

Introduction

A leachables simulation study is a study designed to bridge between materials characterization extractables studies and leachables stability (migration) studies using drug product. Leachables migration studies are performed to assess realistic leachables which occur under true storage or conditions of use. A simulation study can be used with the primary goal of establishing "Likely" or "Probable" leachables. A secondary goal can be to help focus analytical methodology based on the results of predictive studies.

This presentation details the results of a leachables simulation and migration study performed on a simulated PODP drug products.

Experimental

The migration study was performed using the following solvents and conditions:

- Extracting solvents; pH 2.5, pH 9.5, 1/1 (v/v) IPA/water.
- Extraction Temperature; 40°C
- Storage Intervals; 1, 2 and 6 months
- "Normal" configuration; bottle with label, stored upright.
- "Exaggerated" configuration; bottle with label, stored inverted.

Test System consisted of

- Low Density Polyethylene Bottle (100 mL nominal fill volume)
- Polypropylene Cap
- Adhesive label
- Rubber gasket

Bottles were filled with extracting solvent (100 mL), sealed with gasket/caps, labeled, incubated and extracted for the proposed time intervals. After extraction, solvent was removed for analytical testing.



Picture of Test Article Prior to Filling

Samples were spiked with target leachable compounds to ensure species would be detectable. The following compounds were employed:

Compound	CAS	MW	Supplier
Methyl ethyl ketone (MEK)	78-93-3	72.1	Fluka
Irgacure 1173	7473-98-5	164.2	Sigma-Aldrich
Benzophenone	119-61-9	182.2	Sigma-Aldrich
Dipropylene glycol diacrylate (DGPTA)	57472-68-1	242.3	TCI Chemicals

Final spiking level in extract solution = 1.25 µg/mL for each

Additional Test Article Details			
Material Type	Material Application	Material Format	Description
Low density polyethylene (LDPE)	Bottle/ Vial	Bottle	4 oz LDPE, part B347A (Container & Packaging Supply)
Polypropylene (PP)	Cap	Cap	PP, Part L764 (Container & Packaging Supply)
Adhesive Label	Label on Container Surface	Label Sheets	Substrate: Unknown Adhesive: Acrylic polymer(s), residual monomers, water, ammonia (99.55%); wetting agent; Surfynol 336, at 0.4% containing CAS 577-11-7 (<25%), CAS 9014-95-1 (<25%), Biocide, Katon LX, at 0.05% containing Chloro-2-methyl-4-isothiazolin-3-one (CAS 26172-55-4), 1,1,1,4,4-tetrahydro-2-methyl-4-isothiazolin-3-one (CAS 2682-20-4), 0.3 - 0.5%, Magnesium Chloride (CAS 7786-30-3), 1.0 - 1.2%, Magnesium nitrate (CAS 10377-69-3), 1.4 - 2.0% Copper nitrate (CAS 3251-23-8) 1,500 - 1,700 ppm, Water, 95 - 97% Printing Ink: Irgacure 369 (CAS 119313-12-1) and Irgacure 1173 (CAS 7473-98-5), photoinitiators; Trimethylolpropane triacrylate (TMPTA, CAS 15625-89-5), Tripropylene glycol diacrylate (TPGDA, CAS 42978-66-5), Glycerol propoxy triacrylate (GPTA, CAS 52408-84-1), monomers, HQME/Mequinox (CAS 150-76-5), stabilizer; Carbon black (CAS 1333-86-4), Pthalato blue (CAS 147-14-8), Carbazole violet (CAS 215247-95-3), pigments Varnish: Unknown
Rubber (Elastomer)	Closures	Gasket/liner	Brominated isobutylene isoprene copolymer (57.3%); calcined aluminum silicate, 38.2%; titanium dioxide, 1.2%; paraffinic oil, 1.2%; zinc oxide, 0.6%; polyethylene, 0.6%; SRF Carbon black mixture, 0.4%; calcined magnesium oxide, 0.3%; 4,4'-dithiodi-morpholine/polyisobutylene, 0.3%

For analysis on GC-MS, each sample was liquid-liquid extracted with an equivalent volume of methylene chloride and the organic layer analyzed directly. For ICP-MS IPA was evaporated prior to analysis. LC-MS samples were analyzed directly.

