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Extractables/leachables from plastic tubing used in product manufacturing

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Abstract

While the ability of packaging systems to contribute leached substances to finished drug products is well established, increasing interest is being focused on the potential contamination of drug substances by plastic materials encountered during their production. The direct contact of such plastic parts (such as tubing, gaskets, filters and temporary storage containers) with the drug substance at some point in its production raises the possibility that plastic-related contaminants (leachables) may be present in the finished drug product. In this study, eight tubing materials potentially encountered in pharmaceutical production facilities, including six silicone materials and two Santoprene materials, were characterized for their extractable substances by static extraction coupled with comprehensive chemical characterization of the resulting extracts. Based on the extractables profiles thus generated, target leachables were identified for each tubing material. The accumulation of these target leachables was studied by subjecting the tubing to dynamic flow, simulated use extractions. The primary organic extractables from the silicone tubing were a homologous series of silicone oligomers, with most of the tubings demonstrating a unique distribution of oligomers. Several of the silicone tubings also possessed extractable dioctyl phthalate and dioctyl adipate. The primary organic extractables from the Santoprene-type tubing included a number of phthalates, a series of alkyl phenols and decomposition products of Irganox-type antioxidants. Inorganic extractables associated with many of the tubings included Ca, Mg, Zn and B. In general, the levels of targeted leachables extracted from the tubing materials under simulated use (flow) conditions was much smaller than the total amount of these leachables in the tubing.

Keywords: Extractables; Leachables; Tubing; Plastic processing materials

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1. Introduction

Plastic materials are widely used in medical items, such as solution containers, associated closures, delivery sets, transfer tubing, and devices. The physiochemical nature of these materials provides medical products with their necessary, desirable performance characteristics. While it is important that plastics used in medical application be chemically inert, leaching of plastic materials by pharmaceutical products is well documented (Arbin et al., 1986; Berg et al., 1993; Danielson et al., 1983; Goydan et al., 1990; Kim-Kang and Gilbert, 1991; Kim et al., 1990; Reif et al., 1996; Sarbach et al., 1996; Snell, 1993; Ulsaker and Hoem, 1978), with both the identities of the leached substances and their accumulation levels impacting product utility.

Interactions between a finished drug product and its packaging (container/closure system) are well known. Regulatory approval of finished drug products and their associated packaging systems is predicated on an extensive assessment of the magnitude and impact of any drug product–packaging system interaction. However, many drug products, especially biotechnology drugs, contact plastic materials during the various phases of their production (generation/synthesis, processing, purification, intermediate storage), including plastic tubing, gaskets, filters, intermediate storage containers, tank liners and the like. It is not unreasonable to hypothesize that plastic-related contaminants (leachables) could be present in the drug products as a result of this contact. In addition to this direct contamination, opportunities for secondary contamination also exist. For example, plastic tubing is used to transport flushing or cleaning solutions through prep-scale chromatography columns used for drug product purification. If such solutions leach substances from the tubing and these substances are sequestered by the chromatography column, these substances could be mobi-

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Table 1
Stoichiometry of static material extracts

Material	Water extract		Ethanol extract			
	Weight (g)	Volume (mL)	Dimensions (length × o.d., in.)	Weight (g)	Start vol. (mL)	End vol. (mL)
Silicone tubing materials						
1	39.20	100	12 × 1 (two reps, combined)	184.3	110	90
2	17.11	50	154 × 0.375	237.8	185	140
3	53.37	100	18 × 1.375	305.6	210	190
4	62.63	100	7.5 × 1.25	108.6	70	68
5	50.17	100	13.5 × 1.25	223.1	140	125
6	51.82	100	20 × 1.365	269.8	240	210
Santoprene tubing materials						
7	29.51	100	11.5 × 1 (two reps, combined)	153.9	118	120
8	30.86	100	144 × 0.5	369.4	220	215

lized into the drug product during its chromatographic purification.

To investigate this phenomenon, the interaction between eight tubing materials potentially used in drug product manufacturing operations and several representative test solutions was investigated. To delineate the materials' extractables profiles, the materials were statically extracted with simulating solvents and the resulting extracts were chemically characterized. To assess the leaching behavior of the materials, targeted leachables were identified for each material, the materials were dynamically extracted (flow conditions) with solutions typically encountered in pharmaceutical manufacturing and the levels of the targeted leachables in the dynamic extracts were measured.

2. Materials and methods

2.1. Tubing materials

Eight commercially available tubing materials that are potentially applicable in pharmaceutical manufacturing operations were examined in this study, including six that were silicone-based and two that were Santoprene-based. The silicone tubing materials are referred to as materials 1 through 6, while the Santoprene materials are designated as materials 7 and 8. Of the silicone materials, materials 3 and 5 were re-enforced with embedded wire.

2.2. Static extractions

Test articles were generated for an extractables survey by static extraction of the tubing with both water and ethanol. The tubing was cut into 0.5–2 in. lengths and autoclaved in water for approximately 1 h at 121 °C. Alternatively, lengths of tubing were filled with 100% ethanol, sealed at the ends with either glass or Teflon stoppers, and stored for 24 h at approximately 55 °C. In the case of tubing #2, the permeability of the tubing was so great that a majority of the ethanol evaporated through the tubing wall into the surrounding air. In order to obtain enough solution to test this material, the extraction was repeated by placing a length of tubing entirely within a 2 L glass bottle and repeating the extraction at 55 °C. Weights of extracted materials and extraction media volumes are summarized in Table 1. Extraction controls were prepared by heating aliquots of the extracting medium (water or ethanol) in glass bottles coincidentally with the tubing extraction units.

2.3. Analysis of the static extracts, identification of extractables

The search for and identification of extractables were carried out using a broad range of survey-type techniques and methods. These techniques are summarized in Table 2. UV absorbance was measured from 190 to 360 nm with a 1 cm quartz

Table 2
Analytical methods used for preliminary extractables survey (static extracts)

Analytical technique or method	Information to be obtained
Total inorganic and organic carbon (TIC and TOC)	Total amount of carbon-based extracted compounds; can distinguish between organic and inorganic carbon
pH and UV absorbance	General information about the chemical nature of the extracted substances
Inductively coupled plasma atomic emission spectroscopy (ICP–AES)	Measures inorganic extractables (trace elements, including heavy metals, and silicon)
Liquid chromatography–mass spectrometry–UV spectroscopy (LC/MS/UV)	Profiles that can include many different semi-volatile and non-volatile organic extractables. Compound or structure type identification is often possible
Gas chromatography–mass spectrometry (GC–MS)	Profiles that can include many different volatile and semi-volatile organic extractables. Compound or structure type identification is often possible
Headspace GC–MS	Profiles that can include many different volatile and semi-volatile organic extractables. Compound or structure type identification is often possible

Table 3
Operating parameters, headspace GC–MS analysis of volatiles from static extracts

Operating parameter	Operating value
A. Headspace autosampler	
Oven temperature (°C)	70[a]
Needle temperature (°C)	150
Transfer line temperature (°C)	155
Carrier gas	He at 5 psi
Cycle time (min)	58[b]
B. GC–MS analyzer	
Column	J&W (Folsom, CA) DB-Wax, 60 m × 0.53 mm i.d., 1 μm film
Oven program	Start at 35 °C, hold for 7 min; ramp at 1 °C/min to 40 °C, hold for 15 min; ramp at 10 °C/min to 100 °C. ramp at 25 °C/min to 215 °C, hold for 5 min[c]
MS ionization mode	EI+, 70 eV
MS transfer line temperature (°C)	220
MS detection mass range (amu)	29–400
Solvent delay (min)	6.0

[a] An oven temperature of 120 °C was used to test the actual tubing materials.

[b] A longer cycle time was used to test the ethanol/water extracts to allow for the elution of the ethanol.

[c] A longer hold time at 215 °C was used to test the ethanol/water extracts (to allow for the ethanol to elute).

cuvette and using water as the reference. General operational details associated with the chromatographic assays (including headspace GC–MS, GC–MS and LC/UV/MS) are summarized in Tables 3–5.

2.4. *Dynamic extracts*

A length of tubing sufficient to contain at least 200 mL of extracting solution was fashioned into a closed loop and filled with the extraction solvent. The extraction solvent was circulated through the tubing loop via a perisaltic pump at a flow rate that was sufficient to provide one complete circulation of extractant every 20 min. Duplicate extracts of each material were generated under the conditions noted in Table 6. While Table 6 indicates total extraction times, each tubing portion was actually subjected to three sequential extractions as follows. Firstly, the tubing was filled with one portion of extracting medium which was pumped through for one third of the total extraction time. The extracting medium was drained from the tubing and saved for analysis. The tubing was then filled with a second portion of extracting medium and the second extraction was performed for one third of the total extraction time, at which point the process was again stopped, the extracting solution collected, the tubing again filled with fresh extracting solution and the extraction restarted. The third extraction was performed for the remaining third of the total extraction time. At the end of the total extraction time, the third extract was removed from the tubing and retained for analysis. The extracting solutions included 35/55 (v/v) ethanol/water, 55/45 (v/v) ethanol/water, an acetate buffer (1 M, pH 4), glacial acetic acid, and laboratory simulations of two commercially available cleaning solutions (Divosan Forte™ and Dioklor™, Johnson-Diversey, Cincinnati, OH). The laboratory simulation of Divosan Forte contained 17% peroxyacetic acid, 16% acetic acid and 24% hydrogen peroxide in water. The Dioklor simulation contained 5% sodium hypochlorite and 15% sodium hydroxide. Each tubing material was extracted with those solutions to which they would be exposed under anticipated manufacturing conditions (see Table 6). Extraction controls or blanks were prepared by placing portions of the extraction media in inert glass bottles and storing the bottles along side the dynamic extraction systems.

