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Low Level Analysis of Extractable and Leachable Phthalates and Nitrosamine from Consumer Packaging Materials; from One Injection

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Introduction

Consumer safety is a broad description of the science that protects humans from harmful chemicals that may be found in everything from drinking water to seafood to pharmaceuticals. In some cases, contact of the product with polymeric containers, storage or drug delivery systems can be the source of these chemicals. The complex nature of polymeric products and their increased use with in pharmaceutical and food manufacturing has led to increased screening of known leachable additives[1] and breakdown products such as bisphenols, phthalates and nitrosamines (dye breakdown products) at low levels. Here we describe a method that provides the low picogram level analysis of these compounds in one GC/MS injection.

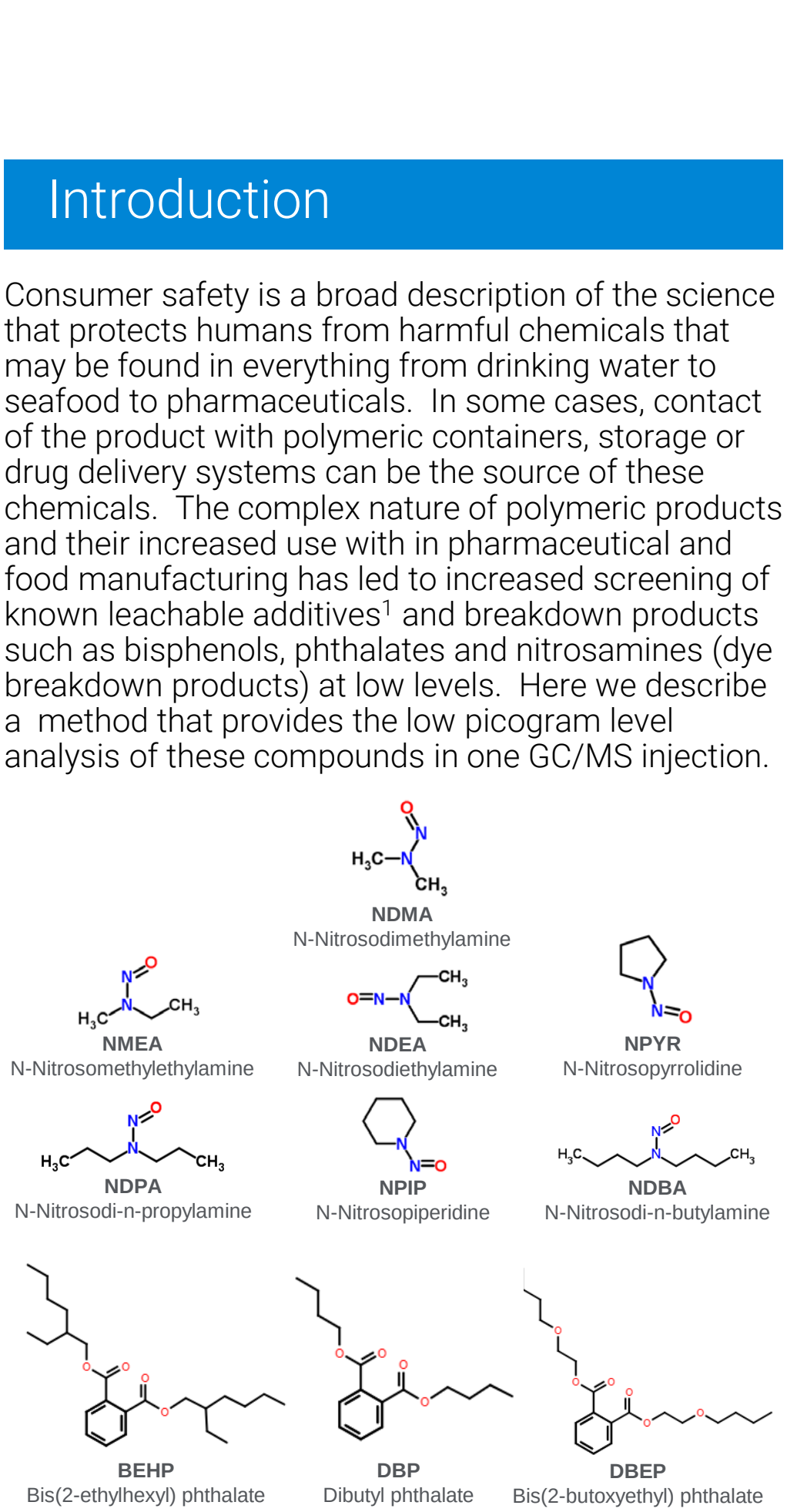

Figure 1: Nitrosamine and phthalate compounds analyzed in this work.

