the ionic liquids (ref. 2). | (1) Akzo Nobel Chemicals, Inc., USA; (2) Chevron USA Inc. | (1) Zhang and Conrad Zhang (2002); (2) O'Rear et al. (2002 pat. appl.) |
| **Reactant:** Anion exchange of $PF_6^-$ with [NBupy]Cl gave $[NBupy]PF_6$. | Conjugated dienes such as butadiene may be telomerized in the presence of $[NBupy]PF_6$ and $Pd(OAc)_2/PPh_3$. | Celanese Chemicals Europe G.M.B.H., Germany | Chauvin et al. (2002 pat. appl.) |

## Table 4. Uses of the Assigned Compounds or Their Derivatives (Continued)

| Use | Comment | Patent Assignee or Other Affiliation | Author |
|---|---|---|---|
| **Reactant:** Anion exchange with $NaPF_6$ in acetone gave 85% $[bmim]PF_6$ | Medium in various industrial reactions | Kuraray Co., Ltd., Japan | Ito et al. (2003 pat. appl.) |
| **Reactant:** Equal molar amounts of [bmim]Cl and $AlCl_3$ were mixed carefully (exothermic reaction) to give the neutral ionic liquid $[bmim]AlCl_4$. Acidic chloroaluminates result when the molar ratio $[bmim]Cl/AlCl_3$ is greater than 1. Basic chloroaluminates result when the molar ratio is less than 1. The melt equilibrium in a basic chloroaluminate liquid contains the species $AlCl_3$, $AlCl_4^-$, and $Al_2Cl_7^-$. Figure 2 of this reference shows the infrared spectra of all three types. | Koel and coworkers are investigating the possibility of using ionic liquids for oil shale kerogen liquefaction. (Estonia mines oil shale for electric power generation, synthetic fuels, and chemical industry feedstocks.) $[bmim]Cl$-$AlCl_3$ and $[bmim]PF_6$ extract organic compounds at 175 °C from kerogen in amounts 10-fold greater than the usual organic solvents (Freemantle, 2000). | Institute of Chemistry, Tallinn Technical University, Tallinn, Estonia | Koel (2000) |
| **Reactant:** Anion exchange of [bmim]Cl gave bmim ionic liquids with the anions $I^-$, $PF_6^-$, $BF_4^-$, & bis(trifluoromethanesulfonyl)imide | Physical properties of the hydrophobic and hydrophilic compounds were compared. | Dept. of Chemistry and Center for Green Manufacturing, University of Alabama | Huddleston et al. (2001) |
| **Reactant:** Reaction of [bmim]Cl with diethylene glycol monomethyl ether and pyridine-$SO_3$ complex | $[bmim][CH_3(OCH_2CH_2)_2OSO_3]$ may be used as the solvent in hydroformylation of alkenes. Solvent Innovation offers this ionic liquid, designated $[bmim][MDEGSO_4]$, as ECOENG™ 41M. | Solvent Innovation, GmbH, Germany | Wasserscheid et al. (2003b pat. appl.); Solvent Innovation (undated-b) |
| **Reactant:** Treating imidazolium chlorides, including [bmim]Cl, with a strong base such as potassium *tert*-butoxide gives imidazole carbenes. | The carbenes are useful for synthesis of ionic liquids. | Queen's University of Belfast, Belfast, Ireland | Earle and Seddon (2001 pat. appl.) |
| **Reactant:** Ultrasound-assisted anion metathesis [exchange] of [bmim]Cl with ammonium tetrafluoroborate, tetraphenylborate, hexafluorophosphate, and trifluoromethylsulfonate with monitoring by ionic conductometry gave the correspoing bmim salts. No purification step was necessary. | | University de Savoie, France<br><br>cf. Roche Vitamins Ag., Switzerland | Leveque et al. (2002)<br>cf. Bonrath et al. (2003 pat. appl.) |
| **Separation:** $[bmim]AlCl_4$ has been studied as an extracting agent for deep desulfurization of diesel fuel. | | Rheinisch-Westfalische Technische Hochschule (RWTH), Aachen, Germany | Boesmann et al. (2001) |
| **Separation:** [bmim]Cl or $[bmim][PF_6]$ may be used as the stationary phase in gas chromatography | Ionic liquids appear to have low polarity as a stationary phase for nonpolar compounds, but they tenaciously retain compounds with strong proton donor groups. [Bmim]Cl and other ionic liquids that had excellent solubilizing properties and vacuum stability have also been examined as matrixes for matrix-assisted laser desorption/ionization mass spectrometry (UV-MALDI) (Armstrong et al., 2001).] | University of Missouri, Rolla, Missouri | Armstrong et al. (1999) |
| **Separation:** Aqueous mixtures of ionic liquids such as [bmim]Cl or $[NBupy][BF_4]$ were used as the mobile phase (eluent) for high performance liquid chromatographic (HPLC) separation of catecholamines with ultraviolet (UV) detection. | Use as the stationary phase in analytical separations appears to be more common than use as the mobile phase. | Chinese Academy of Sciences, Lanzou, China | Zhang et al. (2003). |

## Table 4. Uses of the Assigned Compounds or Their Derivatives (Continued)

| Use | Comment | Patent Assignee or Other Affiliation | Author |
|---|---|---|---|
| **Separation:** Mixtures of dienes and olefins can be separated by extraction with ionic liquid solutions or dispersions of metal salts that preferentially complex dienes. [NBupy]Cl or 1-hexyl-3-methylimidazolium chloride were the ionic liquids indexed in the CAPLUS record. The preferred salts were $AgBF_4$ and AgCuOTf [Tf = trifluoromethanesulfonyl; an ester with the trifluoromethanesulfonate group is called a triflate]. | | USA | Boudreau et al. (2003 pat. appl.) |
| **Solvent and catalyst:** [NBuPy]Cl-AlCl3 has been used as a solvent and catalyst in the Fischer indole synthesis of different ketones. | The chloroaluminate was prepared by reaction of 0.5 mol [NBupy]Cl with 1.0 mol freshly sublimed $AlCl_3$ under nitrogen. In an example, refluxing phenylhydrazine and propiophenone in the presence of the complex gave 3-methyl-2-phenylindole. | University of Mumbai, Mumbai, India | Rebeiro and Khadlikar (2001) |
| **Solvent component:** Preparation of an ion-conductive polymer complex with thiophene in the main chain was done in "room-temperature molten salts" such as [NBupy]Cl-$AlCl_3$. | | Sophia University, Tokyo, Japan | Ogata (1994) |
| **Solvent** in enzymic catalysis. | Numerous studies have shown that ionic liquids enhance enzymic catalysis. In the example in the CAPLUS record, methyl methylimidiazolium methyl sulfate catalyzed enzymic oxidation of formic acid to $CO_2$ coupled with reduction of $NAD^+$ to NADH. | Solvent Innovation, GmbH, Germany | Kragl et al. (2002 pat. appl.) |
| **Solvent:** [bmim]Cl, [bmim][$PF_6$], or [bmim][$BF_4$] is used to dissolve metal salts, ionic species, or both in molten salt reprocessing wastes. Treatment to separate the ionic species is followed by recovery of the metal salt. | Method is applicable to nuclear fuel reprocessing. | British Nuclear Fuels, PLC | Fields et al. (1999 pat. appl.) |
| **Solvent:** [bmim]Cl, [bmim]Br, [bmim][$PF_6$], or [bmim][$BF_4$] as recyclable solvent for halogenations of alkenes and alkynes to replace chlorinated solvents. | | University of Pisa, Pisa, Italy | Chiappe et al. (2001) |
| **Solvent:** Cellulose films may be prepared by dissolution in and casting from [bmim]Cl (ref. 1). | Cellulose may be dissolved in ionic liquids at high concentrations without significant degradation by conventional or microwave heating (ref. 2). | (1) University of Alabama, Tuscaloosa, Alabama | (1) Turner et al. (2003); (2) Chem. Eng. News (Vol. 81, No. 27, 2003) |
| **Solvent:** Poly(*p*-phenylene) was prepared by oxidative dehydropolycondensation of benzene at room temperature in a 1:2 [NBupy]Cl-$AlCl_3$ solution in the presence of $CuCl_2$. The polymer was precipitated from the solution by addition of water. | | | Levi et al., (1992; cited by Freestone, 1992) |
| **Solvent:** Uses of [bmim]Cl-$AlCl_3$ systems as solvents for clean synthesis and catalytic processes. | Review | Queen's University of Belfast, Belfast, Ireland | Seddon (1997) |

## 7.0 Human Exposure

The major routes of potential occupational exposure are likely to be dermal and oral (hand-to-mouth). Drumming and bagging of large quantities of the powdered [bmim]Cl or [NBupy]Cl may lead to ocular and inhalation exposure. Although no specific information was found for the three nominations, the Safety Data Sheets available for several representatives of the imidazolium, pyridinium, and pyrrolidinium classes indicate irritation potential from oral, dermal, eye, and/or inhalation exposure. Ionic liquids with the hexafluorophosphate anion $[PF_6]^-$ and trifluoromethanesulfonate $[F_3CSO_3]^-$ may also be corrosive to mucous membranes (see **Table 5** in **Section 10.0**).

The potential for exposure to ionic liquids via use and disposal of consumer products is only speculation at this time. Consumer products containing ionic liquids may include batteries, photoelectrochemical devices such as dye-sensitized solar cells and electrochromic devices, and fuel cells for automotive consumption and consumer on-site electrical generation (Freemantle, 2000). [Bmim]Cl is included as a suitable quaternary ammonium salt for skin and hair cleansing and conditioning formulations by L'Oreal France (Giroud, 2003 pat. appl.) and a make-up composition patented 30 years ago contained "ionic liquids" (McCarthy, 1974). Ionic liquids might be used as plasticizers, which have been a route of human exposure to the phthalate esters. Scott et al. (2002) of the University of Alabama reported that [bmim]$PF_6$ was an efficient plasticizer for poly(methyl methacrylate). Should $[bmim]^+$-based ionic liquids become widely used as plasticizers, humans may be potentially exposed via leaching, but not by volatilization from the plastics as phthalates do. Surgical implants might use ionic liquids. For example, ionic liquids incorporated as electrolytes in artificial muscles provide a source of ions that migrate into and out of the conducting polymer when millivolts of electricity are applied. The expansion and shrinkage/contraction induced in the polymer mimic the actions of natural muscles (University of Wollongong NewsBytes, 2002; Wallace, 2003 abstr.). If such devices are implanted in humans, the potential exists for exposure via leaching or from leaks resulting from trauma or product defects.

## 8.0 Regulatory Status

No regulations on ionic liquids in general or the three nominated compounds in particular were found.

## 9.0 Toxicological Data

### 9.1 General Toxicology

#### 9.1.1 Human Data

[Bmim]Cl causes irritation to the eyes, skin, and respiratory system (specifically, the mucous membranes in the mouth, pharynx, esophagus, and gastrointestinal tract following swallowing). Inhalation of the compound may result in irritation of the mucous membranes, coughing, and dyspnea (Merck KGaA, 2003c; Solvent Innovation, undated-a).

#### 9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

A theoretical metabolism scheme for $[bmim]^+$ has been reported (see **Figure 1**). The ionic molecule is proposed to undergo cytochrome P450-dependent oxidation in different positions of the alkyl side chain and produce metabolites that can be broken down further to biocompatible fatty acids and imidazole (Jastorff et al., 2003).

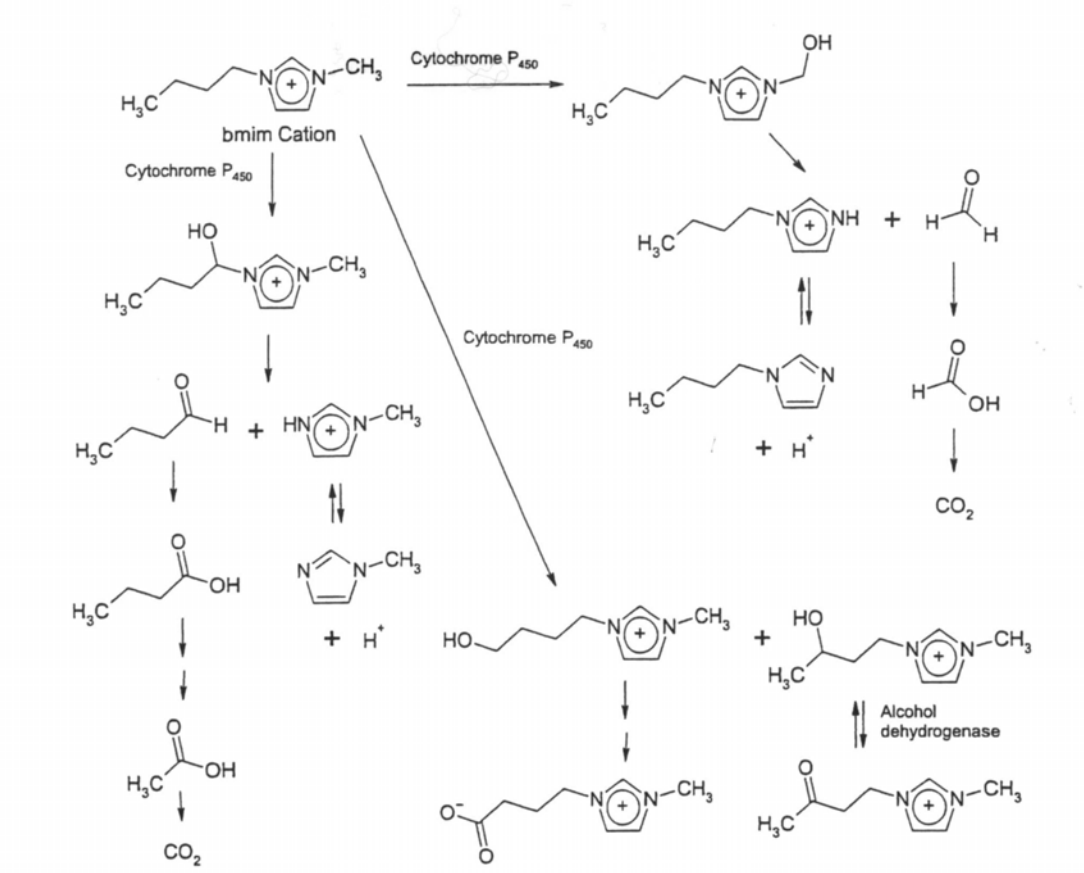



**Figure 1. Theoretically Proposed Metabolic Pathway for [bmim]$^+$ (Jastorff et al., 2003)**

### 9.1.3 Acute Exposure

No data were available.

### 9.1.4 Short-term and Subchronic Exposure

No data were available.

### 9.1.5 Chronic Exposure

No data were available.

### 9.1.6 Synergistic/Antagonistic Effects

No data were available.

### 9.1.7 Cytotoxicity

In J774A.1 macrophage cells, cultures were incubated with [bmim]Cl (0.05-1.0 mg/mL) for up to 72 hours. Cellular viabilities were reduced in a time- and dose-dependent manner. The approximate levels causing 50% cellular death were 0.75, 0.50, and 0.20 mg/mL at 24, 48, and 72 hours (incubation times), respectively (Hassoun et al., 2002).