Table 4
Operating parameters, GC–MS analysis of the static extracts

Operating parameter	Operating value
Column	J&W DB-5HT, 30 m × 0.25 mm i.d., 0.1 μm film
Oven program	Start at 70 °C, hold for 3 min; ramp at 10 °C/min to 250 °C. ramp at 20 °C/min to 310 °C, hold for 7 min; Conditions used for the water extracts, derivatized samples were as follows: start at 40 °C, hold for 1 min; ramp at 10 °C/min to 280 °C, hold for 2 min; ramp at 15 °C/min to 310 °C, hold for 3 min; solvent delay = 4 or 8 min.
Carrier gas	He, 8.20 psi (3.52 psi for aqueous derivatized samples)
Injection	Splitless, 2 μL
Injector temperature (°C)	310
MS transfer line temperature (°C)	310
MS detection details	70 eV (+), mass range of 45–550 amu, 35–550 amu for aqueous derivatized samples
Sample preparation	Liquid/liquid extraction with methylene chloride, with and without pH adjustment. Evaporative concentration of the organic layer of the extracts, samples analyzed underivatized and after TMS-derivatization

Table 5
Operating parameters, LC/MS/UV analysis of the static extracts

Operating parameter	Operating value
Column	Waters (Milford, MA) X-Terra$^{\mathrm{TM}}$ MS C_{18}, 30 mm × 4.6 mm, 3 μm particles
Column temperature (°C)	30
Mobile phase components	A = 10 mM ammonium formate, B = acetonitrile
Mobile phase gradient	Time 0.0; % B 5 Time 1.0; % B 5 Time 20.0; % B 95 Time 30.0; % B 95 Time 31.0; % B 5 Time 35.0; % B 5
Mobile phase flow rate	0.6 mL/min (1.0 mL/min between 31 and 35 min)
Sample size	50 μL
Detection, UV	210, 230, 250, 280 nm
Detection, MS	API-ES, positive ion and negative ion (range 80–800)
Sample preparation	Aqueous, none; ethanol, solvent reduction by evaporation, reconstitution with water

Table 7
Operating parameters, LC/MS/UV method for characterizing the dynamic extracts

Operating parameter	Operating value
Column	Agilent Eclipse DB C_8, 150 mm × 4.6 mm, 5 μm particles
Column temperature	30 °C
Mobile phase components	A = 10 mM ammonium formate, B = acetonitrile
Mobile phase gradient	Time 0.0; % B 40 Time 1.0; % B 60 Time 9.0; % B 60 Time 12.0; % B 95 Time 18.0; % B 95 Time 18.1; % B 40 Time 22.0; % B 40
Mobile phase flow rate	1.0 mL/min
Sample size	50 μL
Detection, UV	250 nm
Detection, MS	API-ES, positive ion mode, single ion monitoring, $\mathrm{M-H^+}$ ions; $m/z = 371$ for di-octyl adipate, 391 for DEHP, and 279 for di-butyl phthalate. $\mathrm{M\text{-}NH_4^+}$ ion, 296 for Irganox degradate #2

2.5. Analysis of the dynamic extracts, accumulation of target leachables

The concentrations of the targeted organic leachables in the dynamic extracts were measured by LC/UV/MS (Table 7). While most samples were analyzed after appropriate dilution, it was expected that injection of strongly oxidizing and/or high pH samples (Divosan and Dioklor) could adversely affect column stability. Thus these samples were subjected to chemical

Table 6
Dynamic extraction conditions[a]

Tubing material	Tubing length (diameter × length)	Extraction medium	Total extraction time (days)[a]	Extraction temperature (°C)
1	17 mm × 45 in.	35/65 Ethanol/water	8	Ambient
		Divosan, 0.6%[b]	2.5	Ambient
		Dioklor, 3%[b]	2.5	Ambient
2	5/16 in. × 144 in.	Acetate buffer, pH 4	10	40
		35/65 Ethanol/water	9	Ambient
		Divosan, 0.6%	2.5	Ambient
		Dioklor, 3%	2.5	Ambient
3	1/2 in. × 72 in.	55/45 Ethanol/water	16	Ambient
		Divosan, 0.6%	2.5	Ambient
		Dioklor, 3%	2.5	Ambient
		Glacial acetic acid	15	40
4	1/2 in. × 72 in.	Divosan, 0.6%	2.5	Ambient
		Dioklor, 3%	2.5	Ambient
5	3/4 in. × 36 in.	35/65 Ethanol/water	9	Ambient
		Divosan, 0.6%	2.5	Ambient
		Dioklor, 3%	2.5	Ambient
6	1 in. × 24 in.	Divosan, 0.6%	2.5	Ambient
		Dioklor, 3%	2.5	Ambient
7	17 mm × 45 mm	35/65 Ethanol/water	9	Ambient
		Divosan, 0.6%	2.5	Ambient
		Dioklor, 3%	2.5	Ambient
8	1/2 in. × 72 in.	Divosan full strength	15	40
		Dioklor full strength	15	40

[a] Divosan and Dioklor are commercially available cleaning solutions. In order to produce extracting solutions that were free from interfering contaminants, these solutions were simulated via laboratory preparations as noted in Section 2.4.

[b] The tubing materials were extracted only with those solutions that they were expected to transport in typical plant operations.

Table 8
Concentrations of metals found in the static ethanol extracts

Trace element	Extracted trace element concentration, μg metal per mL of extracting solution							
	Silicone tubing						Santoprene tubing	
	1	2	3	4	5	6	7	8
Ca	0.004	0.019	<LQD[a]	<LQD	<LQD	<LQD	0.095	Not tested
Mo	<LQD	0.000[b]	0.008	0.000	0.055	0.000		
Ti	<LQD	<LQD	0.000	0.000	0.065	0.000		
Zr	0.000	0.000	<LQD	<LQD	0.079	0.000		
B	0.039	0.476	0.484	0.085	0.189	0.071		
Mn	0.000	0.011	0.000	0.000	0.083	<LQD		
Pt	0.058	0.044	<LQD	<LQD	<LQD	<LQD	Analytical issue	
Sn	0.000	0.053	<LQD	<LQD	<LQD	0.040		
Cu	0.000	0.027	0.034	<LQD	0.031	0.000		
Sb	<LQD	<LQD	0.000	0.000	0.035	<LQD		
Li	0.016	0.021	0.000	0.000	0.093	0.000		
As	0.013	0.000	0.038	0.000	0.000	0.000		
Ag	0.000	<LQD	<LQD	<LQD	0.051	<LQD		
Ni	0.000	0.000	0.074	<LQD	0.098	0.000		

Cd, Ba, Fe and Mg were measured in some extracts but at levels less than 0.02 μg/mL.

[a] <LQD (lowest quantity determinable); the measured value is lower than the minimum amount the method can reliably measure.

[b] All values are corrected for the control (blank) value. A value of 0.000 means the concentration in the sample was the same as, or less than, the concentration in the control, meaning that the level of extracted element is too low to measure.

modification. Specifically, sodium bisulfite was added to these samples to reduce their oxidizing nature while hydrochloric acid was added to lower sample pH.

The levels of the targeted inorganics were measured by ICP-AES, using optimized and qualified operating conditions. Samples were prepared for analysis by dilution, by addition of nitric acid, and by chemical modification with sodium bisulfite, as appropriate. All samples were prepared to contain 1 mg/L yttrium as an internal standard.

2.6. Instrumentation

LC/MS/UV analyses were performed on an Agilent (Palo Alto, CA) 1100 HPLC system (pump, autosampler, column oven, PDA detector) coupled to either an Applied Biosystems (Toronto, Canada) MDS SCIEX API 2000 or Agilent Series 1100 mass detector. The GC Headspace analyzer used was a Perkin-Elmer (Norwalk, CT) model HS 40XL coupled to an Agilent 6890N GC system. UV absorbance measurements

Table 9
Concentrations of metals found in the static water extracts

Trace element	Extracted trace element concentration, μg metal per mL of extracting solution							
	Silicone tubing						Santoprene tubing	
	1	2	3	4	5	6	7	8
Ca	0.000	0.205	0.471	0.089	0.210	1.57	0.259	0.157
Mo	0.000	0.990	<LQD	<LQD	<LQD	<LQD	<LQD	0.043
Ti	0.000	0.895	<LQD	<LQD	<LQD	<LQD	<LQD	0.040
Zr	0.000	0.832	<LQD	0.000	0.000	0.000	0.000	0.036
Ba	<LQD	<LQD	0.050	<LQD	<LQD	<LQD	0.013	<LQD
B	0.334	0.956	1.283	0.436	0.196	0.520	0.092	0.000
Mn	<LQD	0.797	0.068	0.002	0.008	0.003	<LQD	0.038
Fe	<LQD	<LQD	1.592	0.007	0.026	0.008	<LQD	<LQD
Mg	0.007	0.780	0.111	0.030	0.067	0.067	0.007	1.799
Sn	<LQD	0.742	<LQD	<LQD	<LQD	<LQD	<LQD	<LQD
Al	0.000	<LQD	0.152	0.094	<LQD	<LQD	0.000	<LQD
Zn	0.201	0.669	2.705	0.252	0.218	0.081	0.201	0.194
Cu	<LQD	0.000	0.053	<LQD	<LQD	0.020	<LQD	<LQD
Sb	0.000	0.640	<LQD	<LQD	0.280	0.098	0.000	<LQD
Li	<LQD	0.606	<LQD	0.000	0.000	<LQD	<LQD	0.040
Ag	<LQD	0.591	<LQD	<LQD	<LQD	<LQD	<LQD	0.038
Ni	<LQD	0.552	<LQD	<LQD	<LQD	0.024	<LQD	0.037

<LQD (lowest quantity determinable): the measured value is lower than the minimum amount the method can reliably measure. All values are corrected for the control (blank) value. A value of 0.000 means the concentration in the sample was the same as, or less than, the concentration in the control, meaning that the level of extracted element is too low to measure. Sr and Pt were measured in some extracts but at levels less than 0.02 μg/mL.

Table 10
Levels of silicon in the static extracts of the tubing materials

Extractant	Extracted silicon concentration, μg Si per g of material							
	Silicone tubing						Santoprene tubing	
	1	2	3	4	5	6	7	8
Ethanol	765	1360	1860	1120	1300	739	N/A[a]	Not tested
Water	101	<0.2	66.0	130	87.3	<0.2	<0.2	0

[a] Data suspect due to particulate problems resulting from tubing disintegration.