Figure 2: Agilent 7010B GC/QQQ

Experimental

Sample Preparation:

Note: contact with plastic and rubber gaskets was minimized during sample preparation and sample injection. Glass microdispensers were used, and the plastic seals normally found on autosampler wash vials were replaced with aluminum foil.

Standard analyte mixtures for the nitrosamines and phthalates were purchased from Accustandard (New Haven, CT). Internal standards Bis(2-ethylhexyl)-d4 phthalate, Di-iso-butyl phthalate-d4, and N-nitrosodi-n-propylamine-d14 were used for quantitation. Stock analyte solutions were made to 400 pg μL^{-1} concentration in dichloromethane, then were sequentially diluted 1:2. ISTDs were spiked at 25 pg μL^{-1}.

Sample extracts were created from black rubber syringe plungers. 0.5 g of plunger material was placed into a vial with one of three different extraction solvents: 100% DCM, 100% isopropyl alcohol, or 1:1 H_2O/EtOH. After 30 minutes at room temperature, the extracts were transferred to glass 200 µL vial inserts for 2 mL GC autosampler vials.

GC/MS Configuration:

The purged ultimate union was connected to the center of the 30 m DB-1701 column to perform post-acquisition backflush. This increased throughput by eliminating the long bake-out usually needed with a thick-film column. Backflush ran for 2.5 min, equivalent to 12 void volumes.

Table 1: Agilent 7010B; 7890B GC Parameters

GC and MS Conditions:		
Column	DB-1701, 30 m, 0.25 mm ID, 1 µm film; cut in half for backflush	
Injection	Cold-Splitless 1µL	2mm Dimpled UI
MMI Inlet	35 °C for 0.05 min, then 600 °C to 300 °C	
Oven temperature program	45 °C for 1 min	
	25 °C/min to 120 °C	
	45 °C/min to 255 °C hold for 8 min	
	30 °C/min to 295 °C hold for 8.7 min	
Carrier gas	Column 1 flow; 1 mL min^{-1} Column 2 flow; 1.6 mL min^{-1}	
Transfer line temperature	290 °C	
Source temperature	275°C	
Quadrupole temperatures	150°C	
MS Acquisition	Dynamic MRM	