### 9.2 Reproductive and Teratological Effects
No data were available.

### 9.3 Carcinogenicity
No data were available.

### 9.4 Initiation/Promotion Studies
No data were available.

### 9.5 Anticarcinogenicity
No data were available.

### 9.6 Genotoxicity
No data were available.

### 9.7 Cogenotoxicity
No data were available.

### 9.8 Antigenotoxicity
No data were available.

### 9.9 Immunotoxicity
No data were available.

### 9.10 Other Data
Ionic liquids, unlike organic solvents of similar polarity, often do not inactivate enzymes. In addition to greater enzyme stability, higher selectivity and faster rates were seen in biocatalytic reactions in the liquids (Park and Kazlauskas, 2003).

When exposed to [bmim]Cl (1.0-5.0 mg/mL), *Caenorhabditis elegans* did not show any adverse effects (Swatloski et al., 2004).

[NBuPy]Cl exhibited a medium affinity in blocking the rate of 86Rb release from the occluded state of dog kidney Na,K-ATPase (Forbush et al., 1988).

## 10.0 Structure-Activity Relationships
Experimental toxicity information about imidazolium and pyridinium compounds obtained from biomedical databases and Internet searches based on information about research groups known to be conducting toxicity studies on ionic liquids are summarized here. Many of the compounds found in these searches are apparently not ionic liquids.

Rachaman et al. (1997 pat.) indicated that pharmacokinetics, acute toxicity, and anticholinesterase activity as well as physical-chemical properties have been studied for a group of 1-alkyl-3-hydroxypyridinium compounds including 1-butyl-3-hydroxypyridinium bromide. A *tert*-butyl-3-hydroxypyridinium chloride derivative appeared to be a cholinesterase reactivator (Grubic and Tomazic, 1989; Harris et al., 1976, 1978; Stalc and Sentjurc, 1990) and one bound

DNA *in vitro* (Santos Peinado et al., 1989). Ferguson and Baguley (1983) reported on petite mutants in yeast induced by non-intercalative DNA-binding antitumor agents, including 1-butylpyridinium/quinolinium and other alkylpyridinium compounds. One 1-butylpyridinium compound was evaluated for cytotoxicity in a promyelocytic leukemia cell line (Morris-Natschke et al., 1990). The rat oral and rabbit skin $LD_{50}$ doses were each >2000 mg/kg (DSBG, 2002).

Toxicity data for some ionic liquids are presented in **Table 5**.

Alkylpyridinium Cations

In multi-drug resistant cells (MDR+), $[NBuPy]^+$ had a partition coefficient (log P) of -1.00. At chain lengths >4, the toxicity of aromatic alkylpyridiniums in MDR- and MDR+ cells increased with increasing chain length and log P; however, toxicity for MDR+ cells was significantly less than that for MDR- cells (Dellinger et al., 1992).

Alkylpyridinium cations (1-methylpyridinium [NMePy] and dimethylpyridinium) have been identified in roasted and ground coffee as products of thermal decomposition of trigonelline. The highest concentration of NMePy, 0.25%, was found in dark roasted arabica coffee beans. Coffee extracts contained dimethylpyridiniums at concentrations of 5 to 25 mg/kg (Stadler et al., 2002a,b). When fed coffee beverage and an NMePy-containing diet, plasma total antioxidant capacity and plasma tocopherol were increased in rats (Somoza et al., 2000). In a separate rat study, NMePy induced CYP1A1 activity (ethoxyresorufin *O*-deethylase), protein levels, and mRNA level in the lung, kidney, and liver (Iba et al., 2000).

1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim]$PF_6$) [CASRN 174501-64-5]

In the rat, an oral $LD_{50}$ ranging from 300 to 500 mg/kg and a dermal $LD_{50}$ of >2000 mg/kg for [bmim]$PF_6$ were reported. In the rabbit, minimal irritation was seen when the compound was tested in the eye, while no irritation was observed when applied dermally. It was not a skin sensitizer when tested on guinea pigs. Additionally, [bmim]$PF_6$ was not mutagenic in the Ames test (Chemada Fine Chemicals, 2003).

Paraquat (1,1′-Dimethyl-4,4′-bipyridinium) [CASRN 4685-14-7]

Note: There often appears to be no distinction between paraquat and its dichloride form in published toxicity reviews and abstracts; paraquat is given as a synonym for paraquat dichloride and vice versa. The Pesticide Action Network (PAN) Pesticides Database (URL http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC33358; last accessed on April 28, 2004) and the National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards (URL http://www.cdc.gov/niosh/npg/npgd0478.html; last accessed on April 28, 2004) use CASRN 1910-42-5 for the paraquat dichloride and CASRN 4685-14-7 for the paraquat dication, as does ChemFinder (URL http://chemfinder.cambridgesoft.com/. However, the CASRN 1910-42-5 is used for paraquat in the Integrated Risk Information System (IRIS) database, while the CASRN 4685-14-7 is used for the compound in the Hazardous Substances Data Bank (HSDB).

Paraquat was an herbicide used to destroy green plant tissue and control broad-leaved and grassy weeds. Its use in registered pesticide products, however, has been cancelled. During the period 1971-1985, of pesticide-related illnesses in California, 231 paraquat-related cases (26% skin, 32% eye, 3.5% respiratory, and 38.5% systemic) were reported (HSDB, 2003). Its toxicological

## Table 5. Toxicity Statements from the Merck KGaA Safety Data Sheets* for Other Ionic Liquids

| Name | CASRN | Irritation | | | | Burns |
|---|---|---|---|---|---|---|
| | | Oral | Skin | Eye | Inhal | |
| **Structurally Related Compounds** | | | | | | |
| 1-Butyl-3-methylimidazolium hexafluorophosphate ($bmim^+ PF_6^-$) | 174501-64-5 | | X | X | | |
| 1-Butyl-3-methylimidazolium methylsulfate ($bmim^+ CH_3SO_4^-$) | | | X | X | | |
| 1-Butyl-3-methylimidazolium tetrafluoroborate ($bmim^+ BF_4^-$) | 174501-65-6 | | X | X | X [2] | |
| 1-Butyl-3-methylimidazolium trifluoromethanesulfonate ($bmim^+ F_3CSO_3^-$) | 174899-66-2 | | | | X [2] | X [3] |
| 1-Butyl-1-methylpyrrolidinium hexafluorophosphate ($bmpy^+ PF_6^-$)** | 330671-29-9 | | | | X [2] | X [3] |
| *N*-Butylpyridinium hexafluorophosphate ($NBuPy^+ PF_6^-$)** | 186088-50-6 | | | | X [2] | X [3] |
| **Other Ionic Liquids** | | | | | | |
| 1,3-Dimethylimidazolium methylsulfate ($dim^+ CH_3SO_4^-$) | 97345-90-9 | | X | X | | |
| 1,3-Dimethylimidazolium trifluoromethanesulfonate ($dim^+ F_3CSO_3^-$) | 121091-30-3 | | X | X | | |
| 1-Butyl-2,3-dimethylimidazolium hexafluorophosphate ($bdim^+ PF_6^-$) | 227617-70-1 | X [1] | X | X | X [2] | |
| 1-Butyl-3-ethylimidazolium trifluoromethanesulfonate ($beim^+ F_3CSO_3^-$)** | 145022-48-6 | | | | X [2] | X [3] |
| 1-Butyl-4-methylpyridinium chloride ($NBuPy^+ Cl^-$) | 112400-86-9 | | X | X | | |
| 1-Butyl-4-methylpyridinium hexafluorophosphate ($NBuPy^+ PF_6^-$) | | | X | X | | |
| 1-Butyl-4-methylpyridinium tetrafluoroborate ($NBuPy^+ BF_4^-$) | | | X | X | X [2] | |
| 1-Ethyl-3-methylimidazolium bromide ($emim^+ Br^-$) | 65039-08-9 | X [1] | X | X | X [2] | |
| 1-Ethyl-3-methylimidazolium chloride ($emim^+ Cl^-$) | 65039-09-0 | | X | X | X [2] | |
| 1-Ethyl-3-methylimidazolium hexafluorophosphate ($emim^+ PF_6^-$) | 155371-19-0 | | X | X | | |
| 1-Ethyl-3-methylimidazolium tetrafluoroborate ($emim^+ BF_4^-$) | 143314-16-3 | X [1] | X | X | X [2] | |
| 1-Ethyl-3-methylimidazolium trifluoromethanesulfonate ($emim^+ F_3CSO_3^-$) | 145022-44-4 | X [1] | X | X | X [2] | |
| 1-Hexyl-3-methylimidazolium chloride ($hmim^+ Cl^-$) | 171058-17-6 | X [1] | X | X | X [2] | |
| 1-Hexyl-3-methylimidazolium hexafluorophosphate ($hmim^+ PF_6^-$) | 304680-35-1 | X [1] | X | X | X [2] | |
| 1-Hexyl-3-methylimidazolium tetrafluoroborate ($hmim^+ BF_4^-$) | 244193-50-8 | X [1] | X | X | X [2] | |
| 1-Methyl-3-octylimidazolium chloride ($moim^+ Cl^-$) | 64697-40-1 | | X | X | | |
| 3-Methyl-1-octylimidazolium tetrafluoroborate ($moim^+ BF_4^-$) | 244193-52-0 | | X | X | | |

*See Attachment B for source information. **Corrosive

[1]Irritation of the mucous membranes in the mouth, pharynx, esophagus, and gastrointestinal tract after swallowing

[2]Irritation of the mucous membranes, coughing, and dyspnea

[3]Eyes and skin, and the mouth, throat, esophagus, and gastrointestinal tract after swallowing

effects have been reviewed (e.g., Chishiro, 2000; Garnier et al., 2003; HSDB, 2003; U.S. EPA, 2003). This report briefly presents data reported in the HSDB profile for paraquat (note: results from studies that specified use of paraquat dichloride were also available but not included here). Additional data from the IRIS profile [which is cited as (U.S. EPA, 2003)] are also included.

*Human Data*

The toxic concentration of paraquat in blood is 8.5 µg/mL, and the lethal concentration in blood is 35 µg/mL. The minimum lethal dose of paraquat for humans is ~35 mg/kg body weight. The target organs of paraquat exposure are the eyes, respiratory system, liver, kidneys, gastrointestinal tract, and heart. In the workplace, exposure to paraquat generally results in temporary damage to nails and minor irritation of the eyes and nose. An episode of epistaxis has been reported in one worker. In eye splash incidents, commercial preparation of paraquat caused loss of corneal and conjunctival epithelium, mild iritis, and residual corneal scarring; the surfactants in the preparations were considered responsible for the injuries (HSDB, 2003).

Several reports of fatal accidental ingestion by humans exist. Symptoms of fatal poisoning include damage of the lung (hemorrhage, edema, and fibroblastic proliferation in the alveolar walls), liver, and kidney. Myocarditis and transient neurologic signs have also been reported. Death, which occurs usually in three weeks, is generally the result of progressive fibrosis. Survival is possible. A 37-year-old man who ingested paraquat (Gramoxone, 20% w/v) survived, despite suffering from acute oliguric renal failure and mild pulmonary toxicity (HSDB, 2003).

Paraquat is classified by the U.S. Environmental Protection Agency (EPA) as a possible human carcinogen based primarily on the induction of squamous cell carcinoma of the skin in the head region of male and female Fischer 344 rats (see below for further details) (U.S. EPA, 2003).

Currently, studies using paraquat in animal models of Parkinson's disease are being conducted (Betarbet et al., 2002; Dauer and Przedborski, 2003; Dawson et al., 2002; Di Monte, 2003; Fukushima, 2002).

*Animal Data*

*Chemical Absorption, Distribution, and Excretion*: As expected for a cation, paraquat was poorly absorbed after oral administration to rats. Eighty-one percent was excreted in the feces and 16% in urine. Subcutaneous (s.c.) administration resulted in 72% of the dose being excreted in urine and 13% in feces. In general, absorption from the gastrointestinal tract is <20% of the administered dose. Given via gavage to rats and guinea pigs, $^{14}C$ paraquat tissue levels (e.g., the lung) were higher than serum levels, and both urinary and fecal excretion were prolonged. When paraquat was administered orally and intraperitoneally (i.p.) to pregnant mice, accumulation of the compound was found in maternal lungs and in fetal livers and kidneys (HSDB, 2003).

Systemic treatment of rats with paraquat showed the highest levels in the prefrontal cortex and hypothalamus; the levels detected in the former area have been suggested to account for neuronal cell death (HSDB, 2003).

Radiotracer studies in isolated perfused porcine skin flap showed that there was minimal absorption or penetration into the skin; the majority of paraquat (tested as $^{14}C$ paraquat dichloride) remained on top of the application site (HSDB, 2003).

*Acute Toxicity*: The dermal $LD_{50}$ values in the male and female rat were reported to be 80 and 90 mg/kg, respectively. Additionally, an i.p. $LD_{50}$ of 19 mg/kg was calculated in females. In mice, an oral $LD_{50}$ of 98 mg/kg was calculated. In guinea pigs, the oral and i.p. $LD_{50}$s are 22 and 3 mg/kg, respectively. The dermal acute toxicity value is 236 mg/kg in rabbits (HSDB, 2003).

In rats and guinea pigs, acute toxicity symptoms included anorexia, adipsia, diarrhea, hyperpnea, dyspnea, tachycardia, and necrosis of the liver, kidney, and gastrointestinal tract, with primary lesions in the lungs. Paraquat has been studied in other species, including dogs, horses, hens, monkeys, and buffalo calves; clinical signs included central nervous system (CNS) depression and anorexia. In most species, a single large dose of paraquat given orally or by s.c. or i.p. injection produced an early onset of hyperexcitability and eventually death in about ten days. Other symptoms were pulmonary congestion, edema, and fibrosis. Inhalation of paraquat aerosols for several hours produced severe congestion alveolar edema, and bronchial irritation in two to three hours. If the animal survived past the three hours, no further chronic fibrosis occurred (HSDB, 2003).

*Short-term or Subchronic Toxicity*: When rabbits were administered paraquat (3, 6, or 12 mg/kg) via i.p. injection daily for up to two weeks, 100% mortality was observed in the high-dose group in four days. Rabbits receiving the low and mid doses exhibited significant decreases in body, liver, kidney, heart, and lung weights in the first three days of treatment. After one week, the animals showed a significant increase in kidney weight. Additionally, plasma total triglycerides and total cholesterol were increased, while total lipids, total triglycerides, and total cholesterol in liver and kidney homogenates were decreased (HSDB, 2003).

*Chronic Toxicity*: In a 99-week oncogenicity study in mice, the systemic no observable effect level (NOEL) was 12.5 ppm (1.87 mg/kg/day) and the systemic lowest effect level (LEL) was 37.5 ppm (5.62 mg/kg/day). Renal tubular degeneration and weight loss were observed in males, and a decreased intake of food was reported for females. In a two-year feeding study in rats, the NOEL was 25 ppm (1.25 mg/kg/day). There was an increased incidence of opacities, cataracts, and non-neoplastic lesions (U.S., EPA, 2003).

*Reproductive and Teratological Effects*: No significant teratogenic effects were reported for dietary intake or intravenous or i.p. administration of paraquat in experimental animals. Paraquat did not affect fertility and was only fetotoxic at doses that caused maternal toxicity (HSDB, 2003). For mice and rats, the maternal NOEL was 1 mg/kg/day and the maternal LEL was 5 mg/kg/day (piloerection, hunched appearance, and/or weight loss) for oral exposure. The fetotoxic NOEL was 5 mg/kg/day and the fetotoxic LEL was 10 mg/kg/day in mice (partially ossified sternebrae in 26.3% of fetuses), while the values were 1 and 5 mg/kg/day, respectively, in rats (slight retardation in ossification and weight loss) (U.S. EPA, 2003).