Results

Figure Set 1

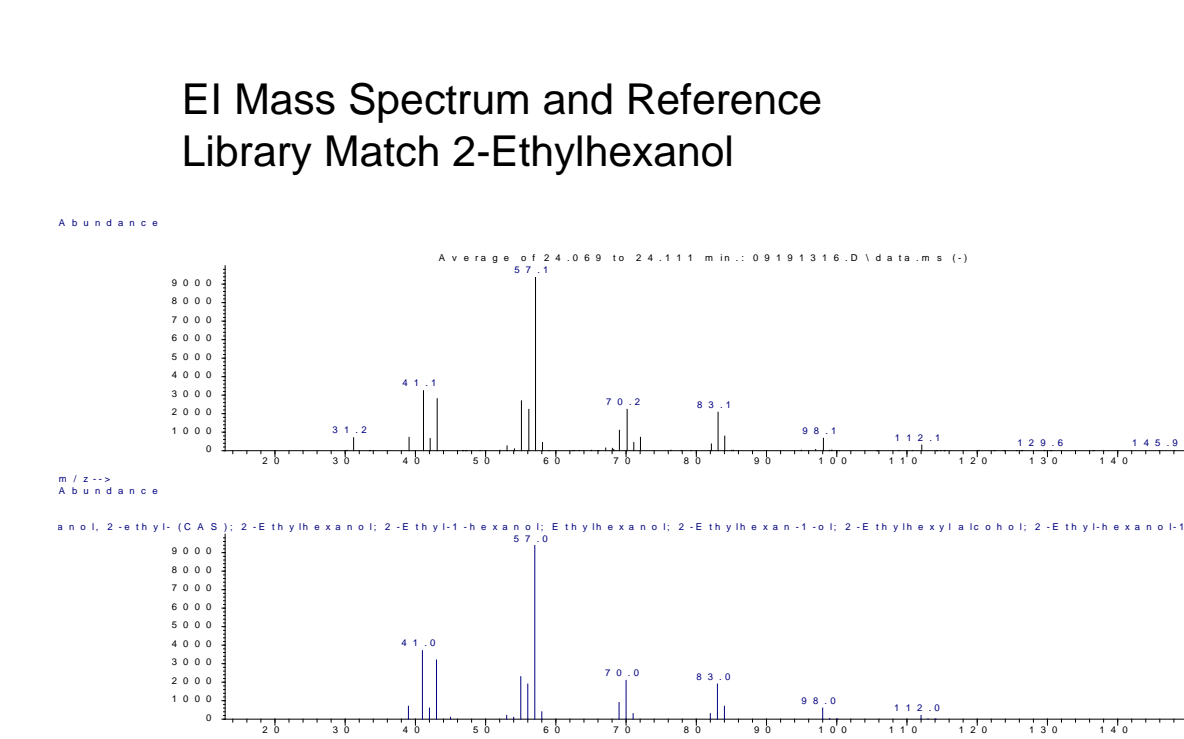
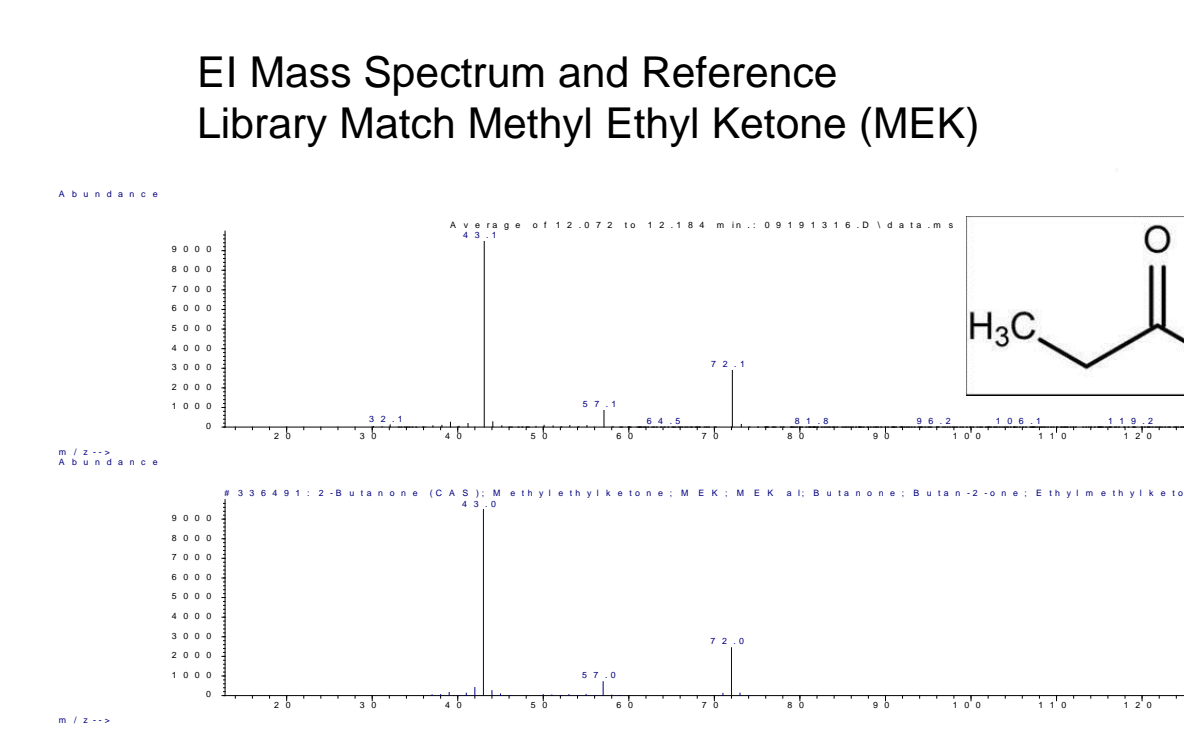
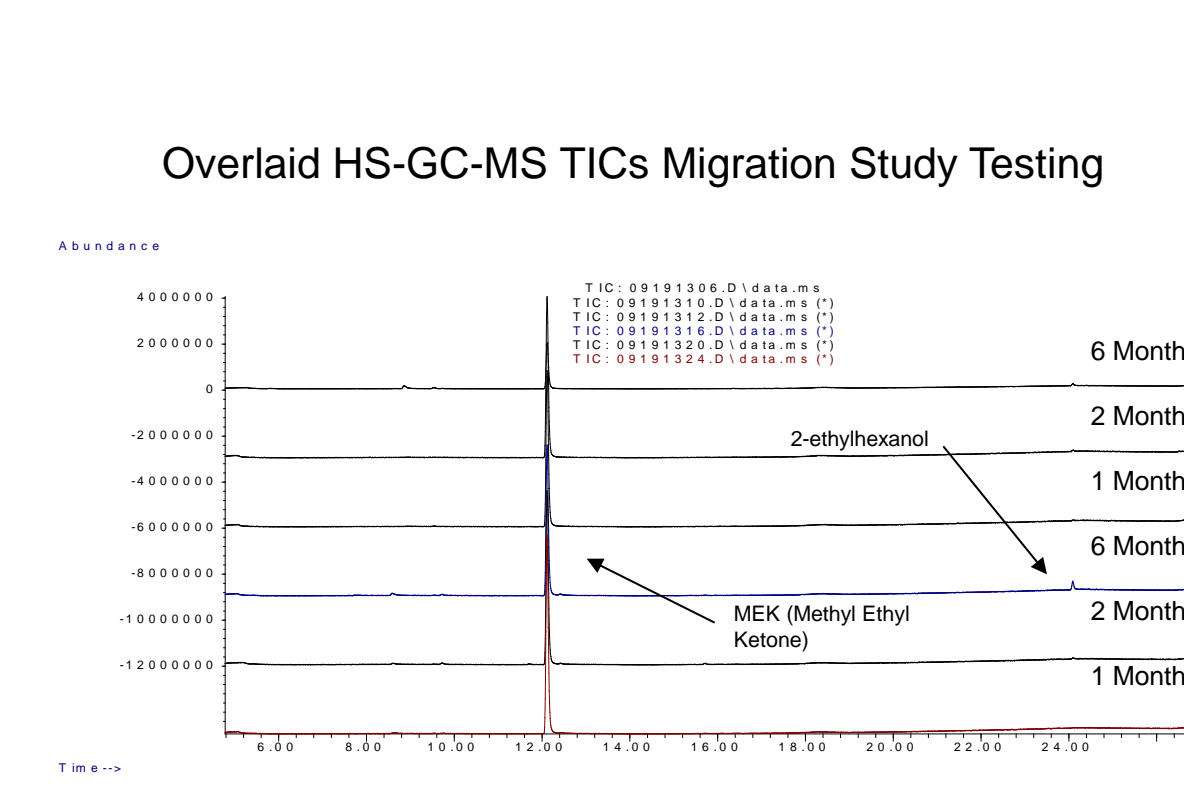