Table 11
General chemical characteristics of the static water extracts

Tubing ID	Total inorganic carbon (TIC, μg C per g material)	Total organic carbon (TOC, μg C per g material)	pH	UV absorbance (nm)		
				220	240	250
A. Silicone tubing						
1	0.0	14.0	6.35	0.080	0.037	0.033
2	0.9	38.1	6.79	0.062	0.029	0.025
3	2.3	250	6.74	1.849	0.499	0.413
4	0.2	34.0	6.57	0.429	0.097	0.069
5	0.0	49.9	6.54	0.249	0.455	0.420
6	0.0	46.9	6.47	0.367	0.469	0.416
B. Santoprene tubing						
7	10.1	16.6	–[a]	–	–	–
8	4.6	13.5	6.86	0.112	0.058	0.050
Blank	N/A	N/A	6.73	<0.037	<0.014	<0.013

[a] Insufficient sample was available to perform this testing.

were made using an Hewlett-Packard (Wilmington, DE) 8452A UV/VIS spectrophotometer. The trace element analyses were performed on a Varian (Walnut Creek, CA) Liberty 220 sequential ICP Emission spectrometer, operated with a cyclonic, double pass glass spray chamber and a Noordermer V-groove nebulizer. The TIC and TOC measurements were made using OI Analytical (College Station, TX) Model 700 and 1010 TOC Analyzers.

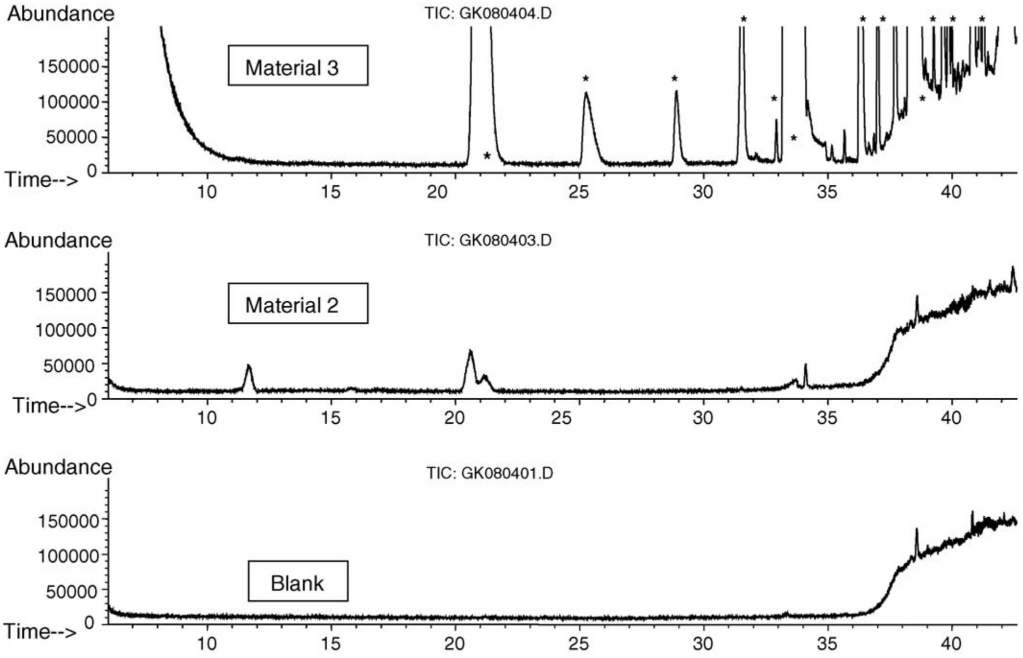


Fig. 1. Headspace GC–MS chromatograms of evolved gases from materials 2 and 3. The chromatograms for materials 3, 4 and 5 were similar in the number and magnitude of peaks while the chromatograms for materials 1 and 2 had similar chromatograms to those for materials 3 through 5 but with fewer and smaller peaks. The peaks denoted with the * have been associated with silicone-type materials. Specifically, the peak at ≈31.7 min has been tentatively associated with trimethylsilanol. Two peaks that have been tentatively associated with non-silicon compounds include the one at ≈41.8 min (2-butoxyethanol) and 42.2 min (*N*,*N*-dimethylacetamide).

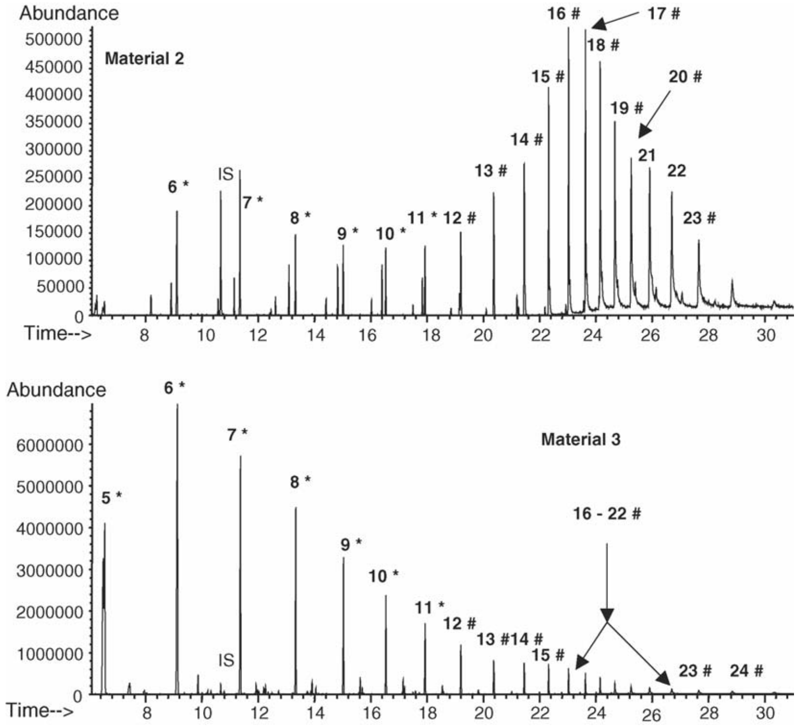


Fig. 2. GC–MS chromatograms of the static ethanol extracts of silicone tubing materials (underivatized). The chromatograms from all the silicone materials were similar (same peaks but different relative sizes) and thus chromatograms from two different silicones are shown. A majority of the peaks are attributable to silicone oligomers. Peaks associated with cyclic oligomers are identified by the number of repeating units, *n*; e.g. $[(CH_3)_2SiO]_n$. Peaks denoted with * produced exact compound matches versus a library of mass spectra while peaks denoted by # produced a library match to the right compound class (cyclic oligomer) but wrong specific oligomer. Small peaks at 7.95, 10.32 and 11.93 min were linked to 5–7 member linear silicone oligomers. IS = internal standard (dimethyl phthalate).

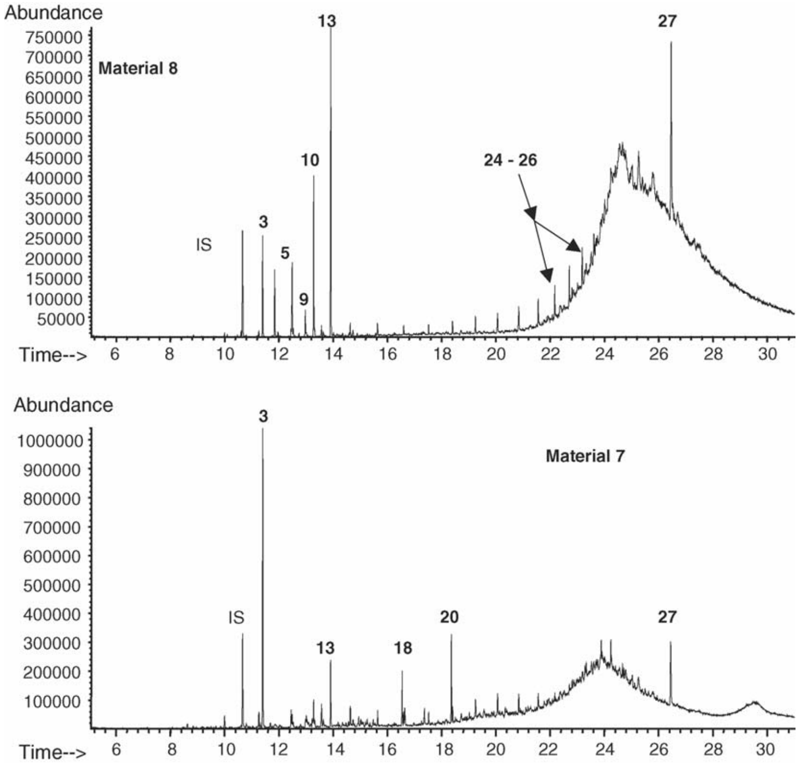


Fig. 3. GC–MS chromatograms of static ethanol extracts of Santoprene tubing materials (underivatized). The chromatograms from these two Santoprene materials were quite different from those of the silicone materials (Fig. 2). IS = internal standard (dimethyl phthalate). See Table 12 for the tentative peak identifications. Only those peaks with recorded spectral library matches are noted for each sample, although retention times and patterns may suggest some additional peak identifications.

Table 12
Peak identifications, static ethanol extracts of santoprene tubing samples 7 and 8

Peak #	Retention time (min)	Tentative compound ID[a]	In material[b]	Present in figures[c]
1	10.7	Internal standard	N/A	3 and 4
2	11.3	Pentadecane	7	3 and 4
3	11.4	2,4-Di-*t*-butylphenol	7 and 8	3 and 4
4	11.9	2,4-Di-*t*-butyl-phenol-TMS	7 and 8	4
5	11.9, 12.5	4-(1,1,3,3-Tetramethybutyl) phenol	8	3
6	12.1	An isomer of octyl phenol (TMS)	8	4
7	12.5	Hexadecane	7	3 and 4
8	13.0	An isomer of octyl phenol (TMS)	8	4
9	13.0	4-Methyl-6-*tert*-octyl phenol	8	3
10	13.3	An isomer of decyl phenol	7 and 8	3
11	13.4	An isomer of nonyl phenol (TMS)	8	4
12	13.6	Heptadecane	7	3 and 4
13	13.9	An isomer of undecyl phenol	7 and 8	3
14	14.6	Octadecane	7	3 and 4
15	14.3	An isomer of decyl phenol (TMS)	8	4
16	15.6	Nonadecane	7	3 and 4
17	16.3	An isomer of undecyl phenol (TMS)	7 and 8	4
18	16.5	Hexadacanoic acid, ethyl ester	7	3 and 4
29	17.1	Irganox degradate #2	7	4
19	17.4	Cyclohexadecane, Heneicosane	7	3,4
28	18.1	Unidentified	7	4
20	18.4	Octadecanoic acid, ethyl ester	7	3 and 4
21	18.4	Docosane	7	3 and 4
22	19.3	Tetratriacontane, 9-methyl-nonadecane	7 and 8	3 and 4
23	20.0	Tetracosane	7	3 and 4
24	20.8	Pentacosane	7 and 8	3 and 4
25	21.6	Hexacosane, nonadecane	7 and 8	3 and 4
26	22.2	Heptacosane	8	3
27	26.5	Irganox 1076	7 and 8	3 and 4

See Figs. 3 and 4.

