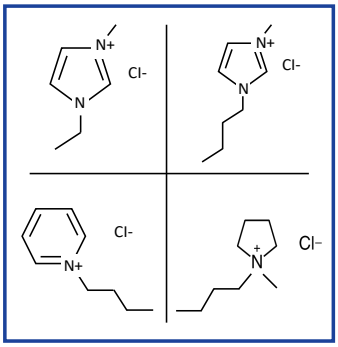
SUMMARY

Background: Ionic liquids (ILs) are synthetic solvents with many industrial applications. They have gained popularity as a potentially less toxic alternative to traditional solvents. Human exposure to ILs may occur through the skin or orally (e.g., via occupational exposure, the use of consumer products, or drinking water contamination). The effects of four ILs in male and female rats and mice were studied to identify the potential toxicity of ILs could be relevant to humans. The four ILs selected for these studies included: 1-ethyl-3-methylimidazolium chloride (Emim-Cl), 1-butyl-3-methylimidazolium chloride (Bmim-Cl), 1-butyl-1-methylpyrrolidinium chloride (Bmpy-Cl), and n-butylpyridinium chloride (NBuPy-Cl). An oral route of exposure (i.e., drinking water) was chosen to mimic the way human exposure commonly occurs.



Methods: Groups of male and female rats and mice were continually exposed to Emim-Cl, Bmim-Cl, Bmpy-Cl, or NBuPy-Cl in drinking water beginning at 5 weeks of age and continuing for 3 months. Concentrations of IL's ranged from 0.1 to 30 milligrams (mg) per milliliter (mL), depending on preliminary information about chemical tolerance by animal and sex. Control animals received 0 mg/mL (drinking water alone). Rats and mice were assessed periodically throughout and/or at the end of the studies for body weight, clinical observations, illness or mortality, reproductive health, blood parameters, and organ weight changes. At the end of the studies, tissues from more than 40 sites from every animal were examined for signs of disease.

Results: Rats exposed to high concentrations of Bmpy-Cl and NBuPy-Cl and mice exposed to high concentrations of all four ILs had lower body weights compared to the control groups. Male mice were more affected than female mice at the same exposure concentrations. Noncancerous tissue abnormalities were observed in the kidney and adrenal gland in mice exposed to IL. Minimal effects on blood parameters were observed. Neither survival, nor male or female reproductive health was influenced. When comparing across the chemicals, an IL with a longer side chain of carbon molecules in its structure (i.e., Bmim-Cl) exhibited greater toxicity compared to an IL with a shorter side chain (i.e., Emim-Cl). No clear trends related to differences in the main chemical structure (i.e., imidiazolium vs. pyrrolidinium vs. pyridinium) were observed.

Conclusions: *Under the conditions of the 3-month studies, drinking water exposure to ILs resulted in noncancerous tissue abnormalities in the kidneys of male and female mice and in the adrenal glands of female mice in the high exposure groups. Exposure of rats and mice to lower IL concentrations (less than 3 mg/mL) had minimal effects. Exposure to higher IL concentrations (up to 3 mg/mL) had relatively few effects on rats; however, rats exposed to Bmpy-Cl and NBuPy-Cl and mice exposed to high concentrations of all four ILs experienced lower body weights.*