Figure Set 2

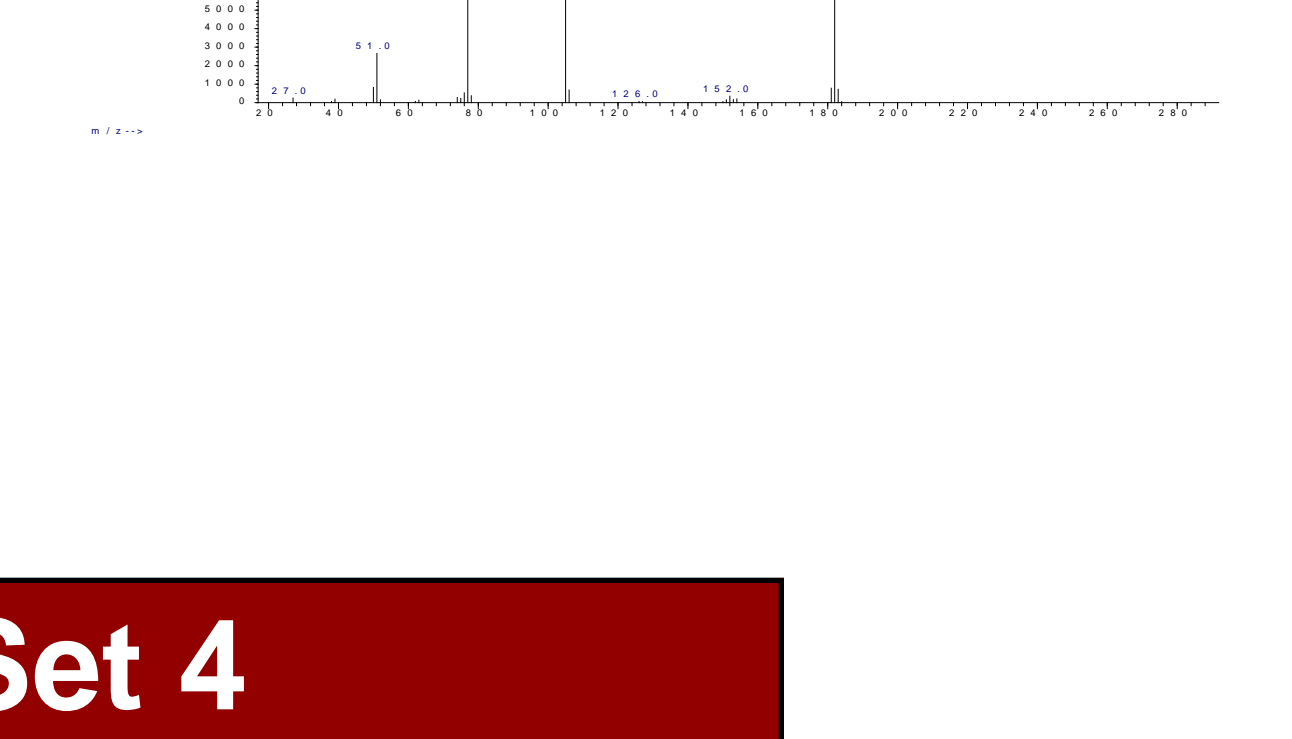
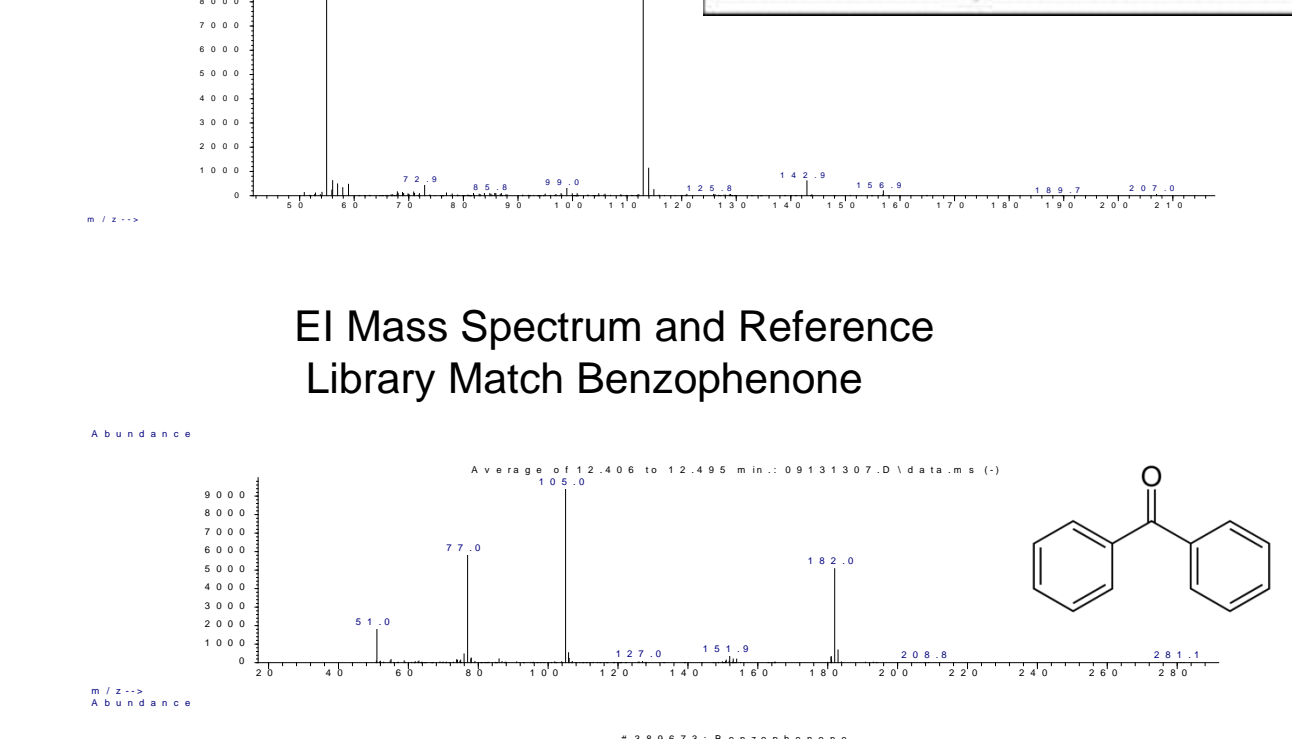