[a] Based on match of peak's MS spectrum with reference MS spectrum in spectral library.

[b] Only those peaks with recorded spectral library matches are noted for each sample, although retention times and patterns may suggest some additional peak identifications.

[c] Fig. 3 = underivatized; Fig. 4 = derivatized.

2.7. Reference materials

Reference materials for several target leachables were internally synthesized. Reference standards for the other targeted extractables were commercially available analytical grade reagents (for example, Aldrich Chemical, Milwaukee, WI, USA), 99% purity or greater.

3. Results and discussion

3.1. Static extractions, inorganic extractables profiles

The ICP-AES analysis included 29 elements (other than silicon), many of which were either not found in detectable levels in any of the tested samples (extracts or extraction controls) or were present in the extracts at the same (or lower) levels than in the extraction controls. Such elements are not extracted from the tubing in measurable amounts.

Inorganics that were not extracted from the tubing materials in measurable levels by ethanol included: Sr, Be, Co, Cr, Al, Zn, Se, V, Ge, Pb, and Bi. The remaining elements were measured in the ethanol extracts of at least one tubing material and the results for these elements are summarized in Table 8. Material 7 partially disintegrated during ethanol extraction, resulting in particulate matter in the sample that produced very low recovery of added metals with the exception of calcium.

Inorganics that were not extracted from the tubing materials in measurable levels by water included: Be, Co, Cr, Cd, As, Se, V, Ge, Pb, and Bi. The remaining elements were measured in the water extracts of at least one tubing material and the results for these elements are summarized in Table 9.

Noteworthy aspects of Tables 8 and 9 are as follows.

1. In general the levels of the extracted elements are greater in the water extracts versus the ethanol extracts. This trend may reflect differences in both the extraction conditions used for each extracting medium and the relative solubility of the extracted substances in ethanol versus water.
2. Materials 2, 3, 6, 7 and 8 had relatively high levels of extractable calcium and magnesium. The presence of these elements in the Santoprene materials (7 and 8) may be related to the elevated inorganic carbon levels in the water extract of these materials, since alkaline earth carbonates are common additives in Santoprene.
3. Materials 3 and 5 had higher amounts of several metals (e.g. Mo, Ti, Zr, Mn, Zn, Fe) than did many of the other materials.

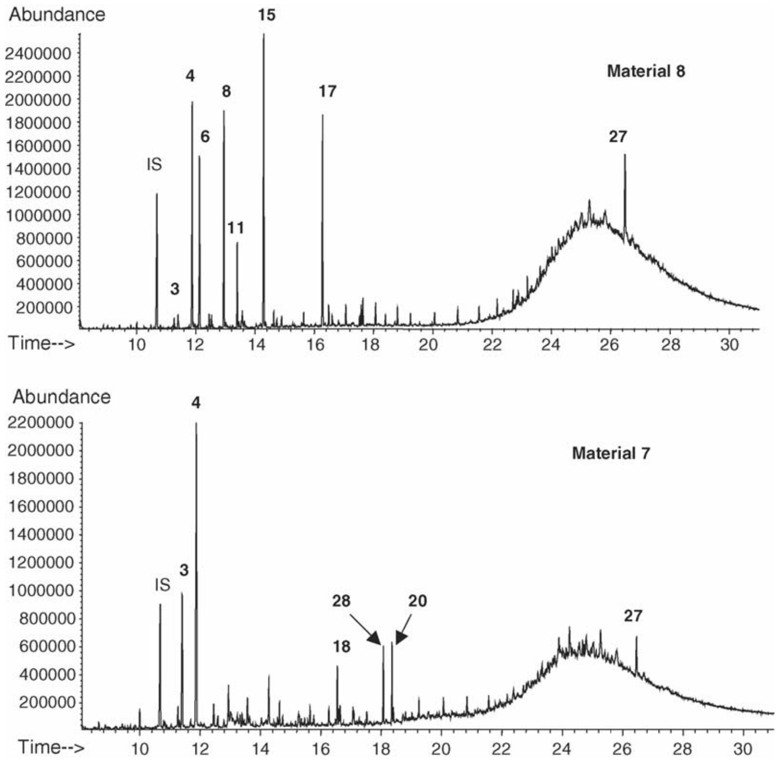


Fig. 4. GC–MS chromatograms of static ethanol extracts of Santoprene tubing materials (derivatized). The chromatograms from these two Santoprene materials were quite different from those of the silicone materials. IS = internal standard (dimethyl phthalate). See Table 12 for a list of the tentative peak identifications. Only those peaks with recorded spectral library matches are noted for each sample, although retention times and patterns may suggest some additional peak identifications.

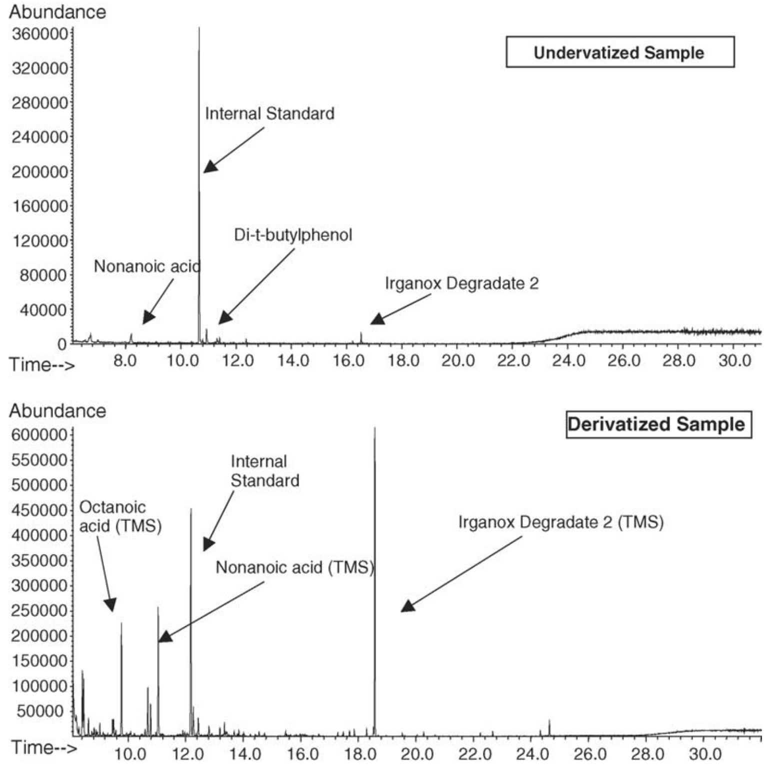


Fig. 5. GC–MS chromatograms of static water extracts of Santoprene tubing material # 7. Compared to the chromatograms from the ethanol extracts, the chromatograms for the water extracts are relatively devoid of large responses associated with extracted substances.

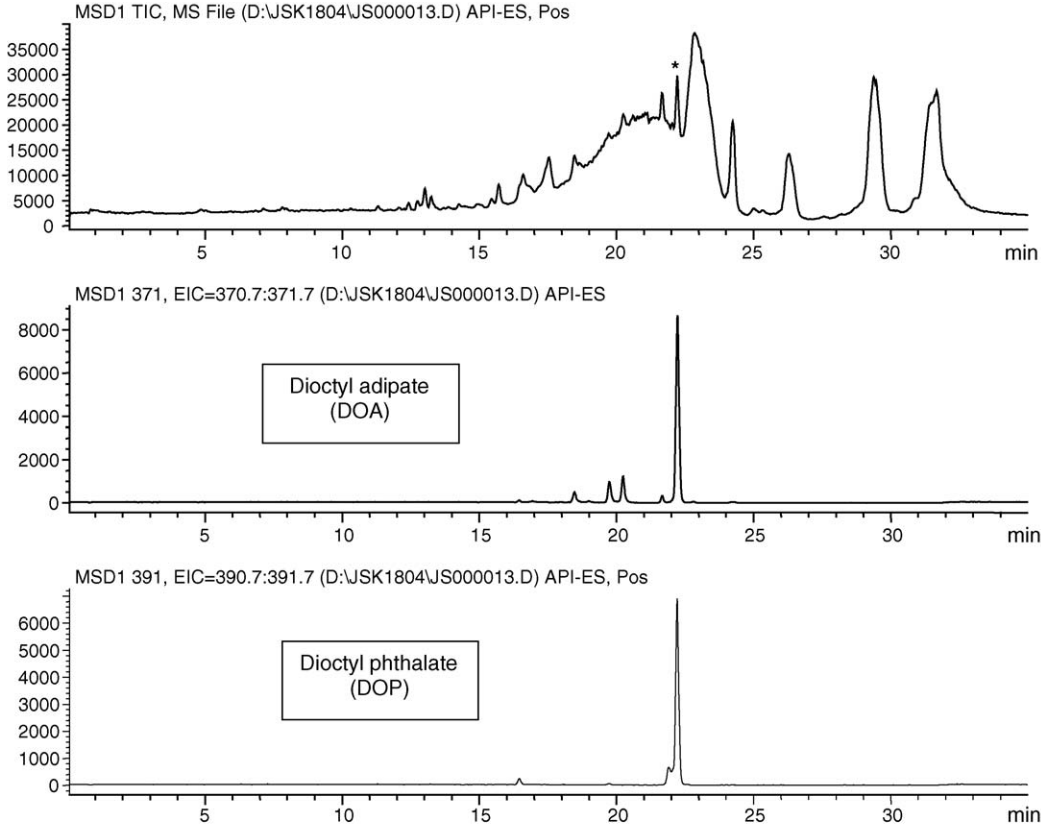


Fig. 6. LC/MS chromatograms of the static ethanol extract of silicone tubing material 6. The upper chromatogram is the total ion current (TIC) while the remaining chromatograms are extracted ion chromatograms obtained at a mass to charge ratio indicative of a particular compound. The strong signal for the indicated compounds implies that they are present in the ethanol extract of this material. The peaks denoted by the * in the TIC chromatogram are those peaks that are most likely linked to the indicated compounds.