Results and Discussion

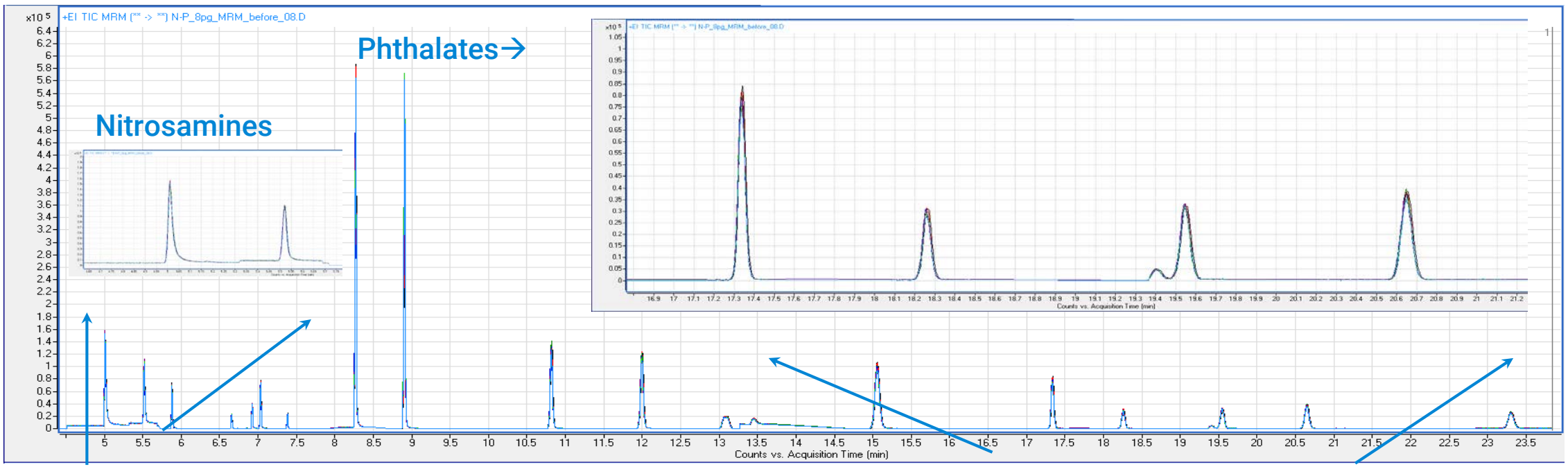

Figure 3: 8 replicate injections of 8 pg on-column overlaid to show injection and detection precision.

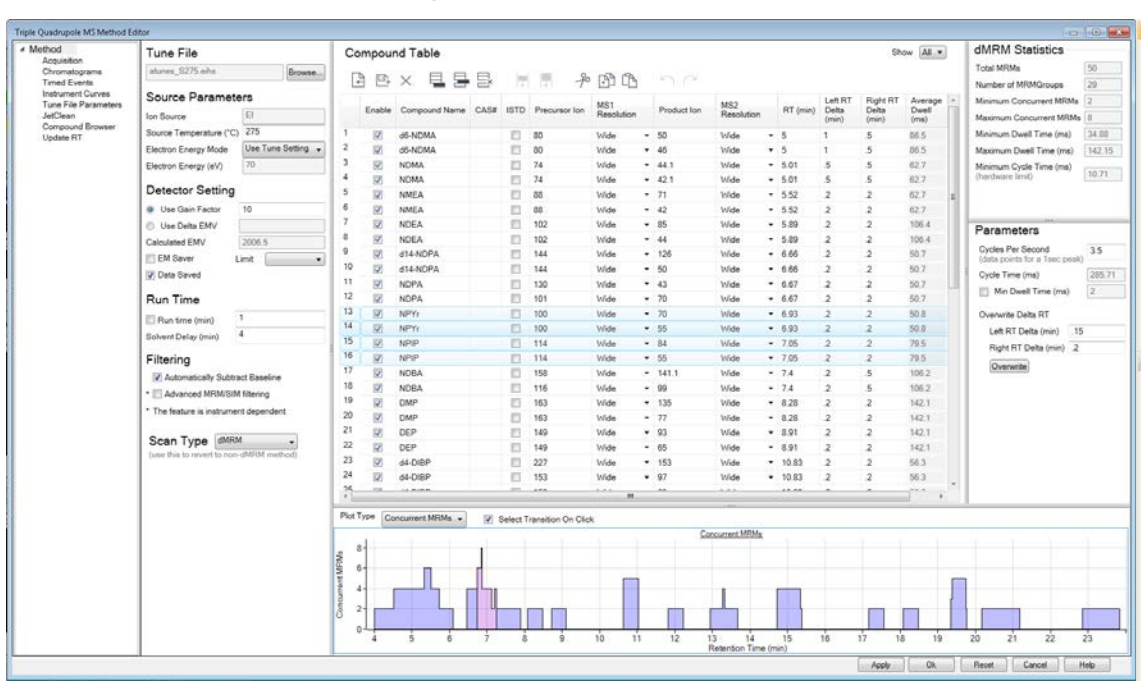

Figure 4: dMRM acquisition allowed for quick method development, and optimal dwell times were automatically determined by the software.