In a three-generation study in rats, the systemic NOEL was 25 ppm (1.25 mg/kg/day) and the systemic LEL was 75 ppm (3.75 mg/kg/day) for oral exposure. An increased incidence of

alveolar histiocytosis in the lungs was seen. The reproductive NOEL was 150 ppm (7.5 mg/kg/day) (U.S. EPA, 2003).

*Carcinogenicity*: Mice fed paraquat (0, 12.5, 37.5, or 100 ppm) in the diet for 35 weeks, followed by a dose of 125 ppm for the remainder of life had no treatment-related tumors. At the high dose, increased mortality was reported for females, and at the mid dose, evidence of renal tubular degeneration was seen in males (U.S. EPA, 2003).

Paraquat (0, 25, 75, or 150 ppm) fed to Fisher 344 rats for up to 124 weeks produced squamous cell carcinoma of the skin mainly in the head region in 51.6% of the animals; this was significantly increased in males at the high dose. Additionally, lung adenomas and carcinomas, pituitary adenomas and carcinomas, thyroid adenomas, adrenal pheochromocytomas, pancreatic islet cell adenomas, mammary fibroepithelial and testis interstitial cell tumors, malignant lymphomas, and skin lysomas were also seen (U.S. EPA, 2003).

*Genotoxicity*: Paraquat was nonmutagenic in the Ames test in the presence or absence of metabolic activation (S9), in dominant lethal tests using mice, and in rat bone marrow chromosomal aberration tests. The analytical grade was mutagenic in the mouse lymphoma assay, both with and without S9, while the technical grade gave positive results only with S9. Paraquat induced sister chromatid exchange in Chinese hamster lung fibroblast cells and unscheduled DNA in human embryo epithelial cells. It was positive or weakly positive in DNA repair assays, in a forward mutation assay in *Salmonella typhimurium* and *Saccharomyces cerevisiae* (U.S. EPA, 2003).

*Mechanism of Action*: The toxicity of paraquat is the result of a metabolically catalyzed single electron oxidation reduction reaction in which potentially toxic forms of oxygen, such as the superoxide radical, are produced. These oxygen species are believed to attack the polyunsaturated lipids of cell membranes (HSDB, 2003).

## 11.0 Online Databases and Secondary References

### 11.1 Online Databases

National Library of Medicine Databases (TOXNET)
ChemIDplus
EMIC and EMICBACK
HSDB
TOXLINE

STN International Files

| | | | |
|---|---|---|---|
| AGRICOLA | CABA | IPA | PROMT |
| BIOSIS | CANCERLIT | MEDLINE | Registry |
| BIOTECHNO | CAPLUS | NIOSHTIC | RTECS |
| CA | EMBASE | NTIS | TOXCENTER |

TOXLINE includes the following subfiles:

| | |
|---|---|
| Toxicity Bibliography | TOXBIB |
| International Labor Office | CIS |

| | |
|---|---|
| Hazardous Materials Technical Center | HMTC |
| Environmental Mutagen Information Center File | EMIC |
| Environmental Teratology Information Center File (continued after 1989 by DART) | ETIC |
| Toxicology Document and Data Depository | NTIS |
| Toxicological Research Projects | CRISP |
| NIOSHTIC® | NIOSH |
| Pesticides Abstracts | PESTAB |
| Poisonous Plants Bibliography | PPBIB |
| Aneuploidy | ANEUPL |
| Epidemiology Information System | EPIDEM |
| Toxic Substances Control Act Test Submissions | TSCATS |
| Toxicological Aspects of Environmental Health | BIOSIS |
| International Pharmaceutical Abstracts | IPA |
| Federal Research in Progress | FEDRIP |
| Developmental and Reproductive Toxicology | DART |

Other Internet Databases or Web Sites
IRIS (Integrated Risk Information System); URL http://www.epa.gov/iris/
NIOSH Pocket Guide to Chemical Hazards; URL http://www.cdc.gov/niosh/npg/npg.html
PAN (Pesticide Action Network) Pesticide Database; URL http://www.pesticideinfo.org/Index.html

National Archives and Records Administration
Code of Federal Regulations (CFR)

In-House Databases
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

### 11.2 Secondary References

Aldrich. 2003. 1-Butylpyridinium-$d_{14}$ chloride. Handbook of Fine Chemicals and Laboratory Equipment 2003-2004. Sigma Aldrich, St. Louis, MO, p. 364.

## 12.0 References

ABCR GmbH KG. 2003. 1-*n*-Butylpyridinium chloride. ABCR Product List, January 13, 2003. Search result from CHEMCATS 2002:710918.

Acros Organics. 2003. 1-Butyl-3-methylimidazolium chloride. Order No. 35409. Acros Organics, January 30, 2003. Search result from CHEMCATS 2002:1282364.

Acros Organics. Undated. Ionic Liquids Handbook. Available at Internet address: http://www.fisher.co.uk/whats_new/newprods/chems/Graphics/IonicLiquids_UK.pdf.

Alfa Aesar. 2003. *N*-*n*-Butylpyridinium chloride. Alfa Aesar, May 14, 2003. Search result from CHEMCATS 2003:1802390.

Alfassi, Z.B., Huie, R.E., Milman, B.L., and Neta, P. 2003. Electrospray ionization mass spectrometry of ionic liquids and determination of their solubility in water. Anal. Bioanal. Chem. 377(1):159-164. Abstract from PubMed 12827339.

Armstrong, D.W., He, L., and Liu, Y.-S. 1999. Examination of ionic liquids and their interaction with molecules, when used as stationary phases in gas chromatography. Anal. Chem. 71(17):3873-3876. Abstract from CAPLUS 1999:474358.

Armstrong, D.W., Zhang, L.-K., He, L., and Gross, M.L. 2001. Ionic liquids as matrixes for matrix-assisted laser desorption/ionization mass spectrometry. Anal. Chem. 73(15):3679-3686. Abstract from CAPLUS 2001:453590.

Atkins, M.P., Davey, P., Fitzwater, G., Rouher, O., Seddon, K.R., and Swindall, J. 2004. Ionic liquids: A map for industrial innovation. Available at Internet address: http://quill.qub.ac.uk/map/map.html. Last accessed on April 27, 2004.

Basset, J.M., Chauvin, Y., and Galland, J.C. 2003 pat. appl. Process for manufacture of nitrile and dinitrile compounds by reaction of alkenes or unsaturated nitriles with hydrogen cyanide in ionic liquid solvents and application to the production of adiponitrile. Rhodia Polyamide Intermediates. Fr. Demande, 22 pp. Abstract from CAPLUS 2003:223752.

Betarbet, R., Sherer, T.B., and Greenamyre, J.T. 2002. Animal models of Parkinson's Disease. Bioessays 24(4):308-18. Abstract from MEDLINE 2002211309.

Boesmann, A., Datsevich, L., Jess, A., Lauter, A., Schmitz, C., and Wasserscheid, P. 2001. Deep desulfurization of diesel fuel by extraction with ionic liquids. Chem. Commun. 23:2494-2495. Abstract from CAPLUS 2001:153666.

Bonrath, W., Leveque, J.-M., Luche, J.-L., and Petrier, C. 2003 pat. appl. Production of ionic liquids. Roche Vitamins Ag. PCT Int. Appl., 8 pp. Abstract from CAPLUS 2003:454255.

Boudreau, L.C., Driver, M.S., Munson, C.L., and Schinski, W.L. 2003 pat. appl. Separation of dienes from olefins using ionic liquids and metal salt complexing agents. U.S. Pat. Appl. Publ., 15 pp. Abstract from CAPLUS 2003:512134.

Chauvin, Y., Magna, L., Niccolai, G.P., and Basset, J.-M. 2002 pat. appl. Process and catalysts for telomerizing conjugated dienes. Celanese Chemicals Europe G.m.g.H. Eur. Pat. Appl., 33 pp. Abstract from CAPLUS 2002:330253.

Chemada Fine Chemicals. 2003. Material safety data sheet (MSDS): 1-Butyl-3-methylimidazolium hexafluorophosphate. Available at Internet address: http://www.chemada.com/cat1/items/BMIHFP.pdf.

Chemical Engineering News. 2003. 2003 Hancock Award honors student research. Chem. Eng. News 81(27):76-68. Available at Internet address: http://bama.ua.edu/~cgm/CEN_Hancock.htm. Last accessed on January 13, 2004.

Chiappe, C., Capraro, D., Conte, V., and Pieraccini, D. 2001. Stereoselective halogenations of alkenes and alkynes in ionic liquids. Org. Lett. 3(7):1061-1063. Abstract from MEDLINE 2001190464.

Chishiro, T. 2000. Clinical aspects of accidental poisoning with paraquat. Asian Med. J. 43(3):114-120. Abstract from TOXCENTER 2000:146353.

Comline Chem. Mater. 1987. Nisshin Steel establishes new aluminum electroplating process. Comline Chem. Mater., December 8, 1987, p. 1. Abstract from PROMT 88:2593.

Crowhurst, L., Mawdsley, P.R., Perez-Arlandis, J.M., Salter, P.A., and Welton, T. 2003. Solvent-solute interactions in ionic liquids. Phys. Chem. Chem. Phys. 5(13):2790-2794. Abstract available at Internet address: http://www.rsc.org/Cfmuscat/intermediate_abstract.cfm?FURL=/3j/CP/2003/b303095.PDF. [Supplement information available at Internet address: http://www.rxc.org/suppdata/CP/b3/b303095d/experimental.doc. Last accessed on January 6, 2003.

C-TRI Dtld. GmbH (ChemTech Research Incorporation, Deutschland GmbH). 2003. [Ionische Flüssigkeiten (Ger.).] Available at Internet address: http://www.smsites.de/c-tri/ger/prod_ionic.php. Last accessed on December 1, 2003.

Dauer, W., and Przedborski, S. 2003. Parkinson's disease: Mechanisms and models. Neuron 39(6):889-909. Abstract from EMBASE 2003378239.

Dawson, T.M., Mandir, A.S., and Lee, M.K. 2002. Animal models of PD: Pieces of the same puzzle? Neuron 35(2):219-222. Abstract from BIOSIS 2002:452133.

Dellinger, M., Pressman, B.C., Calderon-Higginson, C., Savaraj, N., Tapiero, H., Kolonias, D., and Lampidis, T.J. 1992. Structural requirements of simple organic cations for recognition by multidrug-resistant cells. Cancer Res. 52:6385-6389.

DePaoli, D. 2003 poster. Overview: Technical summaries on ionic liquids in chemical processing. Chemical Industry Vision 2020 Technology Partnership Workshop, "Barriers to Ionic Liquid Commercialization," September 22, 2003, New York, NY. Available at Internet address: http://www.chemicalvision2020.org/pdfs/ionic_liquids.pdf.

Di Monte, D.A. 2003. The environment and Parkinson's Disease: Is the nigrostriatal system preferentially targeted by neurotoxins? Lancet Neurol. 2(9):531-538. Abstract from MEDLINE 2003403526.

DSBG (Dead See Bromine Group). 2002. Material safety data sheet: *N*-Ethyl-*N*-methylpyrrolidiniumbromice (MEP). Available at Internet address: http://www.dsbg.com/brome/brome.nsf/0a03dde88bb2d9c7422567760036799d/70322a46b3c8a45142256cd00028c895/$FILE/8110mepb_enMEP.pdf.

Dupont, J., Consorti, C.S., Suarez, P.A.Z., and de Souza, R.F. 2002. Preparation of 1-butyl-3-methyl imidazolium-based room temperature ionic liquids. Org. Synth. 79:236 ff.

Earle, M.J., and Seddon, K.R. 2001 pat. appl. Preparation of imidazole carbenes and the use thereof for the synthesis of ionic liquids. Queen's University of Belfast, UK. PCT Int. Appl., 21 pp. Abstract from CAPLUS 2001:762973.

Ferguson, L.R., and Baguley, B.C. 1983. Induction of petite mutants in yeast by non-intercalative DNA-binding antitumor agents. Eur. J. Cancer Clin. Oncol. 19:1575-1583. Abstract from TOXCENTER 2002:405567.

Fields, M., Thied, R.C., Seddon, K.R., Pitner, W.R., and Rooney, D.W. 1999 pat. appl. Treatment of molten salt reprocessing wastes. British Nuclear Fuels PLC. PCT Int. Appl., 26 pp. Abstract from TOXCENTER 1999:134199.

First Reaction. 2002. *N*-*n*-Butylpyridinium chloride. First Reaction Product List, March 21, 2002. Search result from CHEMCATS 2002:718416.

Forbush, B., III, Jones, G., and Barberia, J.T. 1988. The interaction of amines with the occluded state of the Na,K-pump. J. Biol. Chem. 263(17):7979-7988.

Freemantle, M. 2000. Eyes on ionic liquids. Chem. Eng. News 78(20):37-50. Available at Internet address (C&EN Online): http://quill.qub.ac.uk/pages/publications-set.html. [Note: one of four choices on this page.]

Freemantle, M. 2003. BASF's smart ionic liquid. Chem. Eng. News 81(13):9. Available at Internet address (C&EN Online): http://pubs.acs.org/cen/topstory/8113/print/8113notw7.html. Last accessed on January 7, 2004.

Freestone, N. 1992. A selection of recent topics from the chemical literature. Chemistry and Industry, September 7, 1992, No. 17, pp. 657 ff. Text from PROMT 92:690949.

Fukushima, T. 2002. Elucidation of paraquat poisoning mechanism and development of the neuronal death model (Jpn.). Nippon Eiseigaku Zasshi. Jpn. J. Hyg. 57(1):83-86. Abstract from MEDLINE 2002195685.

Garnier, R., Bazire, A., and Chataigner, D. 2003. Risks of occupational paraquat exposure. A review. Archives des Maladies Professionnelles et de Medecine du Travail 64(5):310-324. Abstract from CABA 2003:188050.

GeReSo mgH. 2003. [Produktübersicht—Ionische Flüssigkeiten (Ger.).] Available at Internet address: http://www.designer-solvents.de/docu/ionic_2.pdf.

Giroud, F. 2003 pat. appl. Cosmetic compositions comprising an organic salt for cleansing and conditioning hair. L'Oreal, France. Eur. Pat. Appl., 15 pp. Abstract from CAPLUS 2003:909140.

Green, K.J., Barnes, P.N., Lever, N.D.J., and Grant, K.A. 2000 pat. appl. Industrial process and catalysts. The Secretary of State for Defence, United Kingdom. PCT Int. Appl., 21 pp. Abstract from CAPLUS 2000:475747.

Gubric, Z., and Tomazic, A. 1989. Mechanism of action of HI-6 on soman inhibition of acetylcholinesterase in preparations of rat and human skeletal muscle; comparison to SAD-128 and PAM-2. Arch. Toxicol. 63(1):68-71. Abstract from EMBASE 89075986.