A possible source for these metals is the tubing's reinforcing wire. Material 2 also had high levels of certain extractable metals, however the source could not be embedded wire as this material had none.

4. While many metals were associated with only a few of the tubing materials, all the tubing materials contained water extractable Ca (except for material 1), Mg, Zn and B (except for material 8).
5. Material 2 had the highest levels of water-extractable inorganics. While this material did not have the highest level of a particular element, it had high levels (>0.5 μg/mL) of many elements including Mo, Ti, Zr, B, Mn, Mg, Sn, Zn, Sb, Li, Ag and Ni.
6. Of all the materials tested, material 1 had the lowest level of water-soluble elements. Other than B and Zn, the levels of all other water-soluble elements in this material were less than 0.01 μg/mL.

3.2. Static extractions, extractable silicon

The silicon levels in the tubing extracts is summarized in Table 10. Silicon was readily extracted from all the silicone materials by ethanol. Silicon was also extracted from all the silicone materials by water except for materials 2 and 6. One anticipates that the differences in ethanol-soluble and water-soluble silicon among the silicone tubing materials reflect a difference in the distribution of the silicone oligomers present in these materials. Not surprisingly, it is noted that the non-silicone materials (7 and 8) contained little, if any, extractable silicon.

3.3. Static extractions, organic extractables profiles

3.3.1. General chemistry

The general chemical characteristics of the water extracts of the tubing materials provide insight into the chemical nature of the organic extractables (Table 11). The larger values for total inorganic carbon (TIC) in the Santoprene materials (samples 7 and 8) versus the silicones suggests the presence of inorganic carbonates. The high TOC value for material 3 suggests that this material has the highest organic extractables burden. The pH of the extracts is not significantly different than that of the extraction controls, implying that the extracted substances are neither acidic nor basic. The high UV absorbances at 240 and 250 nm for the extracts of materials 3, 5 and 6 suggest that these materials contain conjugated (aromatic) extractables while the relative lack of such absorbances in the extracts of the other materials suggests that their organic extractables are primarily aliphatic.

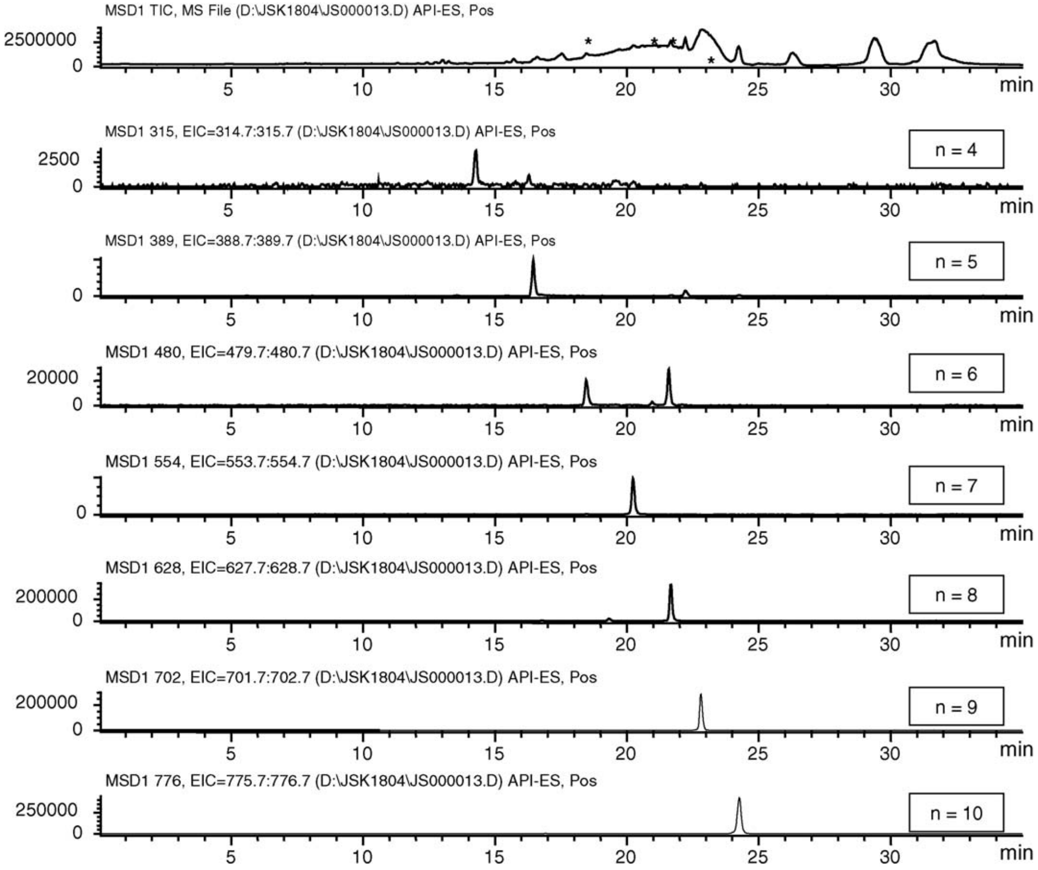


Fig. 7. LC/MS chromatograms of the static ethanol extract of silicone tubing material 6. The upper chromatogram is the total ion current (TIC) while the remaining chromatograms are extracted ion chromatograms obtained at a mass to charge ratio indicative of a particular compound, in this case linear polydimethysilicones of the with the general formula $(CH_3)_3SiO[(CH_3)_2SiO]_nSi(CH_3)_3$. The strong signal for the indicated compounds implies that they are present in the ethanol extract of this material. The peaks denoted by the * in the TIC chromatogram are those peaks that are most likely linked to the indicated compounds.

3.3.2. Headspace GC–MS

This technique reveals volatile organic tubing-related leachables. Direct analysis of the tubing materials (≈1 g heated to 120 °C) indicated the presence of several volatiles in all of the silicone materials (see Fig. 1). Many of the peaks observed in the chromatograms for these samples were attributed to silicone-type compounds, although some non-silicone compounds were also tentatively identified. The chromatograms for samples 3, 4 and 5 were similar in the number and magnitude of peaks while the chromatograms for materials 1 and 2 were similar to those for materials 3 through 5 but with fewer and smaller peaks. As was the case with the extracts, the direct analysis chromatograms for the Santoprene materials 7 and 8 were essentially devoid of peaks. Analysis of the water and ethanol extracts of the tubing produced chromatograms that contained few, if any, small and unidentifiable peaks.

3.3.3. GC–MS, ethanol extracts

Fig. 2 is a typical GC–MS chromatogram for the ethanol extracts (underivatized) of two silicone materials and are dominated by large peaks attributable to a homologous series of polydimethylsiloxanes. The predominant peaks are associated with cyclic oligomers with the general structural formula $[(CH_3)_2SiO]_n$. Direct matches with a MS spectral library allows for the tentative identification of oligomers from $n = 5$ through $n = 11$, while retention time patterns and spectral evaluation allows for additional tentative identifications to be made up to $n = 25$. It is probable that higher molecular weight oligomers are present but these cannot be assessed with the analytical methodology used. The presence of numerous linear polydimethylsiloxanes (general formula = $(CH_3)_3SiO[(CH_3)_2SiO]_nSi(CH_3)_3$) and branched siloxane oligomers can be inferred from retention patterns and qualitative elucidation of the MS spectra associated with specific chromatographic peaks.

While chromatograms from all the silicone materials contain essentially the same peaks, the distribution of the peaks (i.e., the relative size of individual peaks) varies from material to material. Thus in Fig. 2 one observes that the chromatogram for material 3 is dominated by peaks at the low range for n while the oligomer distribution for material 2 is decidedly shifted towards higher molecular weight. The oligomer distribution for materials 4, 5 and 6 is similar to that of material 3 (bias towards lower molecular weight oligomers) while the distribution for material 1 is intermediate between the extremes of materials 3 and 4. The polydimethylsiloxane oligomer peaks are so large they interfere with the ability to assess whether the ethanol extracts contain additional non-silicone extractables.

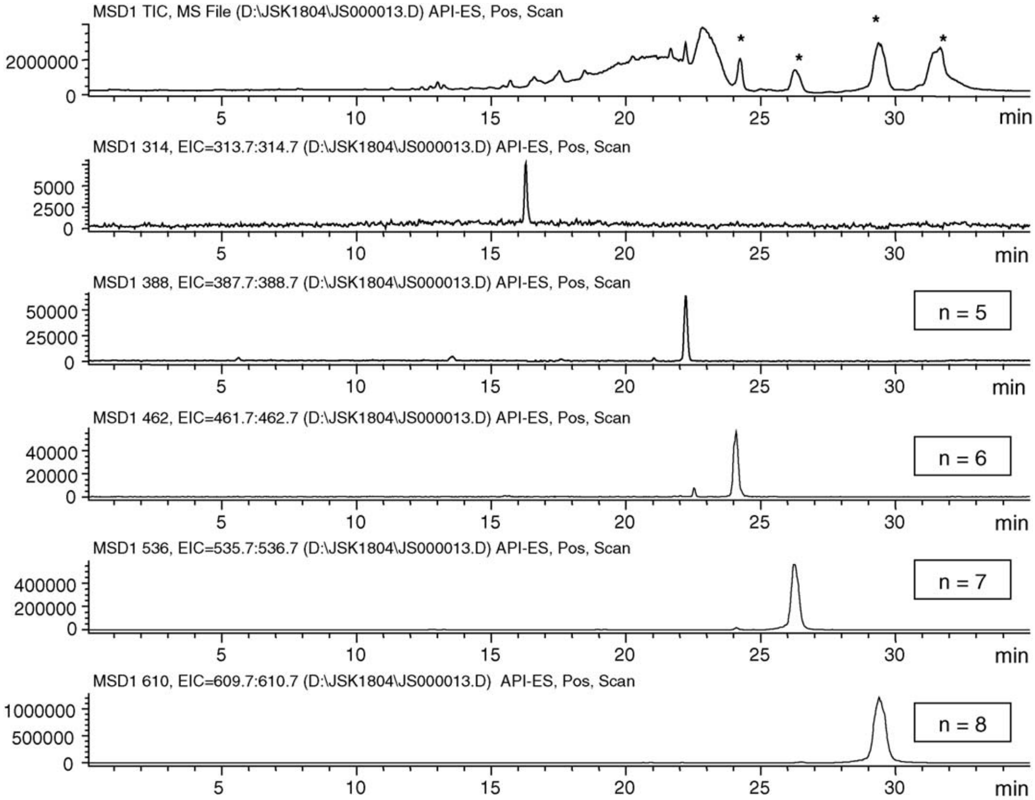


Fig. 8. LC/MS chromatograms of the static ethanol extract of silicone tubing material 6. The upper chromatogram is the total ion current (TIC) while the remaining chromatograms are extracted ion chromatograms obtained at a mass to charge ratio indicative of a particular compound, in this case cyclic polydimethysilicones of the with the general formula $[(CH_3)_3SiO]_n$. The strong signal for the indicated compounds implies that they are present in the ethanol extract of this material. The peaks denoted by the * in the TIC chromatogram are those peaks that are most likely linked to the indicated compounds.