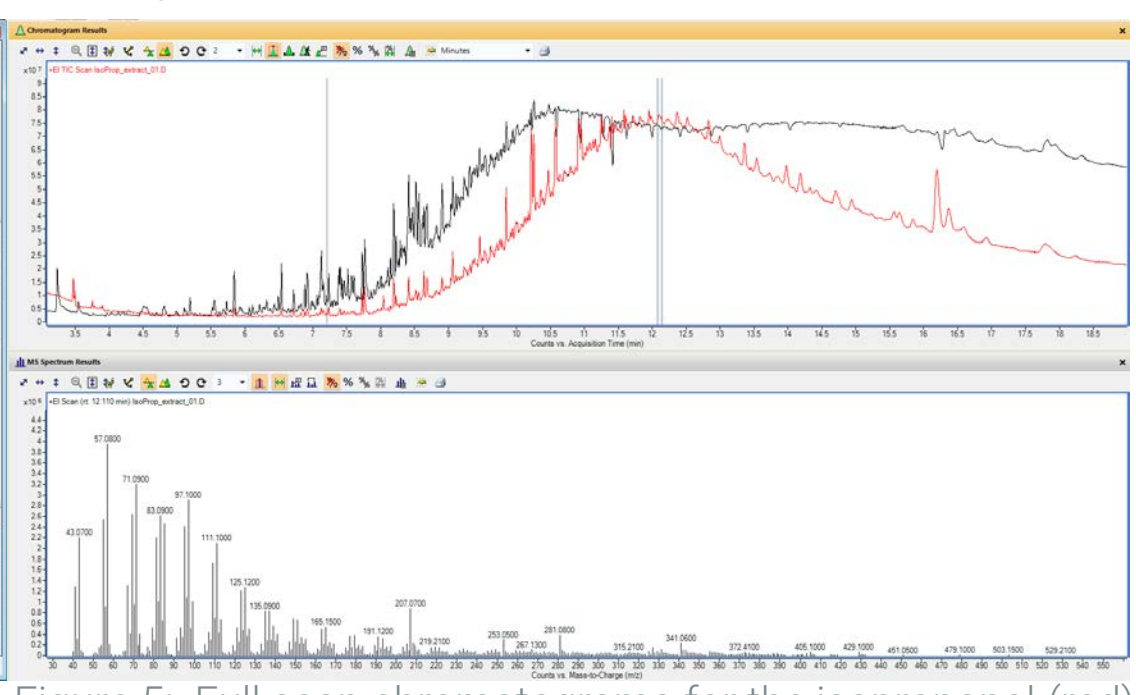

Figure 5: Full scan chromatograms for the isopropanol (red) and DCM (black) extracts illustrating the need for the selectivity of MS/MS, and backflush to clean the column.