Hamaguchi, H., Ozawa, R., Hayashi, S., and Saha, S. 2003 abstr. X-ray and Raman spectroscopic studies of the structure of [bmim]X, where X=Cl, $BF_4$, $PF_6$. IEC Abstract No. 51. Presented at the 226th ACS National Meeting, Division of Industrial and Engineering Chemistry; September 7-11, 2003; New York, NY. Available at Internet address: http://membership.acs.org/I/IEC/docs/NewYork2003-IEC-Abstracts.pdf.

Harris, LW., Heyl, W.C., Stitcher, D.L., and Broomfield, C.A. 1978. Effects of 1,1´-oxydimethylene bis(4-tert-butylpyridinium chloride) (SAD-128) and decamethonium on reactivation of soman- and sarin-inhibted cholinesterase by oximes. Biochem. Pharmacol. 27(5):757-761. Abstract from MEDLINE 78186739.

Harris, LW., Stitcher, D.L., Heyl, W.C., et al. 1976. Effects of 1,1´-oxydimethylene bis(4-tert-butylpyridinium chloride) (SAD 128) on inhibition of aging and reactivation of soman inhibited cholinesterase by an oxime. Pharmacologist 18/2 (Number 184). Abstract from EMBASE 77141895.

Hassoun, E.A., Abraham, M., Kini, V., Al-Ghafri, M., and Abushaban, A. 2002. Cytotoxicity of the ionic liquid, 1-*N*-butyl-3-methyl imidazolium chloride. Res. Commun. Pharmacol. Toxicol. 7(1-2):23-31. Abstract from EMBASE 2003222702.

Holbrey, J.D., and Seddon, K.R. 1999. Ionic liquids. Clean Prod. Proc. 1:223-236.

Holbrey, J.D., Reichert, W.M., Nieuwenhuyzen, M., Johnston, S., Seddon, K.R., and Rogers, R.D. 2003. Crystal polymorphism in 1-butyl-3-methylimidazolium halides: Supporting ionic liquid formation by inhibition of crystallization. Chem. Commun. 9(14):1636-1637.

HSDB (Hazardous Substances Data Bank). 2003. Paraquat (4685-14-7). Provided by the National Library of Medicine (NLM) on STN International. HSDB No. 1668. Profile last updated on February 14, 2003.

Huddleston, J.G., Visser, A.E., Reichert, W.M., Willauer, H.D., Broker, G.A., and Rogers, R.D. 2001. Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation. Green Chem. 3(4):156-164. Abstract from CAPLUS 2001:601201.

Iba, M.M., Fung, J., Giannone, J.V., and Okey, A.B. 2000. Comparative induction of CYP1A1 expression by pyridine and its metabolites. Arch. Biochem. Biophys. 378(2):299-310. Abstract from PubMed 10860547.

Ito, T., Tsuji, Y., Torihara, M., and Iwasaki, H. 2003 pat. appl. Process for preparation of n-alkyl-n'-alkylimidazolium salts. Kuraray Co., Ltd., Japan. PCT Int. Appl., 14 pp. Abstract from CAPLUS 2003:875258.

Jastorff, B., Störmann, R., Ranke, J., Mölter, K., Stock, F., Oberheitmann, B., Hoffmann, W., Hoffman, J., Nüchter, M., Ondruschka, B., and Filser, J. 2003. How hazardous are ionic liquids? Structure-activity relationships and biological testing as important elements for sustainability evaluation. Green Chem. 5:136-142.

Juffernholz, T. 2003. [Kombinationswirkungen in terrestrischen Ökosystemen: Effekte einer neuen Klasse von Lösungsmitteln (Ionische Flüssigkeiten) und Schwermetalle auf Collembolen und Enchytraeiden (Ger.).] Presented at the SETAC GLB, Heidelber, Germany, September 21-23, 2003. Available at Internet address: http://www.uft.uni-bremen.de/uft/ionic_liquids.ilpublications2.htm. Last accessed on December 1, 2003.

Kamavaram, V., Reddy, R.G., Wu, B., Rogers, R.D., Bonrath, W., Leveque, J.-M., Luche, J.-L., and Petrier, C. 2003 abstr. Physicochemical properties of ionic liquids used in aluminum electrorefining at low temperatures. IEC Abstract No. 198. Presented at the 226th ACS National Meeting, Division of Industrial and Engineering Chemistry; September 7-11, 2003; New York, NY. Abstract from TOXCENTER 2003:206820.

Khadilkar, B.M., and Rebeiro, G.L. 2001. Microwave assisted synthesis of room temperature ionic liquid precursor quaternary salts in closed vessel. Org. Proc. Res. Dev. 6(6):826-828.

Koel, M. 2000. Physical and chemical properties of ionic liquids based on the dialkylimidazolium cation. Proc. Estonian Acad. Sci. Chem. 49(3):145-155.

Koura, N., Ejiri, H., and Takeishi, K. 1993. Polyaniline secondary cells with ambient temperature molten salt electrolytes. J. Electrochem. Soc. 140(3):602-606. Abstract (No. 30) available at Internet address: http://www.ci.noda.sut.ac.jp:1803/eng/etc/aboutProf/abstract.html. Last accessed on January 6, 2004.

Koura, N., Endo, T., and Idemoto, Y. 1996. The electrodeposition of amorphous Co-Zn alloy from ambient temperature molten salt electrolytes. J. Non-Cryst. Solids 205-207:650-655. Abstract (No. 67). available at Internet address: http://www.ci.noda.sut.ac.jp:1803/eng/etc/aboutProf/abstract.html. Last accessed on January 6, 2004.

Kragl, U., Kaftzik, N., Schoefer, S., and Wasserscheid, P. 2002 pat. appl. Enzymatic catalysis in the presence of ionic liquids. Solvent Innovation Gmbh, Germany. Eur. Pat. Appl., 15 pp. Abstract from CAPLUS 2002:364059.

Lamberti, G., Lodge, D., et al. Undated. Aquatic toxicology of ionic liquids. Available at Internet address: http://www.nd.edu/~ed/IL_toxicology.htm. Last accessed on December 1, 2003.

Leveque, J.-M., Luche, J.-L., Petrier, C., Roux, R., and Bonrath, W. 2002. An improved preparation of ionic liquids by ultrasound. Green Chem. 4(4):357-360. Abstract from CAPLUS 2002:590885.

Levi, M.D., Pisarevskaya, E.Y., Molodkina, E.B., and Danilov, A.I. 1992. [title not provided] Chemistry and Industry, September 7, 1992, No. 17, p. 149. Cited by Freestone (1992).

McCarthy, J.P. 1974. Some aspects in formulating pigmented cosmetic lotions. Cosmet. Perfum. 89:65-66. Abstract available from TOXLINE Special at Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~futkuS:3. Last accessed on January 13, 2004.

Merck Ionic Liquids Database. 2004. Ionic liquids—Suchergebnisse (search results regarding the miscibility of specific ionic liquids). Available at Internet address: http://ildb.merck.de/ionicliquids/ASP/IonicLiquidsRead_SearchQueryBuilder.asp. Last accessed on April 28, 2004.

Merck KGaA. 2002. Safety data sheet: 1-Butyl-1-methylpyrrolidinium chloride. According to EC Directive 91/155/EEC; issued on December 17, 2002. Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/show/1127800/490028.pdf.

Merck KGaA. 2003a. Complete ionic liquids list. Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/show/1063420/IL-Catalog_01_08_03.pdf.

Merck KGaA. 2003b. Product data sheet: BMIM chloride (1-Butyl-3-methylimidazolium chloride). Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/menu/1256290_ePRJ-MERCK-EN_p… Last updated on May 11, 2003. Last accessed on December 31, 2003.

Merck KGaA. 2003c. Safety data sheet: 1-Butyl-3-methylimidazolium chloride. According to EC Directive 91/155/EEC; issued on July 4, 2003. Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/show/1138270/490079_e.pdf.

Merck KGaA. 2003d. Safety data sheet: *N*-Butyl-pyridinium chloride. According to EC Directive 91/155/EEC; issued on March 3, 2003. Available at Internet address: http://pb/merck/de/servlet/PB/show/1133020/490042.pdf.

Merck KGaA. 2004a. Hydrophobicity of ionic liquids. Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/menu/1303700_ePRJ-MERCK-EN_pc… Last accessed on April 28, 2004.

Merck KGaA. 2004b. Viscosity of ionic liquids. Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/menu/1302610_ePRJ-MERCK-EN_pc… Last accessed on April 28, 2004.

Merck KGaA. 2004c. Ionic liquids. New materials for new applications. Available at Internet address: http://pb.merck.de/servlet/PB/show/1316380/flyer_new.pdf.

Merck KGaA. 2004d. Frequently asked questions. Available at Internet address: http://www.ionicliquids-merck.de/servlet/PB/menu/1047790_ePRJ-MERCK-EN_pc… Last accessed on April 28, 2004.

Merck Schuchardt OHG. 2002. 1-Butyl-3-methyl-imidazolium chloride. Merch Schuchardt Catalog, June 19, 2002. Search result from CHEMCATS 2001:2462701.

Mölter, K., Stock, F., Ranke, J., Bottin-Weber, U., Poczobutt, J., Hoffmann, J., Ondruschka, B., Filser, J., and Jastorff, B. 2003 abstr. (Eco)toxicological screening of selected ionic liquids. Presented at the SETAC Europe 13th Annual Meeting, Hamburg, Germany, April 27-May 1, 2003. Available at Inter address: http://www.uft.uni-bremen.de/uft/ioni_liquids/abstracts/Moelter%20et%20al%202003.pdf.

Mori, K., and Takahashi, S. 1990 pat. appl. Recovery of electrolyte from fused-salt aluminum electroplating bath. Nisshin Steel Co., Ltd., Japan. Japan Kokai Tokkyo Koho, 4 pp. Abstract from CAPLUS 1990:187984.

Morris-Natschke, S.L., Meyer, K.L., Marasco, C.J., Jr., Piantadosi, C., Rossi, F., Godwin, P.L., and Modest, E.J. 1990. Synthesis of quaternary amine ether lipids and evaluation of neoplastic cell growth inhibitory properties. J. Med. Chem. 33(6):1812-1818. Abstract from BIOSIS 1990:334058.

Moulton, R. 2003 pat. appl. Electrochemical process for producing ionic liquids. U.S. Pat. Appl. Publ., 8 pp. Abstract from CAPLUS 2003:396162.

Namboodiri, V.V., and Varma, R.S. 2002. Solvent-free sonochemical preparation of ionic liquids. Org. Lett. 4(18):3161-3163. Abstract from CAPLUS 2002:608626.

Nardi, J.C., et al. 1979 pat. appl. 1-Alkyl pyridinium chlorides. United States Dept. of the Air Force. U.S. Pat. Appl., 6 pp. Abstract from CAPLUS 1979:168467.

Nardi, J.C., Hussey, C.L., King, L.A., and Carpio, R.A. 1978a pat. 1-Alkylpyridinium chlorides. U.S., 3 pp. Abstract from CAPLUS 1979:38798.

Nardi, J.C., Hussey, C.L., and King, L.A. 1978b pat. Aluminum trichloride-1-alkyl pyridinium chloride room temperature electrolytes. United States Dept. of the Air Force. U.S., 3 pp. Abstract from CAPLUS 1979:90084.

Ogata, N. 1994. Intelligent polymers for opto-electronic applications. J. Intell. Mater. Syst. Struct. 5(5):619-625. Abstract from TOXCENTER 1995:213242.

O'Rear, D.J., Boudreau, L.C., Driver, M.S., and Munson, C.L. 2002 pat. appl. Removal of mercaptans from hydrocarbon streams using ionic liquids. Chevron U.S.A. Inc. PCT Int. Appl., 19 pp. Abstract from CAPLUS 2002:332298.

Park, S., and Kazlauskas, R.J. 2003. Biocatalysis in ionic liquids—Advantages beyond green technology. Curr. Opin. Biotechnol. 14(4):432-437. Abstract from MEDLINE (in process) 2003405450.

Rachaman, E., Heldman, E., Adani, R., and Amitai, G. 1997 pat. Pyridnium derivatives and pharmaceutical compositions containing them. PCT Int. Appl. 37 pp. Abstract from TOXCENTER 1997:149584.

Rebeiro, G.L., and Khadilkar, B.M. 2001. Chloroaluminate ionic liquid for fischer indole synthesis. Synthesis 3:370-372. Abstract from CAPLUS 2001:186478.

Rogers, R.D. 2003. Final report: Investigation of room temperature ionic liquids as environmentally benign solvents for industrial separation (TSE99-A). EPA Grant No. R828257. National Center for Environmental Research (NCER), U.S. Environmental Protection Agency (EPA). Available at Internet address: http://cfpub2.epa.gov/ncer_abstract/index.cfm/fuseaction/display.abstractDetail/abstract/782/report/0. Last accessed on January 20, 2004.

Rogers, R.D., and Reichert, W.M. 2002 abstr. Polymorphic 1-butyl-3-methylimidazolium chloride: In search of clues to make ionic salts, ionic liquids. Abstract No. W0032. Presented at the American Crystallographic Association Annual Meeting: Crystal Engineering-II, May 27, 2003, San Antonio, TX. Available at Internet address: http://www.hwi.buffalo.edu/ACA/ACA02/abstracts/text/W0032.html. Last accessed on January 7, 2004.

Sachem. 2003. Ionic liquids. Available at Internet address: http://www.sacheminc.com/othermarkets/group/ionicliquids.php. Last accessed on December 31, 2003.

Saha, S., Hayashi S., Kobayashi, A., and Hamaguchi, H. 2003. Crystal structure of 1-butyl-3-methylimidazolium chloride. A clue to the elucidation of the ionic liquid structure. Chem. Lett. 32(8):740 ff. Abstract available at Internet address: http://www.jstage.jst.go.jp/article/cl/32/32_740/_article/-char/en. Last accessed on January 6, 2004.

Sano, K., Urano, Y., Kimura, T., and Sano, A. 2001 pat. appl. A continuous process for the synthesis of quaternary ammonium salts (e.g., alkyl(pyridinium/imidazolium) halides). Wako Pure Chemical Industries, Ltd., Japan. Eur. Pat. Appl., 13 pp. Abstract from CAPLUS 2001:615530.

Santos Peinado, L., Cornago Ramirez, P., and Lopez Zumel, C. 1989. The *in vitro* interaction with DNA of several hypoxic radiosensitizers. Chem. Biol. Interact. 71:245-253. Abstract from TOXCENTER 2002:425008.

Scott, A. 2002. Ionic liquids start to flow. (Green Chemistry). Chem. Week, September 11, 2002. Available at Internet address: http://www.findarticles.com/cf_dls.m3066/35_164/91915843/p1/article/jhtml. Last accessed on January 12, 2004.

Scott, M.P., Brazel, C.S., Benton, M.G., Mays, J.W., Holbrey, J.D., and Rogers, R.D. 2002. Application of ionic liquids as plasticizers for poly(methyl methacrylate). Chem. Commun. (Camb.) 7(13):1370-1371. Abstract from PubMed 12125560.

Seddon, K.R. 1997. Ionic liquids for clean technology. J. Chem. Technol. Biotechnol. 68(4):351-356. Abstract from BIOTECHNO 1997:27170814.

Sheldon. 2001. [no source information provided] Cited by DePaoli (2003).

Sigma-Aldrich. 2003a. Ionic liquids. Available at Internet address: http://www.sigmaaldrich.com/Brands/Fluka__Riedel_Home/Organic__Synthetic/Ionic_Liquids.html. Last accessed on November 10, 2003.