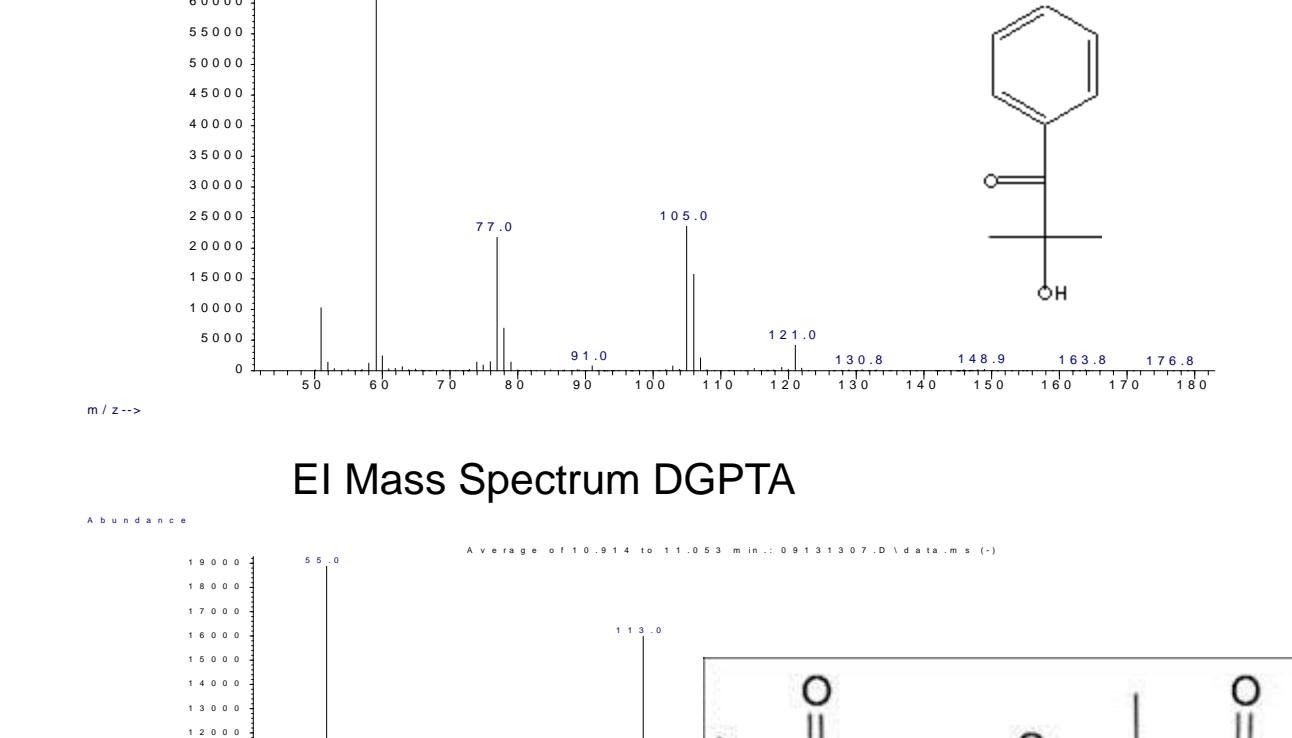
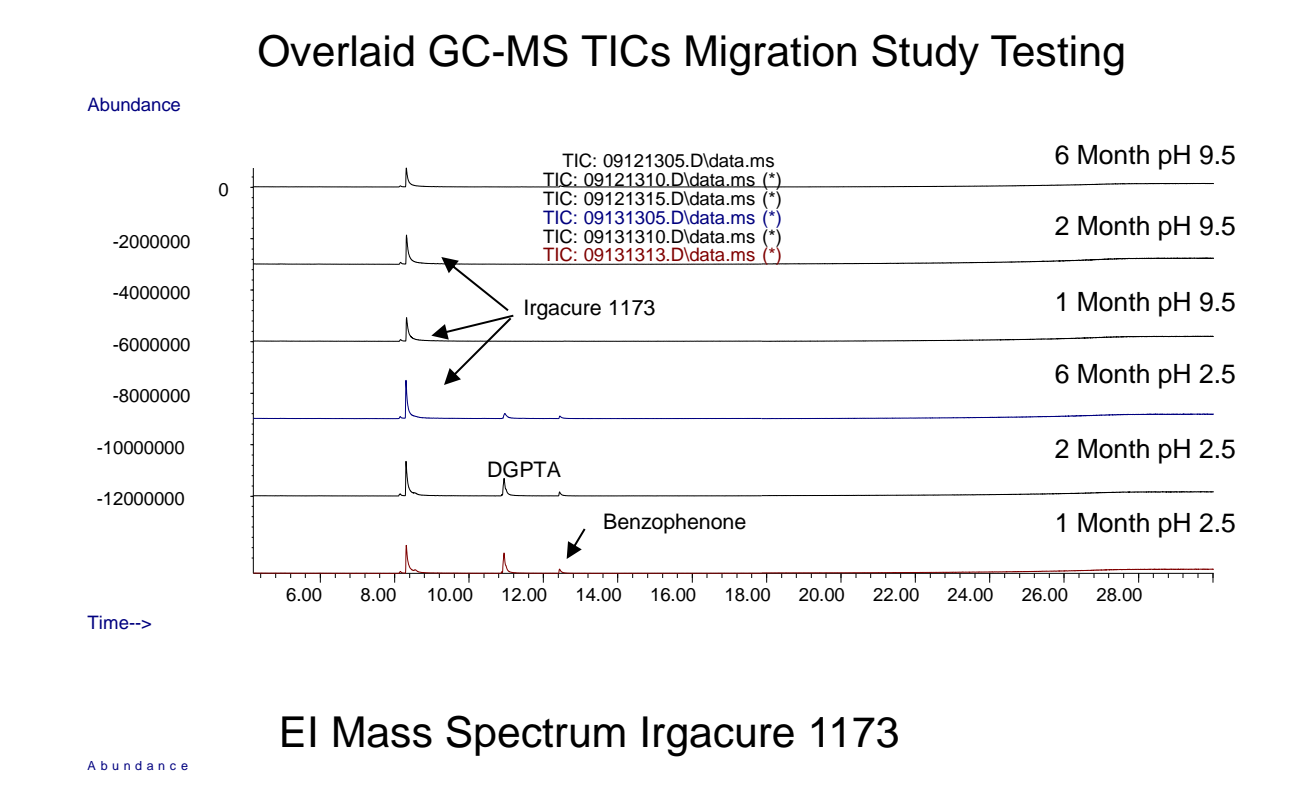