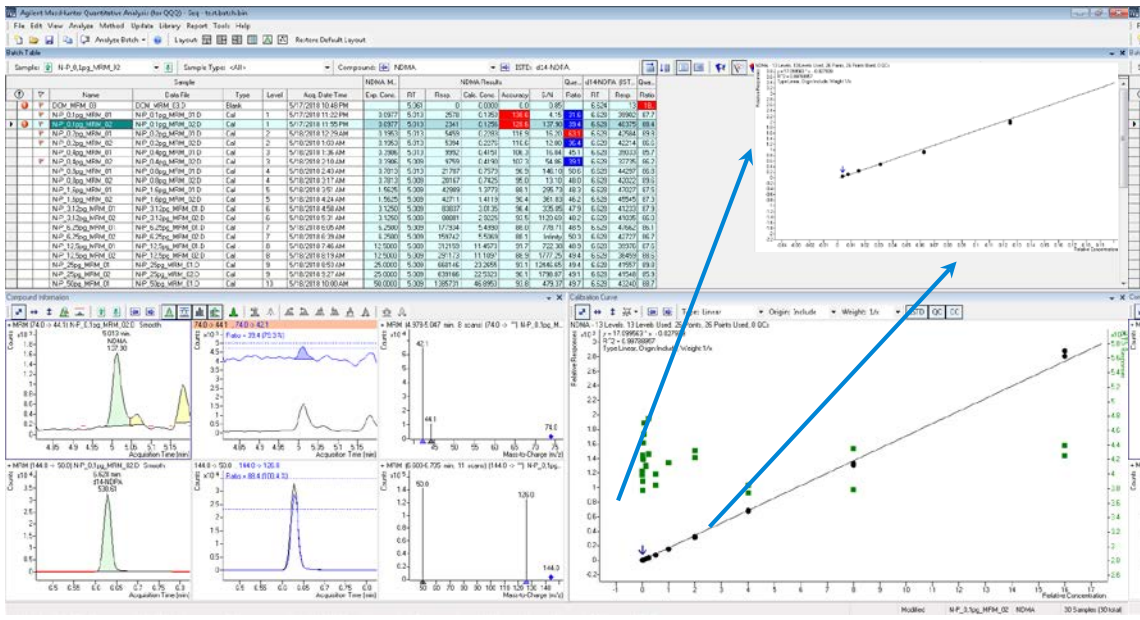

Figure 6: Quantitation data for NDMA. The chromatographic peaks are from the 0.1 pg standard, and the calibration curve is from 0.1 pg μL^{-1} to 200 pg μL^{-1}. Green squares are the ISTD responses.

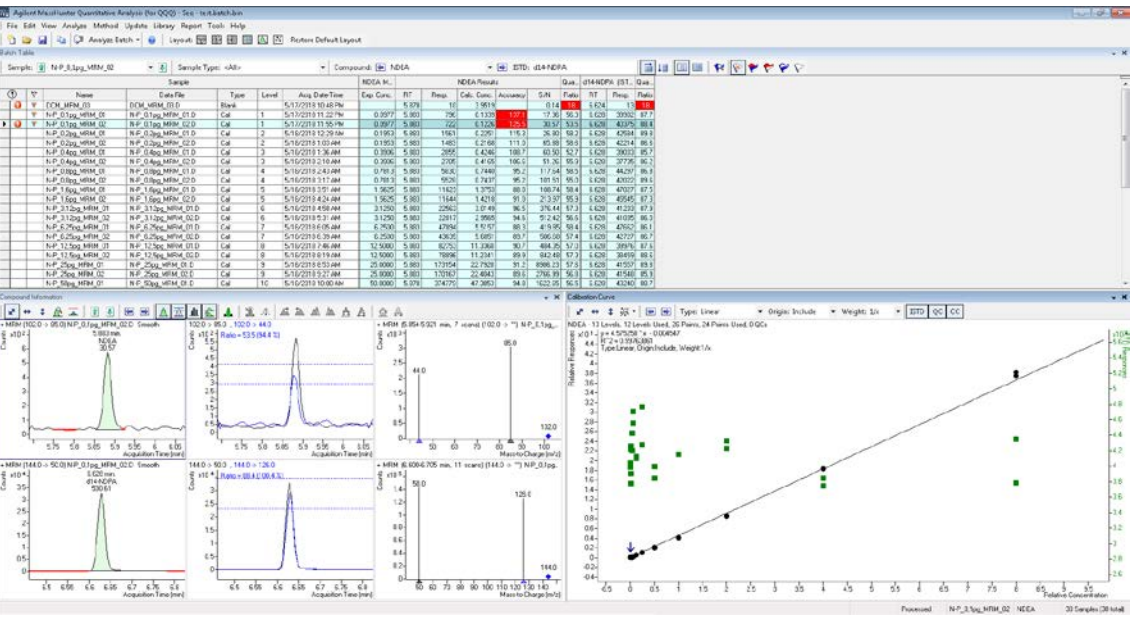

Figure 7: Quantitation data for NDEA. The chromatographic peaks are from the 0.1 pg standard, and the calibration curve is from 0.1 pg μL^{-1} to 200 pg μL^{-1}. Green squares are the ISTD responses.