Sigma-Aldrich. 2003b. Product detail: 1-Butyl-3-methylimidazolium chloride. Available at Internet address: http://www.sigmaaldrich.com/cgi-bin/hsrun/Distributed/HahtShop/HahtShop.htx;start=frmCatalogSearchPost?ProdNo=94128&Brand=FLUKA. Last accessed on November 10, 2003.

Solvent Innovation. Undated-a. Chloride and bromide salts (Ger.). Available at Internet address: http://www.solvent-innovation.com/Englisch/chloride_salts_unten.htm. Last accessed on January 6, 2004.

Solvent Innovation. Undated-b. ECOENG™ Salts. Available at Internet address: http://www.solvent-innovation.com/Englisch/ecoeng_unten.htm. Last accessed on January 12, 2004.

Somoza, V., Lindenmeier, M., Wenzel, E., Frank, O., Erbersdobler, H.F., and Hofmann, T. 2003. Activity-guided identification of a chemopreventive compound in coffee beverage using *in vitro* and *in vivo* techniques. J. Agric. Food Chem. 51(23):6861-6869. Abstract from PubMed 14582987.

Stadler, R.H., Varga, H., Milo, C., Schilter, B., Vera, F.A., and Welti, D.H. 2002b. Alkylpyridiniums. 2. Isolation and quantification in roasted and ground coffees. J. Agric. Food Chem. 50(5):1200-1206. Abstract from PubMed 11853504.

Stadler, R.H., Varga, N., Hau, J., Vera, F.A., and Welti, D.H. 2002a. Alkylpyridiniums. 1. Formation in model systems via thermal degradation of trigonelline. J. Agric. Food Chem. 50(5):1192-1199. Abstract from PubMed 11853503.

Stalc, A., and Sentjurc, M. 1990. A contribution to the mechanism of action of SAD-128. Biochem. Pharmacol. 40(11):2511-2518. Abstract from BIOSIS 1991:76733.

Strem Chemicals, Inc. 2004. Ionic liquids. Available at Internet address: http://www.strem.com/code/template.ghc?direct=ionic. Last accessed on January 6, 2004.

Suzuki, H., Washimi, S., and Iwasaki, H. 1993 pat. appl. Treatment of wastewater from aluminum electroplating. Mitsubishi Yuka Eng. Japan. Japan Kokai Tokkyo Koho, 4 pp. Abstract from TOXCENTER 1994:122512.

Swatloski, R.P., Holbrey, J.D., Memon, S.B., Caldwell, G.A., Caldwell, K.A., and Rogers, R.D. 2004. Using *Caenorhabditis elegans* to probe toxicity of 1-alkyl-3-methylimidazolium chloride based ionic liquids. Chem. Commun. 6:668-669.

Swatloski, R.P., Holbrey, J.D., Spear, S.K., and Rogers, R.D. 2003 abstr. Ionic liquids as green solvents: Engineering new bio-based materials. IEC Abstract No. 90. Presented at the 226th ACS National Meeting, Division of Industrial and Engineering Chemistry; September 7-11, 2003; New York, NY. Available from BIOSIS 2003:533550.

Swatloski, R.P., Visser, A.E., Reichert, W.M., Broker, G.A., Farina, L.M., Holbrey, J.D., and Rogers, R.D. 2001. Solvation of 1-butyl-3-methylimidazolium hexafluorophosphate in aqueous

ethanol—a green solution for dissolving "hydrophobic" ionic liquids. Chem. Commun. (Camb.) 20:2070-2071. Abstract from PubMed 12240168.

Takami, N., and Koura, N. 1993. Electrochemical behavior of $FeS_2$ cathodes for aluminum secondary cells at around 100 ºC. J. Electrochem. Soc. 140(4):928-932. Abstract (No. 31) available at Internet address: http://www.ci.noda.sut.ac.jp:1803/eng/etc/aboutProf/abstract.html. Last accessed on January 6, 2004.

TCI America. 2000. 1-*n*-Butylpyridinium chloride. TCI America, January 1, 2000. Search result from CHEMCATS 2000:810365.

TCI Japan. 2003a. 1-*n*-Butyl-3-methylimidazolium chloride. Tokyo Kasei Kogyo, June 27, 2003. Search result from CHEMCATS 2003:3250629.

TCI Japan. 2003b. 1-*n*-Butylpyridinium chloride. Tokyo Kasei Kogyo, June 27, 2003. Search result from CHEMCATS 2002:3268941.

Tran, C.D., De Paoli, Lacerda, S.H., and Oliveira, D. 2003. Absorption of water by room-temperature ionic liquids: effect of anions on concentration and state of water. Appl. Spectrosc. 57(2):152-157. Abstract from PubMed 14610951.

Turner, M.B., Spear, S.K., Swatloski, R.P., Holbrey, J.D., and Rogers, R.D. 2003 abstr. Cellulose films regenerated from ILs and their role as scaffolding for enzyme attachment via glutaraldehyde. IEC Abstract No. 190. Presented at the 226th ACS National Meeting, Division of Industrial and Engineering Chemistry; September 7-11, 2003; New York, NY. Available at Internet address: http://membership.acs.org/I/IEC/docs/NewYork2003-IEC-Abstracts.pdf.

U.S. EPA (U.S. Environmental Protection Agency). 2003. Integrated Risk Information System (IRIS): Paraquat (CASRN 1910-42-5). Available at Internet address: http://www.epa.gov/iris/subst/0183.htm. Profile last updated on October 28, 2003. Last accessed on April 27, 2004.

U.S. EPA. 2004. [Search by casno….] Non-confidential Production Volume Information Submitted by Companies for Chemicals Under the 1986-2002 Inventory Update Rule (IUR). Office of Pollution Prevention and Toxics (OPPT), U.S. Environmental Protection Agency. Available at Internet address: http://www.epa.gov/cgi-bin/iursrch3_2002.cgi. Last updated on April 27, 2004. Last accessed on April 27, 2004.

University of Notre Dame. ca. 2001. Environmental risk assessments for coastal ecosystems: Determining the environmental impact of room temperature ionic liquids prior to widespread industrial use. Available at Internet address: http://www.nd.edu/~dlodge/Prespective%20Grad%20Student%20Info/Env%20assessment%20of%20chemicals%20project/NOAA%20IL%20proposal%201-4-02.pdf.

University of Wollongong – NewsBytes. 2002. Ionic liquids dramatically improve performance of artificial muscles. Available at Internet address: http://media/uow.edu.au/media/2002/artificial.htm. Last accessed on January 7, 2004.

Varma, R.S., and Namboodiri, V.V. 2001a. An expeditious solvent-free route to ionic liquids using microwaves. Chem. Commun. 7:643-644. Abstract from CAPLUS 2001:228154.

Varma, R.S., and Namboodiri, V.V. 2001b. Solvent-free preparation of ionic liquids using a household microwave oven. Pure Appl. Chem. 73(8):1309-1313.

Wallace, G.G. 2003 abstr. Performance enhancing electrolytes: The impact of ionic liquids on artificial muscle development. IEC Abstract No. 168. Presented at the 226th ACS National Meeting, Division of Industrial and Engineering Chemistry; September 7-11, 2003; New York, NY. Available at Internet address: http://membership.acs.org/I/IEC/docs/NewYork2003-IEC-Abstracts.pdf.

Ward, D.L., Rhinebarger, R.R., and Popov, A.I. 1986. *N*-*n*-Butylpyridinium chloride. Acta Crystallogr., Sect. C: Cryst. Struct. Commun. C42(12):1771-1773. Abstract from CAPLUS 1987:59262.

Wasserscheid, P., Boesmann, A., and Van Hal, R. 2003a pat. appl. Preparation of organic ammonium and phosphonium sulfates as ionic liquids. Solvent Innovation Gmbh, Germany. PCT Int. Appl., 30 pp. Abstract from CAPLUS 2003:221657.

Wasserscheid, P., Boesmann, A., and Van Hal, R. 2003b pat. appl. Preparation and use of halogen-free ionic liquids. Solvent Innovation Gmbh, Germany. PCT Int. Appl., 33 pp. Abstract from CAPLUS 2003:719456.

Wasserscheid, P., van Hal, R., and Boesmann, A. 2002. 1-*n*-Butyl-3-methylimidazolium ([bmim]) octylsulfate - an even 'greener' ionic liquid. Green Chem. 4(4):400-404. Abstract from TOXCENTER 2002:178429.

Wu, B., Reddy, R.G., and Rogers, R.D. 2001 abstr. Potential applications of ionic liquids in aluminum industries. Abstracts of Papers - American Chemical Society 221:IEC-196. Abstract from CAPLUS 2001:92491.

Wu, B., Reddy, R.G., and Rogers, R.D. 2002 pat. appl. Production, refining and recycling of lightweight and reactive metals in ionic liquids. The University of Alabama, USA. U.S. Pat. Appl. Publ., 15 pp. Abstract from TOXCENTER 2002:138490.

Zhang, S., and Conrad Zhang, Z. 2002. Novel properties of ionic liquids in selective sulfur removal from fuels at room temperature. Green Chem. 4(4):376-379. Abstract from CAPLUS 2002:590904.

Zhang, W., He, L., Gu, Y., Liu, X., and Jiang, S. 2003. Effect of ionic liquids as mobile phase additives on retention of catecholamines in reversed-phase high-performance liquid chromatography. Anal. Lett. 36(4):827-838.

## 13.0 References Considered But Not Cited

Allen, D.D., Lockman, P.R., Roder, K.E., Dwoskin, L.P., and Crooks, P.A. 2003. Active transport of high-affinity choline and nicotine analogs into the central nervous system by the

blood-brain barrier choline transporter. J. Pharmacol. Exp. Ther. 304(3):1268-1274. Abstract from PubMed 12604705.

Demberelnyamba, D., Kim, K.S., Choi, S., Park, S.Y., Lee, H., Kim, C.J., and Yoo, I.D. 2004. Synthesis and antimicrobial properties of imidazolium and pyrrolidinonium salts. Bioorg. Med. Chem. 12(5):853-857.

Takahashi, S., Koura, N., and Murase, M. 1986. Structural analysis of $AlCl_3$-*n*-butylpyridinium chloride electrolytes by X-ray diffraction. J. Chem. Soc. 82(1):49-60. Abstract (No. 60) available at Internet address: http://www.ci.noda.sut.ac.jp:1803/eng/etc/aboutProf/abstract.html. Last accessed on January 6, 2004.

**Acknowledgements**

Support to the National Toxicology Program for the preparation of Ionic Liquids: 1-Butyl-3-methylimidazolium Chloride (CAS No. 79917-90-1), *N*-Butylpyridinium Chloride (CAS No. 1124-64-7), and 1-Butyl-1-methylpyrrolidinium Chloride (CAS No. 479500-35-1)—Review of Toxicological Literature was provided by Integrated Laboratory Systems, Inc., through NIEHS Contract Number N01-ES-35515. Contributors included: Raymond R. Tice, Ph.D. (Principal Investigator); Karen E. Haneke, M.S. (Project Coordinator); Marcus A. Jackson, B.A. (Project Coordinator); Bonnie L. Carson, M.S. (Senior Chemical Information Scientist, Major Author); Claudine A. Gregorio, M.A.; Nathanael P. Kibler, B.A.; and Barbara A. Henning.

## Appendix A: Units and Abbreviations

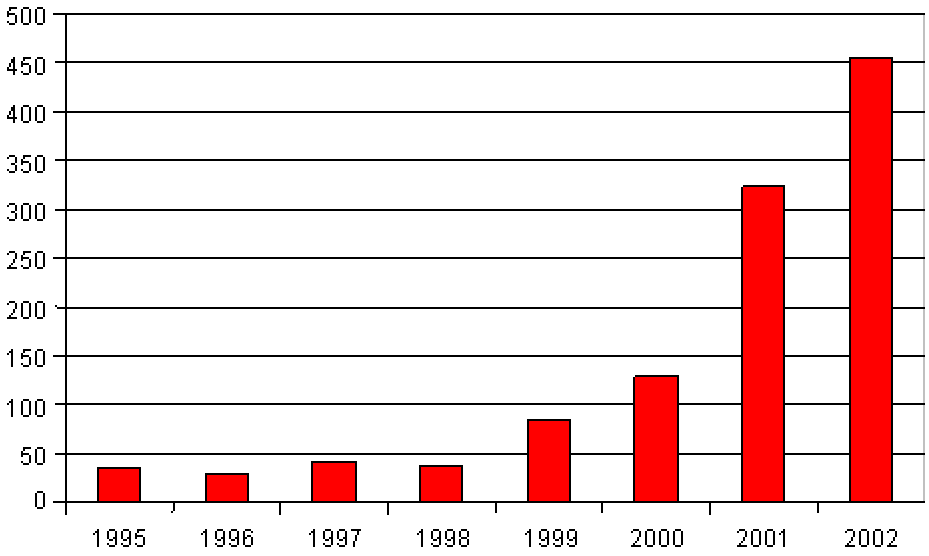
°C = degrees Celsius
µg/L = microgram(s) per liter
µg/$m^3$ = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
[bmim]Cl = 1-butyl-3-methylimidazolium chloride
[bmpy]Cl = 1-butyl-1-methylpyrrolidinium chloride
bw = body weight
CASRN = Chemical Abstract Services Registry Number
CNS = central nervous system
EPA = Environmental Protection Agency
g = gram(s)
g/mL = gram(s) per milliliter
h = hour(s)
HD = high dose
HSDB = Hazardous Substances Data Bank
i.p. = intraperitoneal(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
$LC_{50}$ = lethal concentration for 50% of test animals
$LD_{50}$ = lethal dose for 50% of test animals
LD = low dose
LEL = lowest effect level
MD = mid dose
mg/kg = milligram(s) per kilogram
mg/$m^3$ = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
[NBuPy]Cl = *N*-butylpyridinium chloride
NIEHS = National Institute of Environmental Health Sciences
nm = nanometer(s)
NOEL = no observable effect level
n.p. = not provided
ppb = parts per billion
ppm = parts per million
RTIL = Room Temperature Ionic Liquids

s.c. = subcutaneous(ly)
wk = week(s)
yr = year(s)

## Appendix B: Literature Search Strategy

### I. Nomination

Research on ionic liquids as potentially "green" or environmentally benign alternatives to volatile organic solvents is growing rapidly as reflected by the annual growth in publications shown in the graph below (from overview of the 2003 American Chemical Society Symposium at http://bama.ua.edu/~rdrogers/New%20York/).




To establish the best direction for future research in this area, early toxicity testing on these materials is vital. Without the guidance provided by this testing, true "green" applications of these new solvent classes could be severely delayed. [Adapted from the nomination to the NTP Nominating Faculty, March 10, 2003.] The three compounds recommended for review represent the three most common cation classes being investigated for use in various applications such as catalysis, separations, sensors, and electrochemistry: imidazolium, pyridinium, and pyrrolidinium cations. [Although the chlorides are probably not used as often as ionic liquids with other anions, adverse effects from these salts could be more clearly attributed to the cation.]