Figure Set 3

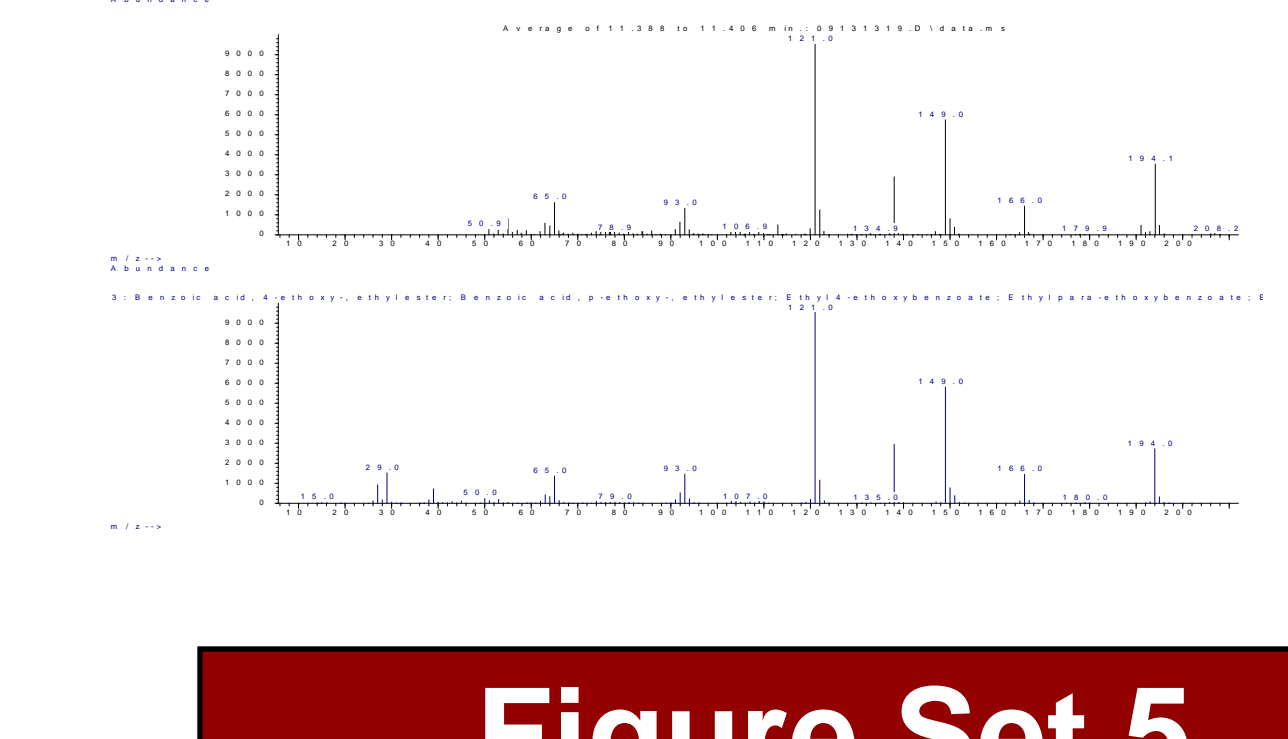
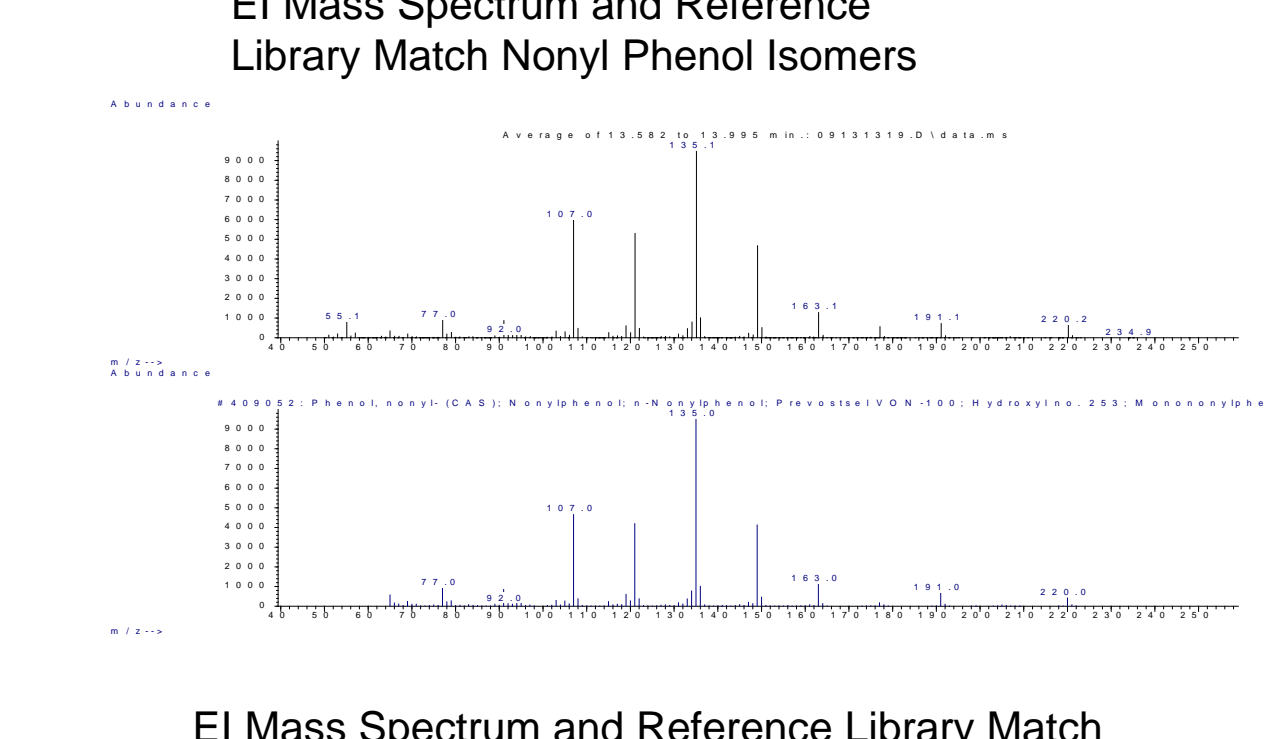