Typical GC–MS chromatograms for the ethanol extracts of the Santoprene materials (7 and 8) are shown in Fig. 3 (underivatized) and 4 (derivatized) and tentative peak identifications, including 2,4-di-*t*-butyl phenol, Irganox 1076, a homologous series of alkyl phenols (C8 and higher), a homologous series of alkanes (C5 and higher) and several higher molecular weight fatty acid ethyl esters, are summarized in Table 12. While the ethanol extractables profiles of both materials are clearly different, both in terms of the relative levels of individual compounds and in terms of the specific compounds present, it is clear that both materials share many common extractables (Fig. 4).

3.3.4. GC–MS, water extracts

GC–MS chromatograms for the water extracts of the silicone materials show little evidence of the silicone oligomers that dominated the chromatograms of the ethanol extracts. The non-derivatized chromatograms are essentially devoid of any major chromatographic responses and while the derivatized chromatograms document the presence of some silicones in the

Table 13
Performance parameters, LC method for target organics quantitation

Compound	Precision (% R.S.D.)[a]		Limit of quantitation (ppb)[b]		Linearity, r^2[c]	
	UV	MS	UV	MS	UV	MS
Irganox Deg. #2	0.4	4.1	720	90	1.000	0.998
Di-butyl phthalate	0.2	0.9	350	20	1.000	0.998
Di-*t*-butyl phenol	0.2	–[d]	380	–[d]	1.000	1.000
Di-octyl phthalate	0.3	1.1	410	<10	1.000	0.999
Di-octyl adipate	–[d]	1.9	–[d]	<10	–[d]	0.999

[a] $n = 3$ at 1 ppm.

[b] Reflecting a 1–10 dilution during sample preparation.

[c] Linear curve used for UV data (range ≈ 250–5000 ppb), quadratic curve used for MS data (range ≈ 250–1000 ppb). Both UV and MS included the injection of a standard blank containing no intentionally added analyte.

[d] This method of quantitation not used for this analyte.

Table 14
Levels of silicon extracted from silicone tubing in dynamic extractions

Medium	Extraction step	Amount of Si extracted, μg Si per cm^2 of tubing surface area (mean, $n = 2$)					
		Material 1	Material 2	Material 3	Material 4	Material 5	Material 6
35/65 Ethanol/water	1	1.7	2.0	–	–	5.4	–
	2	1.3	1.4	–	–	1.4	–
	3	1.2	1.2	–	–	1.2	–
55/45 Ethanol/water	1	–	–	36.0	–	–	–
	2	–	–	15.2	–	–	–
	3	–	–	12.7	–	–	–
Acetate buffer	1	–	2.9	–	–	–	–
	2	–	2.2	–	—	–	–
	3	–	1.8	–	–	–	–
Glacial acetic acid	1	–	–	220	–	–	–
	2	–	–	183	–	–	–
	3	–	–	120	–	–	–
Divosan, dilute	1	0.5	0.4	17.5	2.0	1.6	2.8
	2	0.3	0.3	7.6	0.4	0.9	1.4
	3	0.2	0.2	5.9	0.3	0.5	1.2
Dioklor, dilute	1	39.3	3.6	66.9	8.7	51.6	1.0
	2	46.7	2.9	32.5	7.4	24.0	0.7
	3	44.1	2.7	21.9	6.8	9.4	0.5

–: Extraction of this material with this medium was not performed.

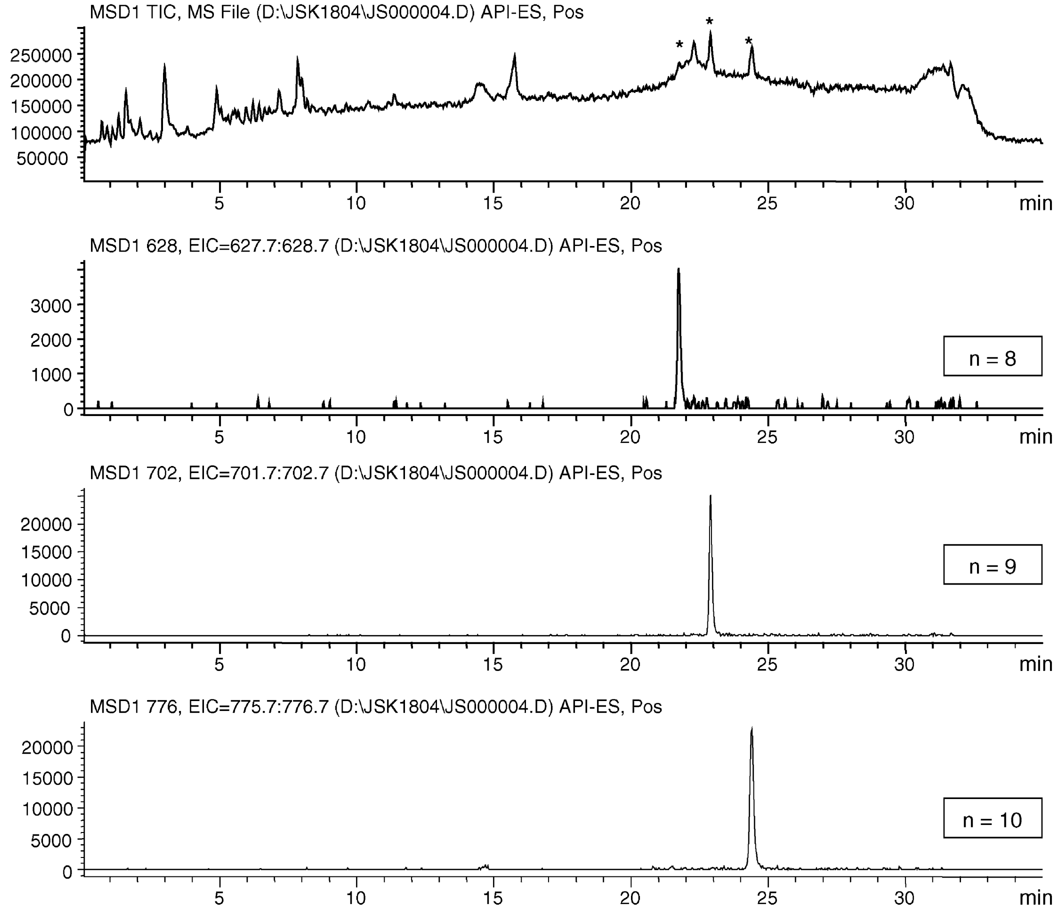


Fig. 9. LC/MS chromatograms of the static water extract of silicone tubing material 6. The upper chromatogram is the total ion current (TIC) chromatogram while the remaining chromatograms are extracted ion chromatograms obtained at a mass to charge ratio indicative of a particular compound, in this case linear polydimethysilicones with the general formula $(CH_3)_3SiO[(CH_3)_2SiO]_nSi(CH_3)_3$. The signal for the indicated compounds implies that they are present in the water extract of this material at low levels. The peaks denoted by the * in the TIC chromatogram are those peaks that are most likely linked to the indicated compounds.