### II. Search Strategy

Details of the search strategy and keywords used on the simultaneous search of several biomedical databases (MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, BIOTECHNO, EMBASE, ESBIOBASE, IPA, BIOSIS, and TOXCENTER) and NTIS on STN International are given in Attachment A. The tally by database for the major answer sets is also given in Attachment A. Essentially, 89 unique records resulted from searches for X0041 OR X0042; 49 were from NTIS. One record resulted for the X0043 cation, and none for the chloride. Searches for the cations for X0041 and X0042 gave 152 unique records (49 from MEDLINE and 56 from EMBASE). An additional 163 records resulted from searches for additional room-temperature ionic liquids. Altogether, titles of 381 records were examined on ionic liquids. Titles of another 110 records on reviews on paraquat OR diquat published since 2000 were printed, mostly from MEDLINE (29) and EMBASE (44). Ninety-nine records were selected for printing. These were primarily from MEDLINE (27), EMBASE (28), and TOXCENTER (23).

The history of most of the Internet searches is given in Attachment B, which contains the URLs of the pdf files collected. Materials collected included full articles, abstracts from the 2002 and 2003 American Chemical Society Symposia on ionic liquids, and numerous safety data sheets, especially from the Merck KGaA complete list of ionic liquids. The efforts on December 1, 2003, were on the research activities on biological activities of ionic liquids mentioned in the Nomination.

Several relatively common imidazolium, pyridinium, and pyrrolidinium compounds were identified by searches of *The Merck Index*, 1996 edition, on CD-ROM. Registry, HSDB, and RTECS records were retrieved for many of the compounds. In addition, studies on MPP+ and Parkinsonism were examined on PubMed. The few selected for printing are included in the package.

## III. Search Results

Search results have been organized by typical report topics for the assigned compounds and by information source for some structural analogs. Other ionic liquids information retrieved from the STN International search is also grouped by report topic.

### III.A. Authoritative Reviews (05)

No governmental agency or authoritative international health organization has evaluated toxicity information on ionic liquids.

### III.B. Other Reviews (11)

Three books and one book chapter regarding the potential uses of ionic liquids have been identified:

- Rogers and Seddon (Editors) (2002)
- Rogers et al. (Eds.) (2001)
- Rooney and Seddon in Wypych (Ed.) (2001), and
- Wasserheid and Welton (2002)

In addition, the proceedings of two American Chemical Society (ACS) Symposia on Green Chemistry and Engineering have been published (ACS Symposium Series 766 and 856). Abstracts from the September 2003 ACS Symposium are available from the Internet at http://bama.ua.edu/~rdrogers/New%20York/Abstracts.pdf.

Reviews on ionic liquid applications retrieved from a search of Current Contents Life Sciences January through September 2003 include Dzyuba and Bartsch (2003), Kragl et al. (2002), Leitner (2003), Park and Kazlauskas (2003), van Rantwijk et al. (2003), and Wilson and Roth (2002).

### III.C. Chemical Identification (Subject Code 13a)

Registry records of the nominated compounds are included in this group.

## III.D. Chemical-Physical Properties (Subject Code 13b)

Some properties for the three nominated compounds were given in the material supporting the nomination. Only a few properties were given for these compounds in the Safety Data Sheets provided by producer/supplier Merck KGaA. [These sheets were included with several others in Group III.N.1.] Additional property information may also be available in the reviews and primary publications on uses. Properties for 1-butyl-3-methylimidazolium (bmim+) chloride and 1-butylpyridinium chloride are available in Beilstein according to their Registry records.

## III.E. Analytical Methods (13c)

Information about analytical methods may be available in the reviews and ACS Symposium abstracts and published proceedings.

## III.F. Commercial Availability (01a/01b)

Several producers/suppliers were listed in the nomination. Information was collected from the web sites of Sigma-Aldrich/Fluka and Merck KGaA. Merck KGaA provided the most comprehensive list of ionic liquids, including all three of the nominated compounds. Product quantities ranged from 1- to 50-g packages. No bulk producers were identified.

## III.G. Production Processes (01d)

Currently, production processes of ionic liquids appear to be laboratory-scale syntheses. References included in this section contain studies primarily about syntheses of bmim+ chloride or other bmim+ salts with less innocuous anions. Sources for abstracts of these studies were mostly biomedical databases (EMBASE and TOXCENTER). No attempt was made to comprehensively search all

## III.H. Production and Import Volumes (01c)

No information was found on any large-scale production or importation of ionic liquid compounds.

## III.I. Uses (01f)

Most of the information on applications of ionic liquids may be found in the reviews. Only a few publications were found on uses of bmim+ chloride and only one on uses of *N*-butylpyridinium chloride. [The best source to search for specific applications of each nominated compound would be CAPLUS. Since the chlorides are meant to represent members of cation classes, this specific information seemed unnecessary for this review.]
The information on uses has been grouped as follows:

**I.1. Uses of 1-Butyl-3-methylimidazolium Chloride,**
**I.2. Uses of *N*-Butylpyridinium Chloride,**
**I.3. Uses of 1-Butyl-3-methylimidazolium Hexafluorophosphate,**
**I.4. Uses of Other Imidazolium Ionic Liquids,**
**I.5. Uses of Other Pyidinium Ionic Liquids, and**
**I.6. Uses of Unspecified Ionic Liquids**

Only one abstract appears in CAPLUS on 1-butyl-1-methylpyrrolidinium chloride.

## III.J. Environmental Releases, Occurrence, and Fate

The complex halide anions in the ionic liquids represent some environmental and safety risks. For example, Swatloski et al. (2003 abstr.) pointed out that during purification of the commonly used bmim hexafluorophosphate (the anion is $PF_6^-$), a simple fluoride hydrate is formed by decomposition. Some aquatic toxicity studies are mentioned below. In a Japanese patent assigned to Mitsubishi Yuka Engineering, Suzuki et al. (1993) described the oxidation of onium halides to biodegradable substances in wastewater from aluminum electroplating. The process used hydrogen peroxide in the presence of iron.

## III.K. Exposure Potential (02)

The major routes of potential exposure are likely to be oral and dermal. Although no specific information was found for the three nominations, the Safety Data Sheets available for several representatives of the imidazolium, pyridinium, and pyrrolidinium classes indicate irritation potential from oral, dermal, eye, and/or inhalation exposure. One of the compounds may also be corrosive.

## III.L. Regulations (24)

No regulations on ionic liquids in general or the three nominated compounds in particular were found.

## III.M. Toxicity

Only one publication was found in the biomedical databases on toxicity of any of the assigned compounds. Hassoun et al. (2002) stated that their cytotoxicity study of bmim+ chloride with J774A.1 macrophage cells was to their knowledge "the first study to address any toxicity of an ionic liquid." Cultures were incubated for up to 72 hours with the compound at concentrations from 0.05 to 1.0 mg/mL. The Merck KGaA Safety Data Sheets for bmim+ chloride stated that the compound is an irritant by oral, inhalation, and skin and eye contact exposures. The Merck KGaA Safety Data Sheets for the other two compounds included no definite toxicity statements.

## III.N. Structure-Activity Relationships (25)

### III.N.1. Ionic Liquids Safety Data Sheets

**Table I** summarizes toxicity statements from the Merck KGaA Safety Data Sheets for eighteen specific ionic liquids, including bmim chloride. These Safety Data Sheets are included in the package plus those for 1-butylpyridinium chloride and 1-butyl-1-methylpyrrolidinium chloride, which have no toxicity information.

## Table I. Toxicity Statements from the Merck KGaA Safety Data Sheets for 1-Butyl-3-methylimidazolium Chloride and Seventeen Other Ionic Liquids

| Name | CASRN | Irritation | | | | Burns |
|---|---|---|---|---|---|---|
| | | Oral | Skin | Eye | Inhal | |
| 1,3-Dimethylimidazolium methylsulfate ($dim^+$ $CH_3SO_4^-$) | 97345-90-9 | | X | X | | |
| 1,3-Dimethylimidazolium trifluoromethanesulfonate ($dim^+$ $F_3CSO_3^-$) | 121091-30-3 | | X | X | | |
| 1-Butyl-2,3-dimethyl-imidazolium hexafluorophosphate ($bdim^+$ $PF_6^-$) | 227617-70-1 | X [1] | X | X | X [2] | |
| 1-Butyl-3-methyl-imidazolium chloride ($bdim^+$ $Cl^-$) | | X [1] | X | X | X [2] | |
| 1-Butyl-3-methyl-imidazolium hexafluorophosphate ($bmim^+$ $PF_6^-$) | 174501-64-5 | | X | X | | |
| 1-Butyl-3-methyl-imidazolium methylsulfate ($bmim^+$ $CH_3SO_4^-$) | | | X | X | | |
| 1-Butyl-3-methyl-imidazolium tetrafluoroborate ($bmim^+$ $BF_4^-$) | 174501-65-6 | | X | X | X [2] | |
| 1-Butyl-3-methyl-imidazolium trifluoromethanesulfonate ($bmim^+$ $F_3CSO_3^-$) | 174899-66-2 | | | | X [2] | X [3] |
| 1-Ethyl-3-methyl-imidazolium bromide ($emim^+$ $Br^-$) | 65039-08-9 | X [1] | X | X | X [2] | |
| 1-Ethyl-3-methyl-imidazolium chloride ($emim^+$ $Cl^-$) | 65039-09-0 | | X | X | X [2] | |
| 1-Ethyl-3-methyl-imidazolium hexafluorophosphate ($emim^+$ $PF_6^-$) | 155371-19-0 | | X | X | | |
| 1-Ethyl-3-methyl-imidazolium tetrafluoroborate ($emim^+$ $BF_4^-$) | 143314-16-3 | X [1] | X | X | X [2] | |
| 1-Ethyl-3-methylimidazolium trifluoromethanesulfonate ($emim^+$ $F_3CSO_3^-$) | 145022-44-4 | X [1] | X | X | X [2] | |
| 1-Hexyl-3-methyl-imidazolium chloride ($hmim^+$ $Cl^-$) | 171058-17-6 | X [1] | X | X | X [2] | |
| 1-Hexyl-3-methyl-imidazolium hexafluorophosphate ($hmim^+$ $PF_6^-$) | 304680-35-1 | X [1] | X | X | X [2] | |
| 1-Hexyl-3-methyl-imidazolium tetrafluoroborate ($hmim^+$ $BF_4^-$) | 244193-50-8 | X [1] | X | X | X [2] | |
| 1-Methyl-3-octyl-imidazolium chloride ($moim^+$ $Cl^-$) | 64697-40-1 | | X | X | | |
| 3-Methyl-1-octyl-imidazolium tetrafluoroborate ($moim^+$ $BF_4^-$) | 244193-52-0 | | X | X | | |

[1] Irritation of the mucous membranes in the mouth, pharynx, esophagus, and gastrointestinal tract after swallowing
[2] Irritation of the mucous membranes, coughing, and dyspnea
[3] Eyes and skin, and the mouth, throat, esophagus, and gastrointestinal tract after swallowing

## III.N.2. Search Results for Other Imidazolium, Pyridinium, and Pyrrolidinium Compounds

Some experimental toxicity information about imidazolium and pyridinium compounds was collected from the search of the biomedical databases and from Internet searches based on information about research groups known to be conducting toxicity studies on ionic liquids available in the nomination. Many of the compounds found in these search results are apparently not ionic liquids.

Rachaman et al. (1997) indicated that pharmacokinetics, acute toxicity, and anticholinesterase activity as well as physical-chemical properties have been studied for a group of 1-alkyl-3-hydroxypyridinium compounds including 1-butyl-3-hydroxypyridinium bromide. A *tert*-butyl-3-hydroxypyridinium chloride derivative appeared to be a cholinesterase reactivator (Grubic et al., 1989; Harris et al., 1976, 1978; Stalc and Sentjurc, 1990) and one bound DNA *in vitro* (Santos et al., 1989). Ferguson et al. (1983) reported on petite mutants in yeast induced by non-intercalative DNA-binding antitumor agents, including 1-butylpyridinium/quinolinium and other alkylpyridinium compounds. One 1-butylpyridinium compound was evaluated for cytotoxicity in a promyelocytic leukemia cell line (Morris-Natschke et al., 1990). The Dead Sea Bromine Group (2002) reported that the rat oral and rabbit skin $LD_{50}$ doses were each greater than 2000 mg/kg.

Searches for studies of biological activities mentioned in the nomination produced an article by Jastorff et al. (2003) that proposed a metabolic pathway for $bmim^+$ and discussed the design of testing ionic liquids. Juffernholz (2003) presented a paper at SETAC 2003 on toxicity of ionic liquids to the soil organisms *Collembolen* and *Enchytraeiden*. Lamberti et al. (undated) reported $LC_{50}$ data for $bmim^+$ $PF6^-$ and $bmim^+$ $BF4^-$ to *Daphnia magna*. Mölter et al. (2003 abstr.) reported results from screening imidazolium ionic liquids with the luminescent bacteria acute toxicity test and tests with two rat cell lines. Ranke et al. (in preparation) have conducted on similar *in vitro* screening assays. These researchers are primarily from the University of Bremen.

This section also includes results from searches of the TSCATS database for imidazolium, pyridinium, and pyrrolidinium compounds:

- Acute aquatic toxicity data for a copolymer of 1-vinyl-3-methyl-1*H*-imidazolium chloride (CASRN 95144-24-4) and vinylpyrrolidone (BASF Corp., 1987, 1993)
- Acute oral toxicity in rats of "Pyridinium, 1-(phenylmethyl)-, ethyl methyl deriv." (CASRN 68909-18-2) [mixture] (Petrolite Corp., 1980)
- Acute oral toxicity in rats and ocular irritation in rabbits for "Pyridinium, 1-(phenylmethyl)-, alkyl derivs." (CASRN 100765-57-9) (Rhodia, Inc., 1989)
- Ames test for pyridinium hydrobromide perbromide (CASRN 66323-10-2)

A number of structural analogs that could be considered for this report are listed in Table II. This table shows the breadth of information available on some of these analogs. The materials retrieved for this search package are summarized in the following section. The subheadings correspond to the groups as they appear in the package and are, for the most part, self-descriptive.

