ADME NTP Study S0930 Ionic liquid (1-Butyl-3-methylimidazolium chloride) Toxicokinetics

The contractor used the abbreviation Bmim-Cl for the test article.
Sex/Species: male F344 rats.
Vehicle: intravenous, saline; oral, saline.

CASRN 79917-90-1, IONICLIQUIDS

Radiolabeled with carbon-14 on the α-carbon of the butyl side chain; N-[1-^{14}C]Butyl-3-methylimidazolium chloride

Studies Performed:

- Single 5 mg/kg intravenous dose with blood sampling 0.125, 0.25, 0.5, 0.75, 1, 1.5, 3, 6, 9, 12, 24, and 36 hours postdose. (n=4)

- Single 50 mg/kg oral gavage dose with blood sampling 0.125, 0.25, 0.5, 0.75, 1, 1.5, 3, 6, 9, 12, 24, and 36 hours postdose. (n=4)

Mean ± standard deviation values for total [^{14}C]Bmim-Cl in blood for the concentration-time curves were displayed in figures for intravenous and oral gavage dosed male rats and are not shown here. No individual animal data for toxicokinetic blood concentrations were available. Blood was collected from jugular vein cannulated animals.

Toxicokinetics:

Concentration-time curves for total [^{14}C]Bmim-Cl in whole blood were modeled assuming first-order kinetics using the WinNonlin program (WinNonlin, Pharsight Corp., Mountain View, CA). Only samples containing quantities of compound above the limit of quantification were used in toxicokinetic analysis; thus, blood data for time points after 6 hours were not used.

The best fit analysis for the single intravenous dose was a two-compartment model. The best fit analyses for the single oral gavage dose used a one-compartment model fit. The absolute oral bioavailability (F) for the single oral gavage dose was calculated using the $[AUC]_{oral}/[AUC]_{IV}$ ratio ($[AUC]_{oral}$: 733.3, $[AUC]_{IV}$ 141.3 μg*min/mL) and adjusted for dose ($dose_{oral}$: 8,756 ± 70 μg/animal, $dose_{IV}$: 1,047 ± 14 μg/animal). F was determined to be 67.1% based on total [^{14}C]Bmim-Cl in whole blood.

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Table 1

Kinetic parameters for Bmim-Cl following IV administration (5 mg/kg, 50 µCi/kg) in male F-344 rats (N=4, mean ± S.D.) based on a best-fit-analyses using a two-compartment model fit (WinNonLin, Pharsight). Kinetic parameters were calculated using concentrations of [^{14}C] Bmim-Cl, as determined byiii HPLC-radiometric analysis.

Dose (µg)	AUC (min*µg/mL)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	CL_b (mL/min)	V_{ss} (mL)
1047.0	141.3	13.0	85.4	7.4	618.2

AUC: area under the blood concentration-time curve from 0 to infinity. $t_{1/2\alpha}$: distribution half life. $t_{1/2\beta}$: initial elimination half life. $t_{1/2\gamma}$: terminal elimination half life. CL_b: systemic clearance from blood. V_{ss}: volume of distribution at steady-state. MRT: mean residence time.

Table 2

Kinetic parameters for Bmim-Cl following oral administration (50 mg/kg, 100 µCi/kg) in male F-344 rats (N=4, mean ± S.D.) based on a best-fit-analyses usingia one-compartment model fit (WinNonLin, Pharsight). Kinetic parameters were calculated using concentrations ofiBmim-Cl, as determined by HPLC-radiometric analysis.

Dose (µg)	AUC (min*µg/mL)	$t_{1/2\beta}$ (min)	CL_b (mL/min)	C_{max} (µg/mL)	T_{max} (min)
8756.0	733.3	77.2	11.9	3.6	67.0

AUC: area under the blood concentration-time curve from 0 to infinity. $t_{1/2\beta}$: half life of elimination. CL_b: systemic clearance from blood. C_{max}: maximum blood concentration. T_{max}: time required to reach maximum blood concentration of Bmim-Cl. *F*: systemic bioavailability.