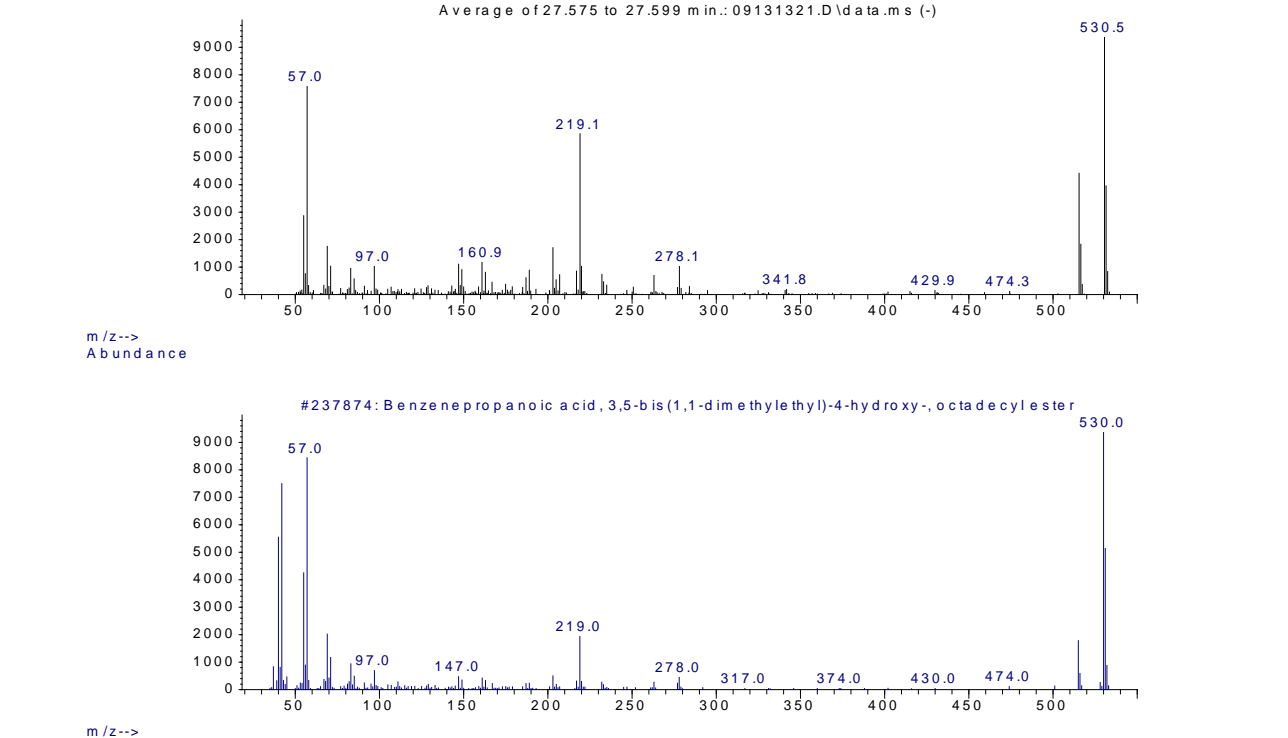
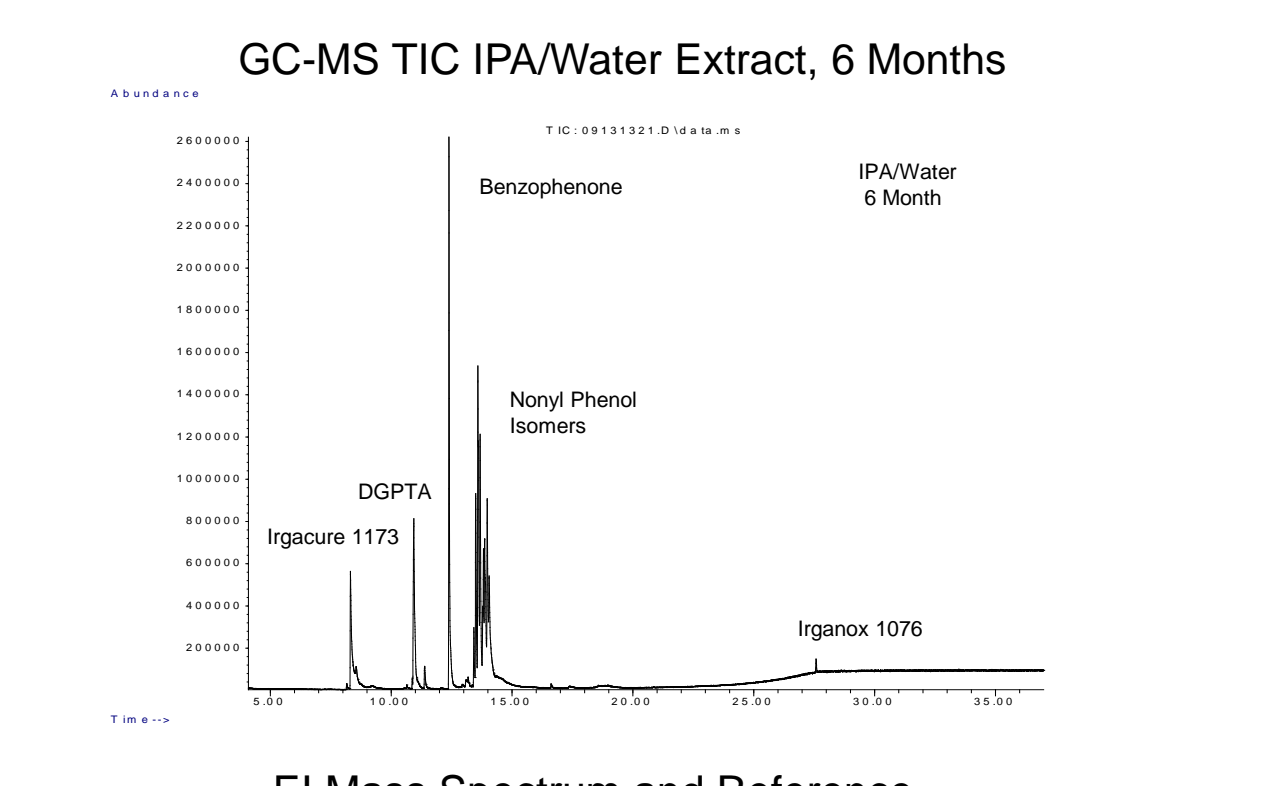