## Table II. Literature Availability in STN International Biomedical Databases for Selected Pyridinium and Pyrrolidinium Compounds

| Chemical Name and Synonyms | Pyridinium | Pyrrolidinium | CASRN | CAPLUS | RTECS | HSDB | MEDLINE | CANCERLIT | AGRICOLA | NIOSHTIC | CABA | BIO-TECHNO | EMBASE | IPA | BIOSIS | TOX-CENTER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Paraquat cation radical | x | | 25239-55-8 | 610 | | | | | | | | | | | | X |
| Paraquat | x | | 4685-14-7 | 5526 | X | X | X | X | X | X | X | X | X | X | X | X |
| Paraquat dibromrde | x | | 3240-78-6 | 61 | X | | | | | | | X | | | X | X |
| Paraquat dichloride | x | | 1910-42-5 | 3136 | X | X | | | X | X | X | X | X | X | X | X |
| Diquat dibromide monohydrate | x | | 6385-62-2 | 4 | | | | | | X | | | | | X | X |
| Diquat dichloride; Diquat hydrochloride | x | | 4032-26-2 | 38 | X | | | | | X | | | X | | X | X |
| Diquat (dication) | x | | 2764-72-9 | 880 | X | | X | X | X | X | X | X | X | | X | X |
| Diquat dibromide | x | | 85-00-7 | 857 | X | X | | | X | X | | X | X | X | X | X |
| $MPP^+$ | x | | 48134-75-4 | 990 | X | | X | X | X | X | X | X | X | | X | X |
| MPTP | x | | 28289-54-5 | 1949 | X | X | X | X | X | X | | X | X | X | X | X |
| MPTP N-oxide | x | | 95969-40-7 | 22 | | | X | | | | | | | | X | X |
| Turicine monohydrate | x | | 6159-37-1 | 0 | | | | | | | | | | | | |
| Turicine; Bacteriocin | | x | 515-24-2 | 6 | | | | | | | | | | | | X |
| Stachydrine methyl ester chloride | | x | 40768-25-0 | 1 | | | | | | | | | | | | |
| Stachydrine monohydrate | | x | 6160-17-4 | 0 | | | | | | | | | | | | |
| Stachydrine; Cadabine; Proline beta | | x | 471-87-4 | 209 | | | X | X | X | | | X | X | X | X | X |
| Betonicine; Betonicin | | x | 515-25-3 | 45 | | | | | X | | | | | X | X | X |
| Pyridostigmine bromide | | x | 101-26-8 | 237 | X | X | X | X | X | X | | X | X | X | X | X |
| 1-Cetylpyridinium bromide | x | | 123-03-5 | 4108 | X | X | X | | X | X | | X | X | | X | X |
| Trigonelline hydrobromide | x | | 64365-49-7 | 2 | | | | | | | | | | | | |
| Trigonellamide | x | | 3106-60-3 | 617 | X | | X | X | X | X | | X | X | X | X | X |
| Trigonellamide chloride | x | | 1005-24-9 | 112 | X | | | | X | | | X | X | X | X | |
| Trigonelline | x | | 535-83-1 | 411 | X | | X | X | X | | | X | X | X | X | X |

Note: X represents one profile in the HSDB and RTECS columns. For the other databases, the availability in the other databases is based on the list of databases in each Registry record. Appearance of a database name in the Registry record indicates that at least one record in that database has the CASRN in its indexing.

## III.N.3. Selected Pyrrolidinium Compounds

### N.3.a. Monographs from The Merck Index (Budavari, 1996) for Pyrrolidinium Compounds

The package includes the more simple pyridinium and pyrrolidinium compounds in The Merck Index. Complex compounds that had similar therapeutic activities were also added.

This group includes monographs on Stachys alkaloids betonicine, stachydrine, and turicine and on several drugs with anticholinergic/antispasmodic activity.

### N.3.b. Registry and/or ChemIDplus Records for the Stachys Alkaloids and Some Derivatives

### N.3.c. Chemical Abstracts Records on Biological Activities of Stachys Alkaloids

When the Registry file was searched for the Stachys alkaloids stachydrine (cadabine), betonicine, and turicine, up to 10 of the most recent CA records for each compound were retrieved by use of the "all" format. Biological activities mentioned in a few of the records include:

- cytotoxicity to cancer cell lines (Aylward, 1995),
- antagonism of plant thermotolerance of high osmolality (Fletcher et al., 2001), and
- *in vitro* inhibition of tyrosinase (Tan et al., 2002a,b).

## III.N.4 Selected Pyridinium Compounds

### N.4.a. Monographs from The Merck Index (Budavari, 1996) for Pyridinium Compounds

Activities and applications of some pyridinium compounds, including paraquat, diquat, $MPP^+$, and MPTP, include the following:

- cholinergic (benzpyrinium bromide),
- cholinesterase inhibitor (distigmine bromide, pyridostigmine bromide),
- cholinesterase reactivator (asoxime chloride, obidoxime chloride, pralidoxime chloride),
- CNS stimulant (comphotamide),
- disinfectant (cetylpyridinium chloride),
- nicotinic acid metabolites (trigonellamide, trigonelline),
- oxidizing agent in organic synthesis (pyridinium chlorobromate), and
- small-scale brominating agent (pyridinium bromide perbromide)

### N.4.b. Registry and/or ChemIDplus Records for Some Pyridinium Compounds

### N.4.c. Paraquat and Diquat

### N.4.c.1. Recent Paraquat and Diquat Reviews (Biomedical Database Records)

### N.4.c.2. RTECS Records for Paraquat, Diquat, and Their Derivatives

### N.4.c.3. Selected Pages from HSDB record for Paraquat

### N.4.d. RTECS Records for Some Other Pyridinium Compounds

- Cetylpyridinium chloride,
- $MPP^+$; *N*-Methyl-4-pyridinium ion,

- MPTP; *N*-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine,
- Pyridostigmine bromide,
- Trigonellamide and Trigonellamide Chloride, and
- Trigonelline

### N.4.e. HSDB Records for Some Other Pyridinium Compounds

- Cetylpyridinium chloride,
- MPTP, and
- Pyridostigmine bromide

### N.4.f. Selected PubMed Abstracts on MPTP and $MPP^+$

This section also includes a report by Pop and Bodor (1992) on a pyridinium salt derivative used to enhance CNS uptake of antiepileptic drugs. No toxic side effects occurred. Usuki et al. (2002) reported that HPTP, the tetrahydropyridinyl dehydration product of haloperidol, may be potentially metabolized to $HPP^+$. HPTP and $HPP^+$ were studied in mouse brain preparations.

## Addendum to Search Strategy Described in the Search Package Summary

Further literature searches on bmim chloride and *N*-butylpyridinium chloride were done in the STN International databases CAPLUS (*Chemical Abstracts*), CHEMCATS (Chemical Catalogs), CEN (*Chemical and Engineering News*), and PROMT on December 31, 2003. The complete history of the online session is shown below. (The switches back and forth between CAPLUS and Registry were automatic.) The searches in CAPLUS took advantage of the Chemical Abstracts Service indexing policy that associates "roles" with the CASRN. In the searches, the roles used were analyte (ANT), analytical studies (ANST), preparative methods (PREP), adverse effects (ADV), biological studies (BIOL), reactant (RCT), and uses (USES). Further analysis of the uses of *N*-butylpyridinium chloride was facilitated by splitting the USES results into patent (patent/DT where DT = document type) and nonpatent groups. Online analysis of the USES results for 1-butyl-3-methylimidazolium chloride showed that the roles ANST, PREP, and RCT and the keywords electr? (where ? indicates truncation), cataly?, synthe?, and solvent covered 92% of the results (97/105). Search results that were not used for further search statements and whose titles were not examined are italicized. Two lines of faulty strategy are crossed out. No searches were done on this date for 1-butyl-1-methylpyrrolidinium chloride because CAPLUS had only one record and the Registry file indicated that its CASRN would not be found in the other databases.

```
FILE 'CAPLUS' ENTERED AT 14:22:51 ON 31 DEC 2003
L1            6 S 1124-64-7/ANST
L2           13 S 1124-64-7/PREP
L3            0 S 1124-64-7/ADV
L4            1 S 1124-64-7/BIOL
L5           22 S 1124-64-7/RCT
SAVE L5 X42REACTANT/A
L6          163 S 1124-64-7/USES
L7          157 S L6 NOT (L2 OR L4 OR L5)
L8          131 S L7 NOT SOLVENT?
SAVE L8 X42USES/A
L9           61 S L8 AND PATENT/DT
L10          81 S L6 AND PATENT/DT
SAVE L10 X42PATENTUSE/A
```

```
L11          82 S L6 NOT L10
SAVE L11 X42NOTPATENT/A
S 45806-95-9/REG#

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 31 DEC 2003
L12           1 S 45806-95-9/RN

FILE 'CAPLUS' ENTERED AT 14:37:55 ON 31 DEC 2003
L13          37 S L12
SAVE L13 X42CATION/A
S 79917-90-1/REG#

FILE 'REGISTRY' ENTERED AT 14:39:54 ON 31 DEC 2003
L14           1 S 79917-90-1/RN

FILE 'CAPLUS' ENTERED AT 14:39:55 ON 31 DEC 2003
L15         213 S L14
L16           0 S 79917-90-1/ANT
L17           6 S 79917-90-1/ANST
L18           3 S 79917-90-1/BIOL
L19          36 S 79917-90-1/PREP
SAVE L19 X41PREP/A
L20          64 S 79917-90-1/RCT
L21          16 S L20 AND L19
L22         105 S 79917-90-1/USES
L23          98 S L22 NOT L19
L24           1 S L22 AND L20
L25          95 S L22 NOT (L19 OR L20 OR L17)
L26          19 S L25 AND ELECTR?
L27          64 S L25 AND CATALY?
L28          13 S L25 AND SYNTHE?
SAVE L20 X41REACT/A
L29          38 S L22 AND SOLVENT?
L30         146 S L22 AND L26 OR L27 OR L28 OR L20
L31           0 S L22 AND L26 AND L27 AND L28 AND L20
L32          13 S L22 NOT (L19 OR L17 OR L20 OR L26 OR L27 OR L28)
L33           8 S L32 NOT L29
S 80432-08-2/REG#

FILE 'REGISTRY' ENTERED AT 15:02:33 ON 31 DEC 2003
L34           1 S 80432-08-2/RN

FILE 'CAPLUS' ENTERED AT 15:02:33 ON 31 DEC 2003
L35          24 S L34
SAVE L35 X41CATION/A

FILE 'CHEMCATS' ENTERED AT 15:02:59 ON 31 DEC 2003
L36           7 S 79917-90-1

FILE 'CEN' ENTERED AT 15:04:09 ON 31 DEC 2003
L37           1 S 1124-64-7

FILE 'CHEMCATS' ENTERED AT 15:04:49 ON 31 DEC 2003
L38           9 S 1124-64-7 OR (BUTYLPYRIDINIUM OR BUTYL(W)PYRIDINIUM)(W)CHLORI

FILE 'PROMT' ENTERED AT 15:07:06 ON 31 DEC 2003
L39           1 S 1124-64-7
L40           7 S (BUTYLPYRIDINIUM OR BUTYL(W)PYRIDINIUM)(W)CHLORIDE
L41           7 S L39 OR L40
L42           0 S 79917-90-1
L43           2 S BUTYL(W)(1 OR 3)(W)(METHYLIMIDAZOLIUM)(W)(CHLORIDE)
L44           0 S METHYL(W)(1 OR 3)(W)(BUTYLIMIDAZOLIUM OR BUTYL(W)IMIDAZOLIUM)
L45           0 S BUTYL(W)(1 OR 3)(W)METHYL(W)IMIDAZOLIUM(W)CHLORIDE
L46           9 L41 OR L43
```

# Attachment A. Detailed Search Strategy and Result Tallies (ILS Assignment Code X0040)

## Distribution of Titles from STN International Search

| NAME AND SYNONYMS | Answer Set | CASRN | MEDLINE | AGRICOLA | CABA | BIO-TECHNO | EMBASE | ESBIOBASE | BIOSIS | TOX-CENTER | NTIS | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1-Butyl-3-methylimidazolium chloride (ILS Code X0041) | L25 | 79917-90-1 | 2 | | | 1 | 6 | | 2 | 10 | | 21 |
| 1-Butylpyridinium chloride (ILS Code X0042) | L26 | 1124-64-7 | 2 | | | 1 | 5 | | 4 | 8 | 49 | 69 |
| Subtotal (saved as X41X42CL) | L29 | | 4 | | | 2 | 11 | | 6 | 17 | 49 | 89 |
| 1-Butyl-3-methylimidazolium cation [results for the chloride were subtracted] | L30 | 80432-08-3 | 46 | 1 | | 11 | 48 | 2 | 7 | 13 | 1 | 129 |
| 1-Butylpyridinium cation [results for the chloride were subtracted] | L31 | 45806-95-9 | 3 | 1 | | | 10 | 2 | 1 | 5 | 3 | 25 |
| Subtotal (saved as X41X42cation) | L33 | | 49 | 2 | | 11 | 56 | 4 | 8 | 18 | 4 | 152 |
| 1-Butyl-1-methylpyrrolidinium [No chloride hits. Anion in the MEDLINE record (an analytical methods paper) was bis(trifluoromethylsulfonyl)imide.] | L20 | | 1 | | | | | | | | | 1 |
| "ionic liquid?" AND ("room temperature" OR RTIL) [minus answer sets already saved] [The NTIS results were not included in the answers saved as X40RTIL.] | L42 | | 52 | 1 | 1 | 3 | 56 | 3 | 14 | 9 | 24 | 163 |
| Total titles printed | | | 105 | 4 | 1 | 16 | 123 | 7 | 28 | 44 | 53 | 381 |
| Total full records printed after examination of the titles | | | 27 | 1 | 1 | 5 | 28 | 1 | 11 | 23 | 2 | 99 |