Results and Discussion

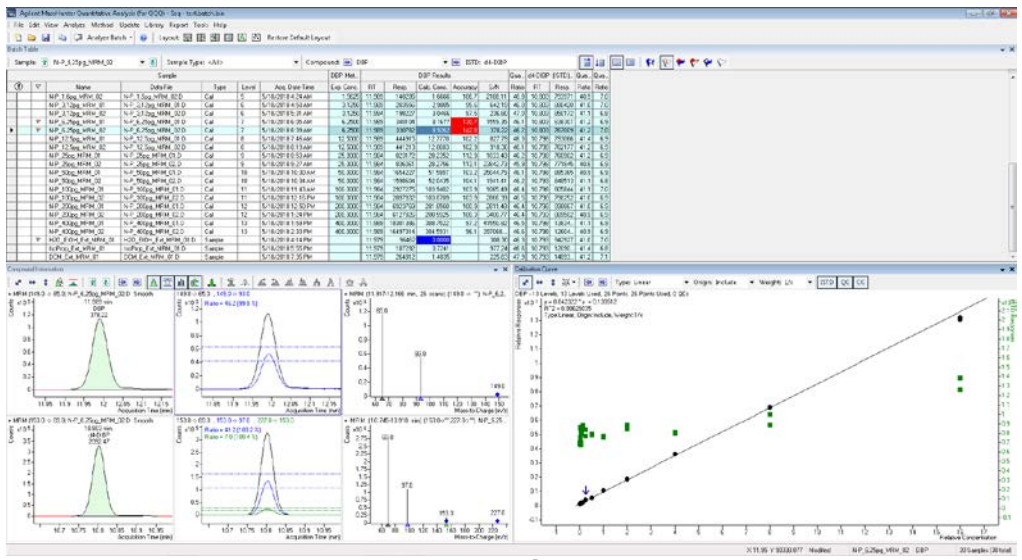

Figure 8: Quantitation data for Dibenzyl phthalate. The chromatographic peaks are from the 6.25 pg standard, and the calibration curve is from 0.1 pg μL^{-1} to 200 pg μL^{-1}. Green squares are the ISTD responses.

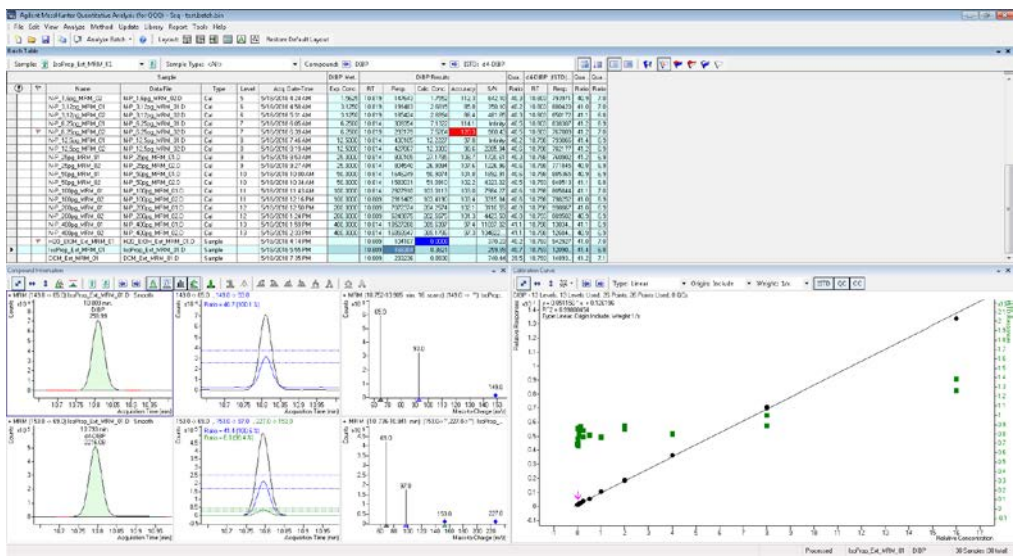

Figure 9: Quantitation data for Dibenzyl phthalate from the isopropanol extract. The calculated concentration is 0.38 pg μL^{-1}. Green squares are the ISTD responses.