Figure Set 4

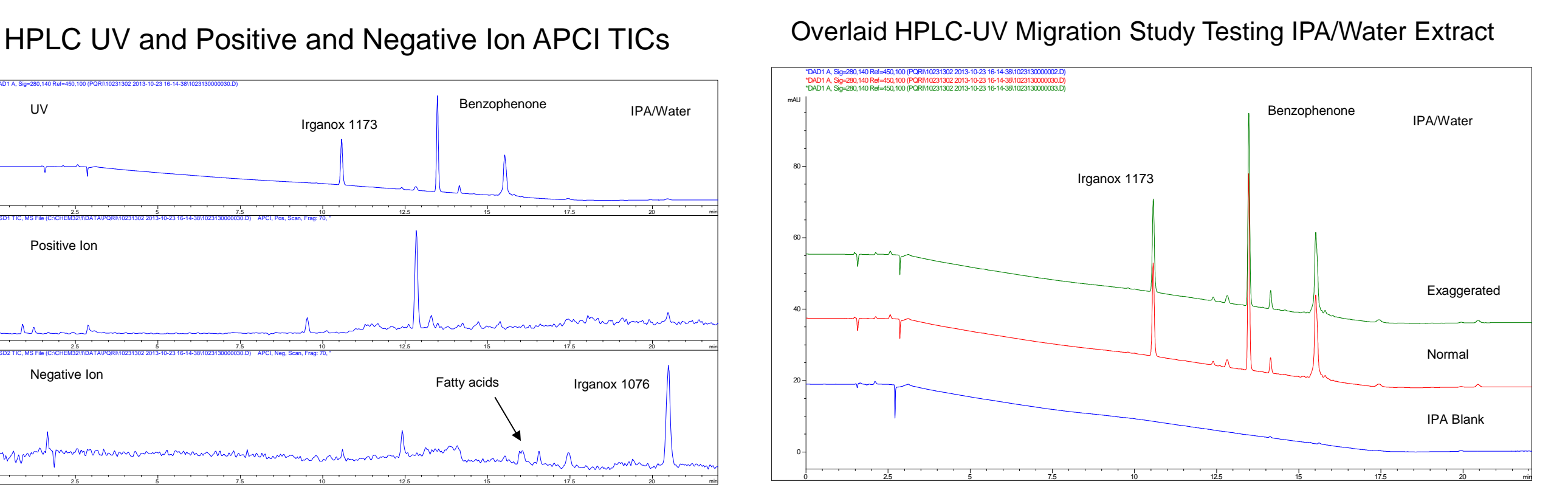
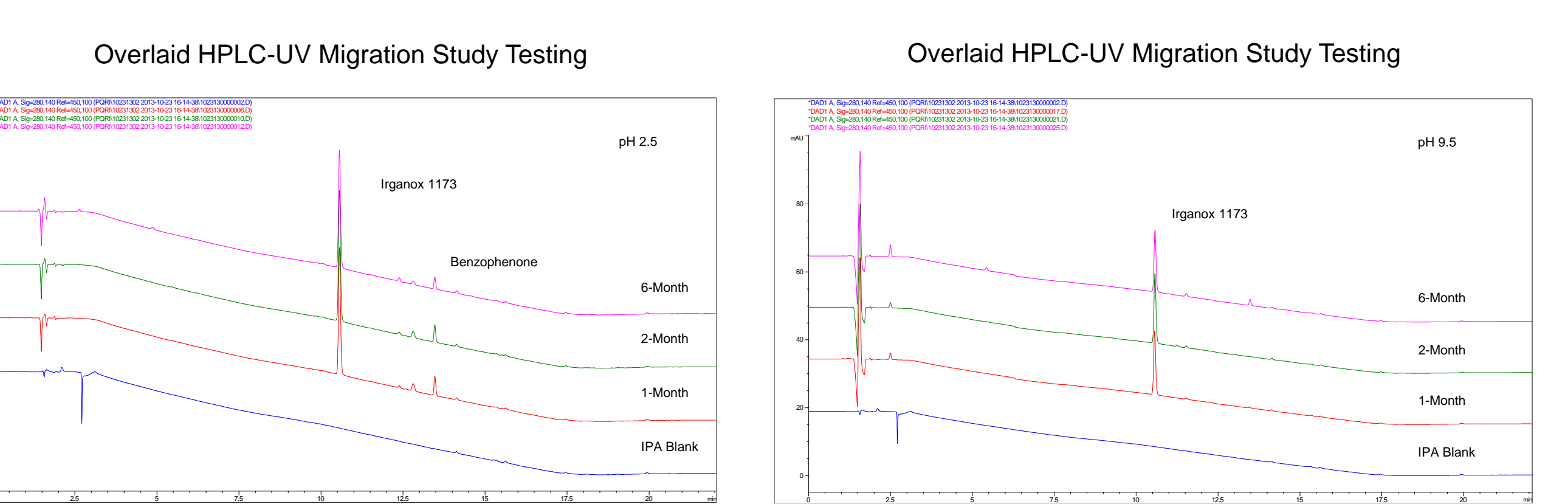


Figure Set 5

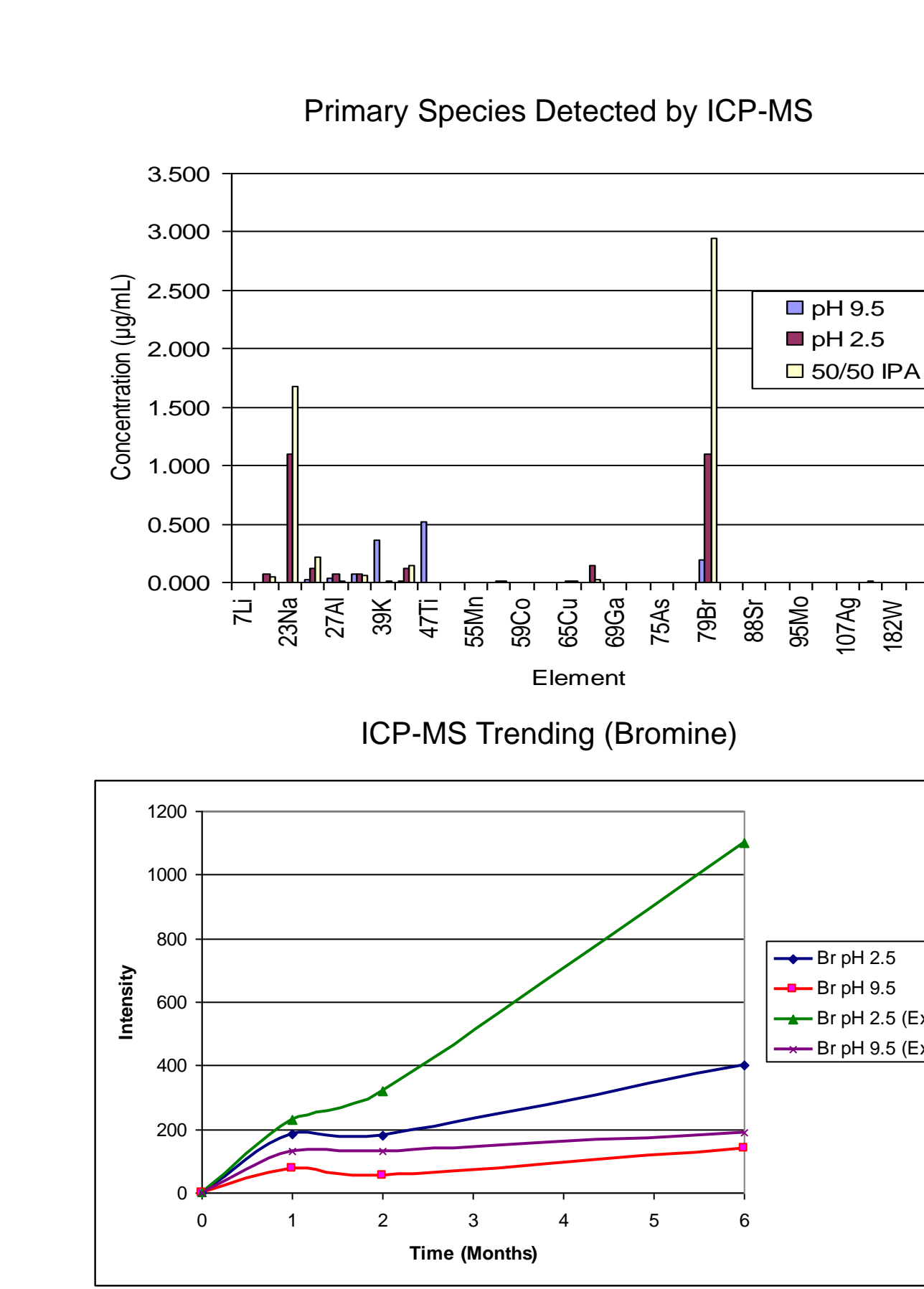
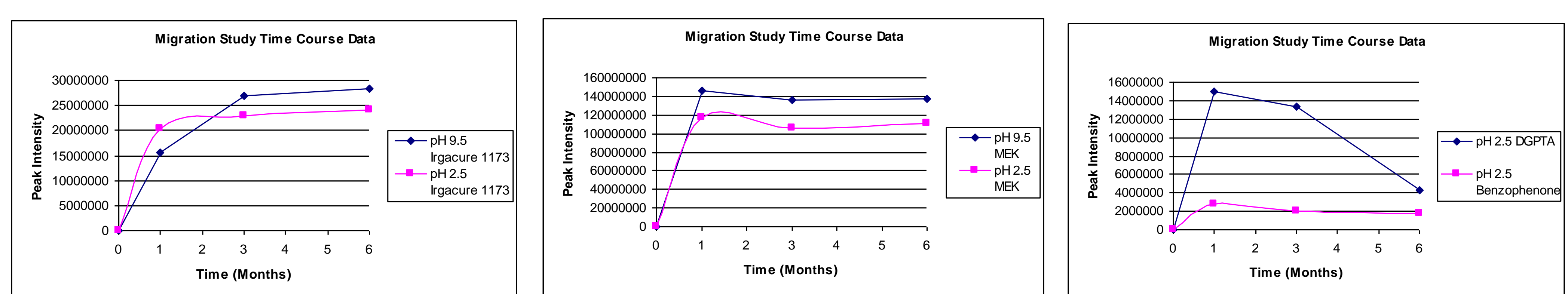