## STN International Search Strategies

The history of the online simultaneous searches of the files MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, CABA, BIOTECHNO, EMBASE, ESBIOBASE, BIOSIS, IPA, TOXCENTER, NTIS, and NAPRALERT on November 20, 2003 is reproduced below.

```
L1           14 S 79917-90-1
L2          228 S (1 OR N)(W)BUTYL(W)(3 OR N)(W)METHYLIMIDAZOLIUM
L3           25 S L2(W)CHLORIDE
L4           28 S L1 OR L3
L5            2 S 80432-08-2
L6          228 S L2 OR L5
L7            5 S 1124-64-7
L8            0 S PYRIDINIUM(W)1(W)BUTYL(W)CHLORIDE
L9           66 S (1 OR N)(W)BUTYLPYRIDINIUM
L10          34 S L9(W)CHLORIDE
L11           0 S BUTYLPYRIDIUM(W)CHLORIDE
L12          32 S BUTYL(W)PYRIDINIUM(W)CHLORIDE
L13          65 S L7 OR L10 OR L12
L14          68 S L9 OR 45806-95-9
L15           0 S 479500-35-1
L16           0 S 223437-10-3
L17           0 S (1 OR N)(W)BUTYL(W)METHYL(W)PYRROLIDINIUM
L18           0 S (1 OR N)(W)(1 OR N)(W)(BUTYL OR METHYL)(W)(METHYL OR BUTYL)(W
L19           0 S (BUTYL OR METHYL)(W)(METHYLPYRROLIDINIUM OR BUTYLPYRROLIDINIU
L20           1 S BUTYLMETHYLPYRROLIDINIUM OR METHYLBUTYLPYRROLIDINIUM
L21         203 S L6 NOT L4
L22          58 S BUTYLPYRIDINIUM(W)CHLORIDE
L23          82 S L7 OR L10 OR L12 OR L22
L24          34 S L14 NOT L23
                SET DUPORDER FILE
L25          21 DUP REM L4 (7 DUPLICATES REMOVED)
                ANSWERS '1-2' FROM FILE MEDLINE
```

```
                ANSWER '3' FROM FILE BIOTECHNO
                ANSWERS '4-9' FROM FILE EMBASE
                ANSWERS '10-11' FROM FILE BIOSIS
                ANSWERS '12-21' FROM FILE TOXCENTER
L26          69 DUP REM L23 (13 DUPLICATES REMOVED)
                ANSWERS '1-2' FROM FILE MEDLINE
                ANSWER '3' FROM FILE BIOTECHNO
                ANSWERS '4-8' FROM FILE EMBASE
                ANSWERS '9-12' FROM FILE BIOSIS
                ANSWERS '13-20' FROM FILE TOXCENTER
                ANSWERS '21-69' FROM FILE NTIS
L27         109 S L4 OR L23
L28          89 DUP REM L27 (20 DUPLICATES REMOVED)
                ANSWERS '1-4' FROM FILE MEDLINE
                ANSWERS '5-6' FROM FILE BIOTECHNO
                ANSWERS '7-17' FROM FILE EMBASE
                ANSWERS '18-23' FROM FILE BIOSIS
                ANSWERS '24-40' FROM FILE TOXCENTER
                ANSWERS '41-89' FROM FILE NTIS
L29          89 SORT L28 1-89 TI
                SAVE L29 X41X42CHLORIDE/A X41X42CL/A
L30         129 DUP REM L21 (74 DUPLICATES REMOVED)
                ANSWERS '1-46' FROM FILE MEDLINE
                ANSWER '47' FROM FILE AGRICOLA
                ANSWERS '48-58' FROM FILE BIOTECHNO
                ANSWERS '59-106' FROM FILE EMBASE
                ANSWERS '107-108' FROM FILE ESBIOBASE
                ANSWERS '109-115' FROM FILE BIOSIS
                ANSWERS '116-128' FROM FILE TOXCENTER
                ANSWER '129' FROM FILE NTIS
L31          25 DUP REM L24 (9 DUPLICATES REMOVED)
                ANSWERS '1-3' FROM FILE MEDLINE
                ANSWER '4' FROM FILE AGRICOLA
                ANSWERS '5-14' FROM FILE EMBASE
                ANSWERS '15-16' FROM FILE ESBIOBASE
                ANSWER '17' FROM FILE BIOSIS
                ANSWERS '18-22' FROM FILE TOXCENTER
                ANSWERS '23-25' FROM FILE NTIS
L32         235 S L21 OR L24
L33         152 DUP REM L32 (83 DUPLICATES REMOVED)
                ANSWERS '1-49' FROM FILE MEDLINE
                ANSWERS '50-51' FROM FILE AGRICOLA
                ANSWERS '52-62' FROM FILE BIOTECHNO
                ANSWERS '63-118' FROM FILE EMBASE
                ANSWERS '119-122' FROM FILE ESBIOBASE
                ANSWERS '123-130' FROM FILE BIOSIS
                ANSWERS '131-148' FROM FILE TOXCENTER
                ANSWERS '149-152' FROM FILE NTIS
L34         152 SORT L33 1-152 TI
                SAVE L34 X41X42CATION/A
L35         241 S L28 OR L33
L36         241 DUP REM L35 (0 DUPLICATES REMOVED)
                ANSWERS '1-53' FROM FILE MEDLINE
                ANSWERS '54-55' FROM FILE AGRICOLA
                ANSWERS '56-68' FROM FILE BIOTECHNO
                ANSWERS '69-135' FROM FILE EMBASE
                ANSWERS '136-139' FROM FILE ESBIOBASE
                ANSWERS '140-153' FROM FILE BIOSIS
                ANSWERS '154-188' FROM FILE TOXCENTER
                ANSWERS '189-241' FROM FILE NTIS
L37        1016 S IONIC(W)LIQUID?
L38         667 DUP REM L37 (349 DUPLICATES REMOVED)
                ANSWERS '1-225' FROM FILE MEDLINE
                ANSWERS '226-229' FROM FILE AGRICOLA
                ANSWERS '230-232' FROM FILE CABA
                ANSWERS '233-256' FROM FILE BIOTECHNO
                ANSWERS '257-436' FROM FILE EMBASE
                ANSWERS '437-447' FROM FILE ESBIOBASE
                ANSWERS '448-449' FROM FILE IPA
                ANSWERS '450-502' FROM FILE BIOSIS
                ANSWERS '503-566' FROM FILE TOXCENTER
```

```
                ANSWERS '567-667' FROM FILE NTIS
L39          319 S (L37 AND ROOM(W)TEMPERATURE) OR RTIL
L40          202 DUP REM L39 (117 DUPLICATES REMOVED)
                ANSWERS '1-71' FROM FILE MEDLINE
                ANSWER '72' FROM FILE AGRICOLA
                ANSWER '73' FROM FILE CABA
                ANSWERS '74-78' FROM FILE BIOTECHNO
                ANSWERS '79-144' FROM FILE EMBASE
                ANSWERS '145-147' FROM FILE ESBIOBASE
                ANSWERS '148-158' FROM FILE BIOSIS
                ANSWERS '159-175' FROM FILE TOXCENTER
                ANSWERS '176-202' FROM FILE NTIS
L41          259 S L39 NOT L35
L42          163 DUP REM L41 (96 DUPLICATES REMOVED)
                ANSWERS '1-52' FROM FILE MEDLINE
                ANSWER '53' FROM FILE AGRICOLA
                ANSWER '54' FROM FILE CABA
                ANSWERS '55-57' FROM FILE BIOTECHNO
                ANSWERS '58-113' FROM FILE EMBASE
                ANSWERS '114-116' FROM FILE ESBIOBASE
                ANSWERS '117-130' FROM FILE BIOSIS
                ANSWERS '131-139' FROM FILE TOXCENTER
                ANSWERS '140-163' FROM FILE NTIS
L43          139 SORT L42 1-139 TI
                SAVE L43 X40RTIL/A
L44         1328 S PARAQUAT AND (REVIEW OR REVIEW/DT)
L45          210 S L44 AND (2000-2003)/PY
L46           11 S DIQUAT AND REVIEW/DT AND (2000-2003)/PY
L47          213 S L45 OR L46
L48          110 DUP REM L47 (103 DUPLICATES REMOVED)
                ANSWERS '1-29' FROM FILE MEDLINE
                ANSWER '30' FROM FILE AGRICOLA
                ANSWERS '31-34' FROM FILE CABA
                ANSWERS '35-51' FROM FILE BIOTECHNO
                ANSWERS '52-95' FROM FILE EMBASE
                ANSWERS '96-98' FROM FILE BIOSIS
                ANSWERS '99-110' FROM FILE TOXCENTER
L49          110 SORT L48 1-110 TI
                SAVE L49 PARAQUAT/A
```

## Attachment B: Merck KGaA MSDS URLs (Compound names as given in MSDS)

http://www.ionicliquids-merck.de/servlet/PB/show/1138140/490040_e.pdf
1-Methyl-imidazolium tosylate

http://www.ionicliquids-merck.de/servlet/PB/show/1224140/490093.pdf
1-Methyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1091430/814955.pdf
1,3-Dimethyl-imidazolium methylsulfate

http://www.ionicliquids-merck.de/servlet/PB/show/1091450/814981.pdf
1,3-Dimethyl-imidazolium trifluoromethanesulfonate

http://www.ionicliquids-merck.de/servlet/PB/show/1109180/490019.pdf
1,3-Dimethyl-imidazolium bis(pentafluoroethyl)phosphinate

http://www.ionicliquids-merck.de/servlet/PB/show/1091300/814940.pdf
1-Ethyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1132990/490038.pdf
1-Ethyl-3-methyl-imidazolium bromide

http://www.ionicliquids-merck.de/servlet/PB/show/1132980/490037.pdf
1-Ethyl-3-methyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1091460/814982.pdf
1-Ethyl-3-methyl-imidazolium trifluoromethanesulfonate

http://www.ionicliquids-merck.de/servlet/PB/show/1091390/814951.pdf
1-Ethyl-3-methyl-imidazolium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1109170/490018.pdf
1-Ethyl-3-methyl-imidazolium bis(pentafluoroethyl)phosphinate

http://www.ionicliquids-merck.de/servlet/PB/show/1109110/490012.pdf
1-Ethyl-3-methyl-imidazolium bis[oxalato(2-)]-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1109120/490013.pdf
1-Ethyl-3-methyl-imidazolium bis[1,2-benzenediolato(2-)-O,O']-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1138270/490079_e.pdf
1-Butyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1224090/490087.pdf
1-Butyl-3-methyl-imidazolium bromide

http://www.ionicliquids-merck.de/servlet/PB/show/1132170/490049.pdf
1-Butyl-3-methyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1109230/490024.pdf
1-Butyl-3-methyl-imidazolium trifluoromethanesulfonate

http://www.ionicliquids-merck.de/servlet/PB/show/1091440/814956.pdf
1-Butyl-3-methyl-imidazolium methylsulfate

http://www.ionicliquids-merck.de/servlet/PB/show/1109140/490015.pdf
1-Butyl-3-methyl-imidazolium dicyanamide

http://www.ionicliquids-merck.de/servlet/PB/show/1091400/814952.pdf
1-Butyl-3-methyl-imidazolium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1224120/490090.pdf
1-Butyl-3-methyl-imidazolium bis(trifluoromethyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1132850/490062.pdf
1-Butyl-3-ethyl-imidazolium trifluoromethanesulfonate

http://www.ionicliquids-merck.de/servlet/PB/show/1109190/490020.pdf
1-Pentyl-3-methyl-imidazolium trifluoromethanesulfonate

http://www.ionicliquids-merck.de/servlet/PB/show/1108990/490000.pdf
1-Pentyl-3-methyl-imidazolium tris(pentafluoroethyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1206890/490083_e.pdf
1-Pentyl-3-methyl-imidazolium tris(nonafluorobutyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1133000/490039.pdf
1-Hexyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1091360/814948.pdf
1-Hexyl-3-methyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1091410/814953.pdf
1-Hexyl-3-methyl-imidazolium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1127840/490031.pdf
1-Hexyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1138260/490078_e.pdf
1-Hexyl-3-methyl-imidazolium tris(pentafluoroethyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1091330/814944.pdf
1-Octyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1091370/814949.pdf
1-Octyl-3-methyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1132970/490036.pdf
1-Octyl-3-methyl-imidazolium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1132940/490033.pdf
1-Decyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1109220/490023.pdf
1-Decyl-3-methyl-imidazolium bromide

http://www.ionicliquids-merck.de/servlet/PB/show/1132950/490034.pdf
1-Tetradecyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1109130/490014.pdf
1-Tetradecyl-3-methyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1206870/490081_e.pdf
1-Hexadecyl-3-methyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1133010/490041.pdf
1-Ethyl-2,3-dimethyl-imidazolium bromide

http://www.ionicliquids-merck.de/servlet/PB/show/1109200/490021.pdf
1-Butyl-2,3-dimethyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1109150/490016.pdf
1-Butyl-2,3-dimethyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1132960/490035.pdf
1-Butyl-2,3-dimethyl-imidazolium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1138250/490077_e.pdf
1-Propyl-2,3-dimethyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1109160/490017.pdf
1-Hexyl-2,3-dimethyl-imidazolium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1206860/490080_e.pdf
1-Hexyl-2,3-dimethyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1206880/490082_e.pdf
1-Hexadecyl-2,3-dimethyl-imidazolium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1133020/490042.pdf
N-Butyl-pyridinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1138160/490051_e.pdf
N-Butyl-pyridinium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1132210/490052.pdf
N-Butyl-pyridinium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1132200/490045.pdf
N-Hexyl-pyridinium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1138180/490070_e.pdf
N-Hexyl-pyridinium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1224100/490088.pdf
3-Methyl-N-butyl-pyridinium bromide

http://www.ionicliquids-merck.de/servlet/PB/show/1091340/814945.pdf
4-Methyl-N-butyl-pyridinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1091380/814950.pdf
4-Methyl-N-butyl-pyridinium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1091420/814954.pdf
4-Methyl-N-butyl-pyridinium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1224150/490094.pdf
4-Methyl-N-octyl-pyridinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1109210/490022.pdf
3,4-Dimethyl-N-butyl-pyridinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1138170/490069_e.pdf
1,1-Dimethyl-pyrrolidinium tris(pentafluoroethyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1127800/490028.pdf
1-Butyl-1-methyl-pyrrolidinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1127810/490029.pdf
1-Butyl-1-methyl-pyrrolidinium trifluoromethanesulfonate

http://www.ionicliquids-merck.de/servlet/PB/show/1132190/490047.pdf
1-Butyl-1-methyl-pyrrolidinium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1138150/490048_e.pdf
1-Butyl-1-methyl-pyrrolidinium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1133030/490044.pdf
1-Butyl-1-methyl-pyrrolidinium dicyanamide

http://www.ionicliquids-merck.de/servlet/PB/show/1132180/490046.pdf
1-Butyl-1-methyl-pyrrolidinium bis(trifluoromethylsulfonyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1206900/490084_e.pdf
1-Butyl-1-methyl-pyrrolidinium tris(pentafluoroethy)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1224160/490095.pdf
1-Hexyl-1-methyl-pyrrolidinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1224170/490096.pdf
1-Octyl-1-methyl-pyrrolidinium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1138190/490071_e.pdf
Tetrabutyl-phosphonium tris(pentafluoroethyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1109020/490003.pdf
Tetrabutyl-phosphonium bis[oxalato(2-)]-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1109090/490010.pdf
Tetrabutyl-phosphonium bis[1,2-benzenediolato(2-)-O,O']-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1206910/490085_e.pdf
Tetrabutyl-phosphonium bis(trifluoromethyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1127790/480369.pdf
Trihexyl(tetradecyl)-phosphonium chloride

http://www.ionicliquids-merck.de/servlet/PB/show/1127830/490027.pdf
Trihexyl(tetradecyl)-phosphonium bromide

http://www.ionicliquids-merck.de/servlet/PB/show/1109040/490005.pdf
Trihexyl(tetradecyl)-phosphonium dicyanamide

http://www.ionicliquids-merck.de/servlet/PB/show/1109030/490004.pdf
Trihexyl(tetradecyl)-phosphonium tetrafluoroborate

http://www.ionicliquids-merck.de/servlet/PB/show/1109070/490008.pdf
Trihexyl(tetradecyl)-phosphonium bis(trifluoromethylsulfonyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1109060/490007.pdf
Trihexyl(tetradecyl)-phosphonium bis(2,4,4-trimethylpentyl)phosphinate

http://www.ionicliquids-merck.de/servlet/PB/show/1109010/490002.pdf
Trihexyl(tetradecyl)-phosphonium tris(pentafluoroethyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1109100/490011.pdf
Trihexyl(tetradecyl)-phosphonium hexafluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1109050/490006.pdf
Trihexyl(tetradecyl)-phosphonium decanoate

http://www.ionicliquids-merck.de/servlet/PB/show/1138240/490076_e.pdf
Trihexyl(tetradecyl)-phosphonium bis[oxalato(2-)]-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1138230/490075_e.pdf
Trihexyl(tetradecyl)-phosphonium bis[1,2-benzenediolato(2-)-O,O']-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1109080/490009.pdf
Tri-iso-butyl(methyl)-phosphonium tosylate

http://www.ionicliquids-merck.de/servlet/PB/show/1206920/490086_e.pdf
Tetramethyl-ammonium bis(trifluoromethyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1127820/490030.pdf
Tetramethyl-ammonium bis[oxalato(2-)]-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1224110/490089.pdf
Tetraethyl-ammonium bis(trifluoromethyl)imide

http://www.ionicliquids-merck.de/servlet/PB/show/1138440/490026_e.pdf
Tetraethyl-ammonium tris(pentafluoroethyl)trifluorophosphate

http://www.ionicliquids-merck.de/servlet/PB/show/1138200/490072_e.pdf
Tetraethyl-ammonium bis[1,2-benzenediolato(2-)-O,O']-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1138210/490073_e.pdf
Tetraethyl-ammonium bis[salicylato(2-)]-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1138220/490074_e.pdf
Tetraethyl-ammonium bis[2,2'-biphenyldiolato(2-)-O,O']-borate

http://www.ionicliquids-merck.de/servlet/PB/show/1206910/490085_e.pdf
Tetrabutyl-ammonium tris(pentafluoroethyl)trifluorophosphate