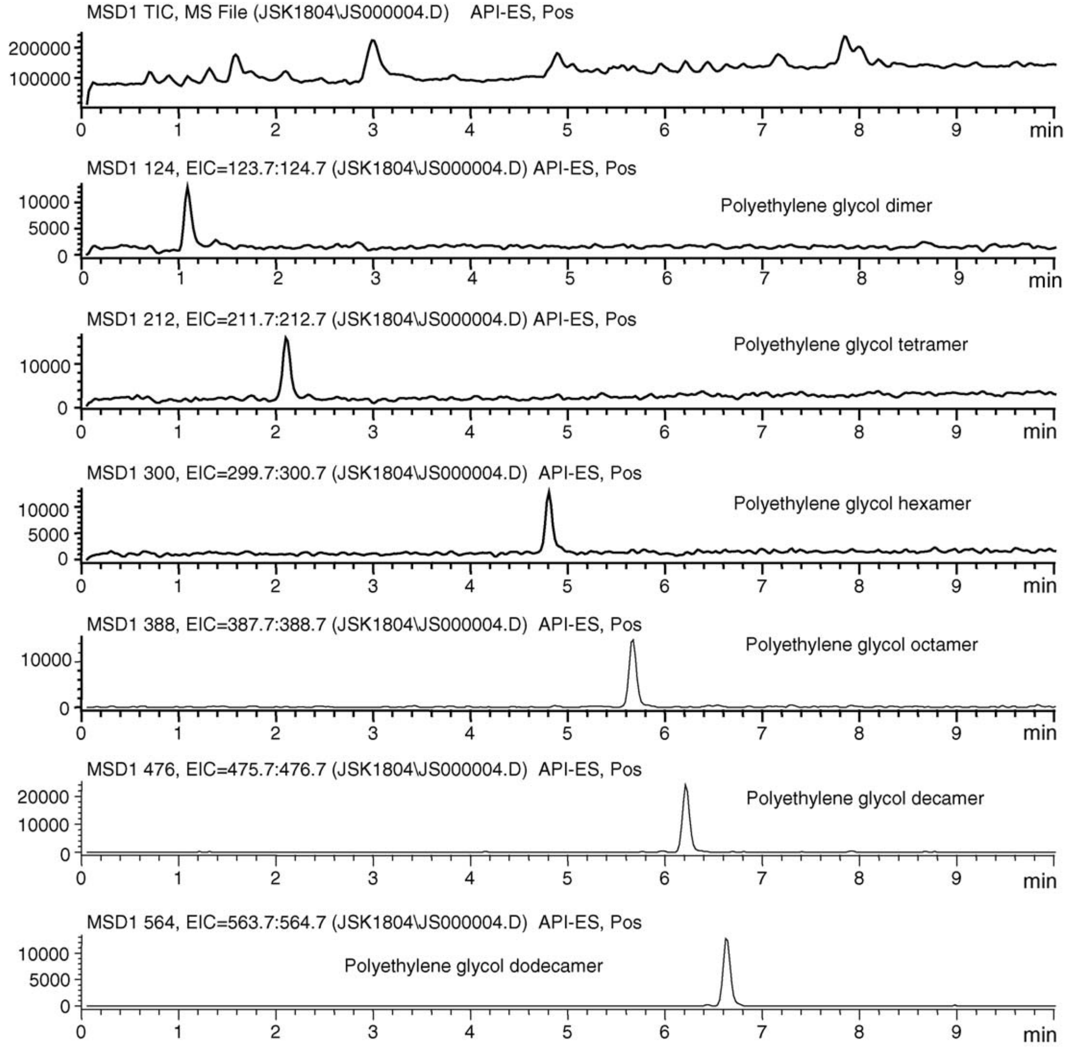


Fig. 10. LC/MS chromatograms of the static water extract of a silicone tubing material 6. The upper chromatogram is the total ion current (TIC) while the remaining chromatograms are extracted ion chromatograms obtained at a mass to charge ratio indicative of a particular compound, in this case polyethylene glycol (PEG) oligomers of the with the general formula $HO(CH_2CH_2–O)_n–H$. The signal for the indicated compounds implies that they are present in the water extract of this material at low levels.

water extracts, these are not the oligomers present in the ethanol extracts. Additional compounds identified in the derivatized portions of the water extracts include carboxylic acids (C8 and higher), phthalates [for example, mono (2-ethylhexyl) phthalate, MEHP] and erucamide.

GC–MS chromatograms for the water extracts of the Santoprene tubing materials contain only small peaks associated with several extracted substances (including C8 and C9 acids, dibutyl phthalate, an Irganox degradation product (see, for example, Cruz et al., 1990; Haider and Karlsson, 2002; Jenke, 2002; Yu et al., 2000; Jenke et al., 2004), and di-*t*-butylphenol, Fig. 5).

3.3.5. LC/MS/UV

The evaluation of the LC/MS/UV data was limited to the silicone tubing materials, addressed two organic compounds (dioctyl adipate and dioctyl phthalate) and silicone oligomers and included an examination of extracted ion chromatograms at *m*/*z* ratios diagnostic of these compounds as follows.

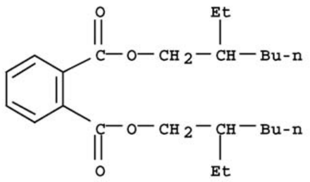
- Dioctyl adipate, $m/z = 371$, $M + H^+$ ion.
- Dioctyl phthalate, $m/z = 391$, $M + H^+$ ion.

Linear polydimethylsilicones with the general chemical formula $(CH_3)_3SiO[(CH_3)_2SiO]_nSi(CH_3)_3$:

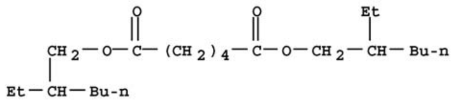
n	Molecular weight	$M + H^+$	$M + NH_4^+$
2	314	315	332
3	388	389	406
4	462	463	480
5	536	537	554
6	610	611	628
7	684	685	702
8	758	759	776

Note: Shaded ion was the one used for peak search.

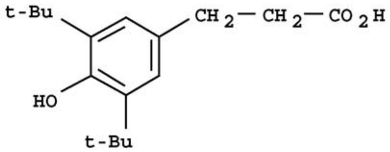
1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester (DEHP), $C_{24}H_{38}O_4$, formula weight = 390.6, CAS RN 117-81-7



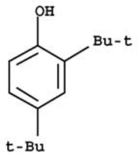
Hexanedioic acid, bis(2-ethylhexyl) ester (Dioctyl adipate), $C_{22}H_{42}O_4$, formula weight = 370.57, CAS RN 103-23-1



Irganox degradate #2; 3,5-bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, $C_{17}H_{26}O_3$, formula weight = 278.4, CAS RN 20170-32-5.



2,4-di-t-butylphenol, $C_{14}H_{22}O$, formula weight = 206.3, CAS RN 96-76-4



1,2-Benzenedicarboxylic acid, dibutyl ester (Dibutyl phthalate), $C_{16}H_{22}O_4$, formula weight = 278.34, CAS RN 84-74-2

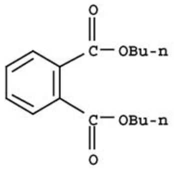


Fig. 11. Structures and general information associated with the target organic leachables.

Cyclic polydimethylsilicones with the general chemical formula $[(CH_3)_3SiO]_n$:

n	Molecular weight	$M+H^+$	$M+NH_4^+$
5	370	371	388
6	444	445	462
7	518	519	536
8	592	593	610
9	666	667	684
10	740	741	758

Note: Shaded ion was the one used for peak search.

The upper range of the series that could be assessed was fixed by the upper m/z limit used for the mass analyzer ($m/z = 800$) and the eluting power of the chromatographic separation (polydimethylsilicones with n greater then 10 did not elute within the analysis time window).

Representative Total Ion Current (TIC) and extracted ion chromatograms for silicone tubing material 6 are shown in Figs. 6–8 (ethanol extract) and Figs. 9 and 10 (water extract). $N = 4$ through 10 linear polydimethylsilicones, $n = 5$ through 9 cyclic polydimethylsilicones and dioctyl adipate (DOA) and dioctyl phthalate (DOP) are present in the ethanol extract. The chromatograms for the ethanol extracts of all the silicone materials all had extracted ion peaks reflecting these linear and cyclic polydimethlysilicones, although the relative intensities of the individual peaks varied across the various materials (as was the case with GC–MS chromatograms). There was some difference between materials in terms of the presence of DOA and DOP in the ethanol extracts. Materials 3 and 4 contained neither DOA nor DOP, material 2 contained only DOP, and the other materials (1, 4, 5 and 6) contained both DOA and DOP.

LC/MS chromatograms for the water extracts of the silicone materials generally contained only small peaks associated with the silicones (for example, see Fig. 9). Additionally, as shown in Fig. 10, a homologous series of polyethylene glycol oligomers, general formula $HO(CH_2CH_2–O)_n–H$ ($n = 2$ through $n > 12$ observed), and DOP were found in the water extracts of all of the silicone tubing materials.

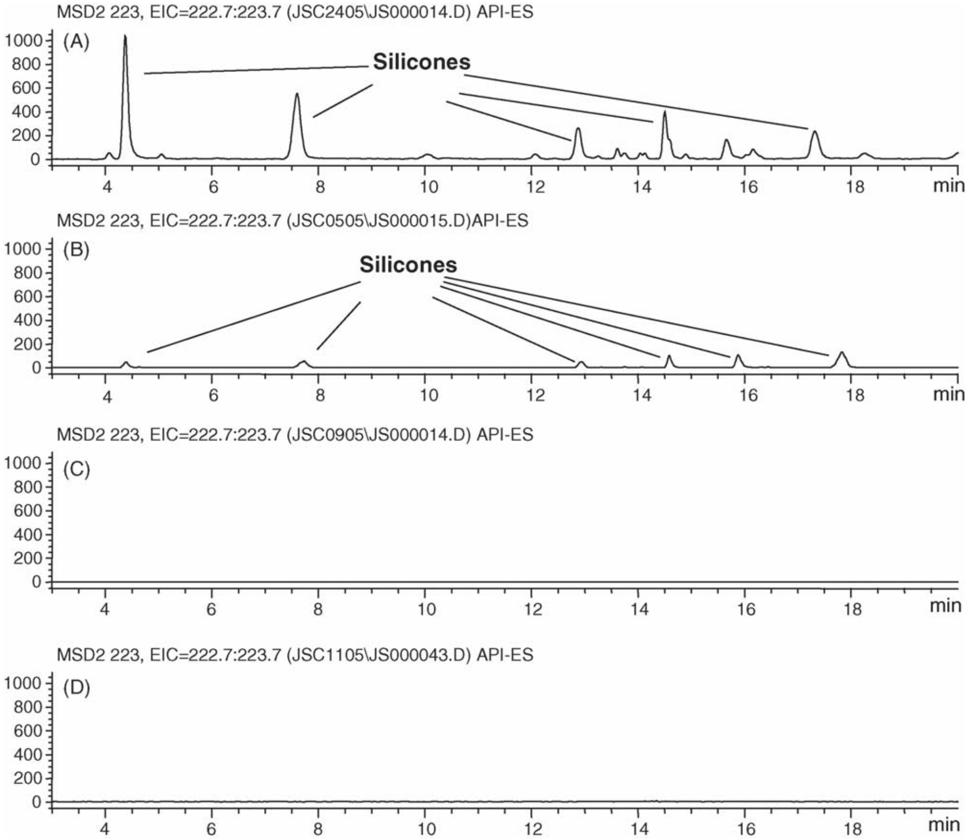


Fig. 12. Distribution of silicone oligomers extracted from tubing material 3 using: (A) glacial acetic acid; (B) 55/45 ethanol/water; (C) Divosan; (D) Dioklor. While the extracts of this material all contain relatively high levels of extracted silicon (Table 14), the form of the extracted silicon varies as a function of the extraction medium. For example, while the levels of extracted silicon are roughly the same in the 35/55 ethanol/water and Dioklor extracting media, the silicon is present as silicones in the 35/55 ethanol/water but another form in the Dioklor.