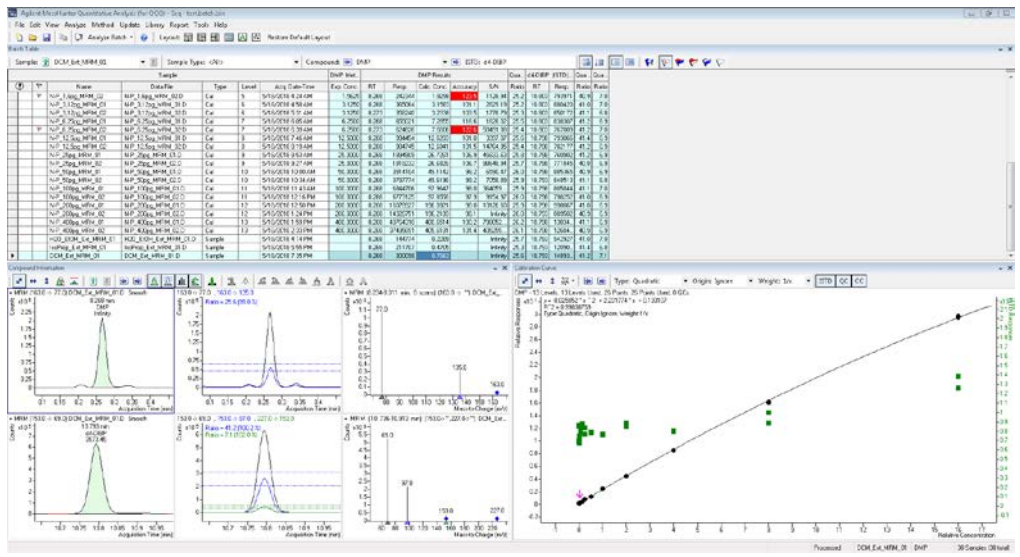

Figure 10: Quantitation data for Dimethyl phthalate from the isopropanol extract. The calculated concentration is 0.76 pg μL^{-1}. Green squares are the ISTD responses.

Table 2: 8 replicate injections of 8 pg μL^{-1} to illustrate RSDs.

Name	RT	Transition	Noise	S/N	Avg Height	Avg. Resp	Resp. RSD
NDMA	5.004	74.0 -> 44.1	212.69	Infinity	82322	160013	1.7
NMEA	5.519	88.0 -> 71.0	176.12	426.94	44138	75893	2
NDEA	5.878	102.0 -> 85.0	59.96	1002.65	34352	46272	1.5
NDPA	6.661	101.0 -> 70.0	57.22	212.31	8162	10227	2.4
NPYr	6.923	100.0 -> 55.0	66.12	330.25	18438	24799	1.7
NPIP	7.035	114.0 -> 84.0	47.05	939.85	34302	44213	2.2
NDBA	7.382	116.0 -> 99.0	26.43	Infinity	15614	19850	2.3
DMP	8.268	163.0 -> 77.0	194.97	2865.2	368176	548958	1.7
DIBP	10.814	149.0 -> 65.0	123.69	1251.05	88388	209221	4.4
DBP	11.984	149.0 -> 65.0	73.66	1544.55	76750	224700	4.2
Bis4MPP	13.057	149.0 -> 65.0	89.63	131.24	10144	60351	3.5
Bis2MoxyEP	13.437	104.0 -> 76.0	495.12	13.62	5144	22326	3.7
Bis2EoxyEP	15.044	149.0 -> 65.0	200.39	369.06	65732	295589	4.2
DHP	17.325	149.0 -> 65.0	87.07	831.13	50620	136551	4.5
BBP	18.248	149.0 -> 65.0	74.3	348.3	19512	60487	4.5
Bis2EHP	19.533	149.0 -> 65.0	145.43	Infinity	18779	67169	3.3
DCycHP	20.631	149.0 -> 65.0	93.6	304.31	21365	85733	4.1
DoctylP	23.274	149.0 -> 65.0	173.63	248.3	16839	91033	3.2

Conclusions

The DB-1701 column was a reasonable starting column for this analysis with good retention of the nitrosamines and separation of the important phthalates.

- A thinner film, and possibly a different column phase could resolve a few of the phthalate coelutions and decrease the run time.
- Phthalates are a difficult analyte to quantitate at very low levels because of the prevalence of them in all areas of the lab. But some are less common, so the best estimate of the detection limit is based on Dicyclohexyl phthalate, at 100 fg μL^{-1}.
- As it happens, none of the nitrosamines were detected in samples extracted by any of the three solvents.

References

[1]Kühne, F., Kappenstein, O., Straßgütl, S., Weese, F., Weyer, J., Pfaff, K., & Luch, A. (2018). N-nitrosamines migrating from food contact materials into food simulants: analysis and quantification by means of HPLC-APCI-MS/MS. Food additives & contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment, 35 4, 792-805.

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