Figure Set 6



Instrumental Methods

Headspace GC-MS

Headspace: Leap Technologies CombiPAL
 GC-MS: Agilent 6890/5973
 Injection Mode: Split
 Injector Temperature: 240 °C
 Column: Restek Rtx-624, 50 m x 0.32 mm ID, 1.8 µm film thickness
 Split Flow: 5.0 mL/min
 Split Ratio: 5:1
 Oven Temperature: 35 °C for 5 minutes, heat at 8°C/minute to 190 °C, hold at 190 °C for 2 minutes, heat at 25°C/minute to 240 °C, hold at 240 °C for 5 minutes
 Pressure Program: Constant flow (Helium) at 1.0 mL/minute
 Transfer Line Temp: 240 °C
 Ionization Mode: Electron Ionization
 Scan Mode: Scanning; m/z 30-650
 Incubation temp: 90 °C
 Incubation time: 60 minutes
 Injection volume: 1 mL
 Agitation on: 3 sec
 Agitation off: 2 sec
 Agitation speed: 500 rpm

ICP-MS

ICP-MS Agilent 5700A
 Forward Power 1300 watts
 Integration Time 0.1 seconds per point
 Rinse Time 180 seconds
 Rinse Rate 0.5 rps
 Uptake Time 45 seconds
 Uptake Rate 0.5 rps
 Stabilization Time 20 Seconds
 Analysis Pump Rate 0.1 rps
 All Other Settings Determined by Tune
 The following metals/elements were tested as part of the ICP-MS analysis: Li, Be, B, Na, Mg, Al, Si, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, As, Se, Br, Rb, Sr, Y, Zr, Nb, Mo, Ru, Rh, Pd, Ag, Cd, In, Sn, Sb, Te, I, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Th, and U

HPLC-DAD-MS

LC/UV/MS Agilent Model 1260/6130 Liquid Chromatograph/Mass Spectrometer with 1260 DAD
 Column: Agilent Zorbax SB-C3, 4.6 x 150mm, 5µm particles
 Column Temp.: 35 °C
 Injection Volume: 10 µL
 Flow Rate: 1.0 mL/min
 Mobile Phase A: 10 mM Ammonium acetate
 Mobile Phase B: 100% Methanol
 Gradient Program:

Time (min.)	%A	%B
0.00	95	5
15.00	5	95
20.00	5	95
20.10	95	5
25.00	95	5

 Stop Time: 25 min.
 Signal = 280nm, Bandwidth = 140nm, Reference = 450nm, Bandwidth = 100nm
 DAD Detector: 205-400nm with Step of 2nm
 Range: Positive and Negative Ion
 Ionization Mode: Atmospheric Pressure Chemical Ionization (APCI)
 Polarity: Positive and Negative Ion
 Mass Range: m/z 100-1350

GC-MS (Direct Inject)

GC-MS Agilent 6890/5973
 Injection Mode: Splitless
 Injection Volume: 1.00 µL
 Injector Temperature: 280 °C
 Column: Restek Rtx-1 30 m x 0.25 mm ID x 0.1 µm film thickness
 Oven Temperature: 40 °C for 1 minute, heat at 10 °C/minute to 300 °C, hold at 300 °C for 10 minutes
 Flow Program: Constant flow (Helium) at 1.00 mL/minute
 Purge Flow: 60.0 mL/minute, on at 1.00 minutes
 Transfer Line: 280 °C
 Ionization Mode: Electron Ionization
 Scan Mode: Scanning; m/z 50-650
 MS Quad Temp: 150 °C
 MS Source Temp: 230 °C

Discussion

Figure set 1 shows the results of the headspace GC-MS testing of the sample solutions. The base peak was attributed to MEK which was spiked in the sample. This indicated that even volatile spiked species survived after 6 months incubation in the test system. Only one other trace level peak was observed attributed to 2-ethylhexanol, a plasticizer precursor.

Figure set 2 shows the results of the GC-MS testing of the aqueous extract sample solutions. The three spiked species were observed to varying degrees in the extract with the Irgacure 1173 being the most prominent. The acidic extracts appeared to retain the spikes better over time, though showed decrease to near zero in some cases.

Figure set 3 shows the IPA/Water extract results for the GC-MS testing and demonstrated the greatest number of leached species, including some which were known additives, such as nonyl phenols (multiple isomers), ethyl-4-ethoxybenzoate and Irganox 1076.

Figure set 4 shows the results of the HPLC-DAD-MS testing of the samples solutions. The profiles were relatively clean, though the spiked species were again observed. When explored, the total ion chromatograms (TICs) revealed species attributed to fatty acids, Irganox 1076 and trace level unknowns. The spiked species or the other leachables detected by GC-MS were the primary species observed in the UV and TICs.

Figure set 5 lists some of the results obtained for the ICP-MS analysis. Most elemental species were not detected (as expected). One observed prominently was Bromine, originating from the bromobutyl rubber in the elastomer. It increased over time and was most prominent in the inverted (exaggerated) condition. Acidic extraction solubilized more species than basic.

Figure set 6 summarizes additional trending noted during testing. Different phenomena are occurring during the course of the migration study, including species which increased over time such as Irgacure 1173 (or as previously mentioned Bromine). The MEK changed little over time. And The DGPTA and Benzophenone decreased slightly over the course of the six months, through degradation or other loss.

Conclusions

A six month migration study was conducted to demonstrate the utility of simulation studies over time to predict leached species based on materials extractables knowledge gleaned through controlled extraction studies. The results showed accumulation of few leachables, but good correlation where leachables did occur as well as good retention of spiked species. Some trending data was of value. The aggressive extraction solvent of IPA/Water showed the greatest number and largest accumulation of leached species.

Acknowledgments

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