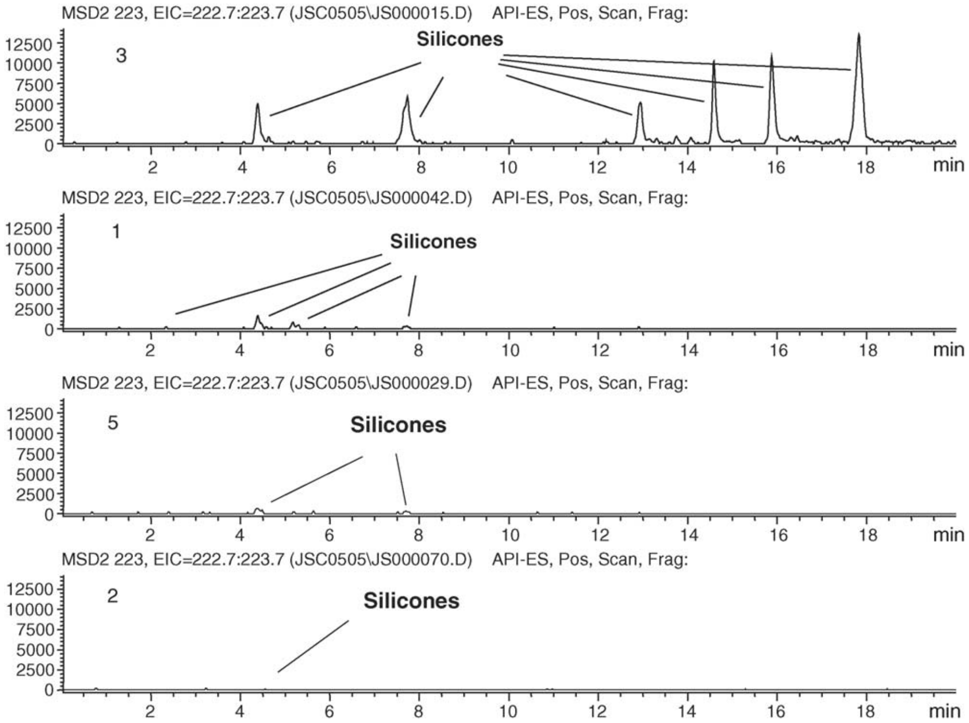


Fig. 13. Silicone distribution in ethanol/water extracts of four silicone tubing materials. The differing solubility of the silicones present in these materials is clearly illustrated by the difference in the chromatographic profiles. Thus for example, while the silicones present in material 3 are primarily low molecular weight (e.g., Fig. 2), the silicones in material 2 are primarily higher molecular weight (and thus less soluble).

3.4. Delineation of the targeted leachables

There are several reasons why it is appropriate to monitor the levels of target leachables as opposed to each individual member of the extractables profile. Firstly, many of the members of the extractables profile accumulate to only very low levels. While such low levels may be measurable in the water solution used in the identification experiments, they may not be measurable (or even detectable) in the more complex buffer solutions. The second reason is strictly practical and reflects the level of effort required to quantitate each member of the profile.

Thus the set of target leachables was established based on four compound characteristics. The first consideration was absolute concentration; thus the target leachables should include those compounds that make up a large portion of the total extracted carbon. The second consideration is chemical nature of the compounds. Targets were chosen to effectively represent the types of functionalities present in the entire profile. Thirdly, the targets were chosen to represent all the components of the manufacturing train that are suspected to possess extractables. Additionally, members of the extractables profile that have a known or suspected impact on product safety or efficacy should be targeted. Lastly, the targeted leachables must be analytically viable, as it is of little use to specify a target that cannot be quantitated effectively. To this end, the following extractables were chosen as target leachables.

- *Trace elements*: All tubing types; Ca, Mg, Zn, B. Specific to material 2; Ni, Sn, Mn, Zr, Ti, Mo.
- *Silicon*: All silicone tubing materials only.
- *Organic targets*: Dioctyl adipate, di-octyl phthalate, di-*t*-butylphenol, di-*t*-butyl phthalate, Irganox Degradate #2. See Fig. 11 for chemical information related to these targeted organic compounds.

3.5. Method qualification

Analytical methods used for the purpose of quantitation of the leachables must have known and acceptable performance characteristics. However, when methods were developed for a specific, single use application, accomplishing this objective may not require the rigor associated with formal analytical method validations.

The ICP-AES analyses included, as part of its system suitability requirements, the determination of linearity, accuracy and sensitivity. The linearity requirements of the standard procedure (r^2 NLT 0.995 over a calibration range of two orders of magnitude) were met in all cases. Sensitivity was assessed as the lowest quantity determinable (LQD), reflecting the variation in a blank signal. LQD values for the elements included in this study were typically 0.01–0.10 mg/L. Accuracy was assessed as the ability to recover an analyte spike added to all sample matrices at a level of 1 mg/L for each analyte. The acceptance criterion for accuracy (% spike recovery in the range of 70–130%) was met for all analytes. Based on these performance characteristics, the ICP-AES method was deemed suitable for use.

The performance characteristics that were determined for the LC/MS method included specificity, sensitivity, linearity and range, accuracy and precision. Specificity was considered in the context of both absolute selectivity (interference due to the extraction matrices) and relative selectivity (cross-interference between analytes). While the method was highly specific in terms of lack of response in the extraction matrices, the effective quantitation of di-octyl adipate was compromised in certain circumstances by the close elution of silicone compounds. Considering sensitivity, the method's limit of quantitation (LOQ), based on ten times the chromatographic signal to noise, is summarized in Table 13. As could reasonably be expected, MS detection is typically more sensitive than UV, except for di-*t*-butylphenol. Precision at a concentration of 1 ppm was typically 2% R.S.D. or less and analyte response was linear over a range from the LOQ to 1 or 5 ppm, respectively for MS or UV detection. While linear calibration functions were used for UV detection, quadratic calibration functions were necessary for MS detection.

Analytical accuracy, calculated as the recovery of a 1 ppm spike added to each sample matrix, was generally between 90% and 110%. UV detection generally provided for better accuracy and thus was adopted as the primary quantitation approach. In several cases, however, the analyte levels in the dynamic extracts were lower then the LOQ obtainable with UV detection. In such cases, MS detection was used to obtain concentration estimates. The only exceptions to this approach was the use of UV detection for all the di-*t*-butylphenol measurements (due to poor MS sensitivity) and the use of MS for all the dioctyl adipate measurements (due to co-elution with silicones).

3.6. Accumulation of target leachables, dynamic extractions

In general, the levels of the targeted leachables were very low in all the dynamic extracts of all the tested materials. The quantities of extracted inorganics were low in all the material extracts (typically less than 0.05 μg/cm^2 of extracted surface area), except for zinc in the Santoprene materials. Low levels of zinc (0.2 μg/cm^2) were extracted from material 7 in the first extraction step by all three extracting media. Higher levels of zinc were extracted in the first extraction step versus the two additional steps, suggesting that the material's pool of zinc is readily depleted. Somewhat higher levels of zinc (0.7 μg/cm^2) were extracted from material 8 by the concentrated Dioklor solutions in all three extraction steps, suggesting that the Zn pool in material 8 is larger than that of material 7.

The levels of organic leachables were generally low, typically less than 0.01 μg/cm^2, except in specific cases. For the silicone materials, higher levels of DOP and di-butyl phthalate were extracted from material 3 by the glacial acetic acid only, approximately 4 and 0.1 μg/cm^2 for all three extraction steps for DOP and di-butyl phthalate, respectively. Di-butyl phthalate was extracted at similar levels from material 4 by the Divosan medium. For the Santoprene materials, di-*t*-butylphenol was the only target extracted at discernible levels into any medium. The levels of di-*t*-butylphenol extracted from material 7 were approximately 0.8 μg/cm^2 for all three extraction steps.

Silicon, representative of silicones, was the only target that accumulated in material extracts to any appreciable and reproducible manner. The Si levels in the dynamic extracts of the silicone materials are summarized in Table 14. The Si levels differ from material to material and between extracting solvents for a particular material. Thus, for example, the level of extracted silicone from material 3 is approximately 18 μg/cm^2 in dilute Divosan but 220 μg/cm^2 in the glacial acetic acid. Such differences reflect the differing conditions of contact (2.5 days at ambient temperature for Divosan versus 15 days at 40 °C for the glacial acetic acid per Table 6), and the differing properties of the extracting media. While the silicon-containing entities extracted into the glacial acetic acid from material 3 are predominantly silicones (Fig. 12), silicones are not present in the Divosan extracts. Such information suggests that the silicones decompose in the highly oxidative and/or caustic matrices such as Divosan and Dioklor.

The differing solubility of the silicones is clearly illustrated by the difference in the LC/MS chromatograms of their dynamic extracts. As shown in Fig. 13, for example, the ethanol/water extracts of material 3 contain a number of silicones that can be chromatographed, while ethanol/water extracts of material 2 produce no silicone-related chromatographic peaks. While the silicones present in material 3 are primarily low molecular weight (e.g., Fig. 2), the silicones in material 2 are primarily higher molecular weight (and thus less soluble).

4. Conclusions

Eight types of tubing potentially used in pharmaceutical production facilities, including six silicone materials and two Santoprene materials, were characterized for their extractable substances by static extraction coupled with comprehensive chemical characterization of the resulting extracts. Based on the extractables profiles thus generated, target leachables were identified for each tubing material. The accumulation of these target leachables was studied by subjecting the tubing to dynamic flow, simulated use extractions. The primary organic extractables from the silicone tubing were a homologous series of silicone oligomers, with most of the tubings demonstrating a unique distribution of oligomers. Several of the silicone tubings also possessed extractable dioctyl phthalate and dioctyl adipate. Organic extractables from the Santoprene-type tubing included a number of phthalates, a series of alkylphenols and decomposition products of Irganox-type antioxidants. Inorganic extractables associated with many of the tubings included Ca, Mg, Zn and B. In general, the levels of targeted leachables extracted from the materials under simulated use (flow) conditions was much smaller than the total amount of these leachables in the tubing.

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