Supporting Information

The detection and identification of leachables in vaccine from plastic packaging materials using UPLC-QTOF MS with self-built polymer additives library

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Sample preparation

For the buffer solutions, 5 mL sample was pipetted into the glass tube. Then, 2 mL trichloromethane was added to the sample. The mixture was vigorously shaken for 10 min. After 1 h standing, the supernatant was eliminated and the lower solution was evaporated to near dryness under a gentle stream of nitrogen at 40°C. Finally, the residue was reconstituted with 500 μL trichloromethane/methanol (1/9, V/V), and 5μL sample was analyzed by UPLC-QTOF MS after the vortex procedure.

The protein should be removed for the protein media firstly. 5 mL sample was pipetted into the glass tube. Then, 0.5 g lead acetate and 1 mL acetonitrile were added into the glass tube, completely mixed and stood for 1 h. After the protein precipitated, the supernatant was removed to another 15 mL glass tube, and 1 mL acetonitrile was used to clean the precipitation, and the supernatants were combined. Then, 3 mL trichloromethane was added to the supernatant to perform the LLE procedure as the buffer solutions.

The finished drug product was transferred 5 mL to a 15mL glass tube first. Then the 5 mL sample was standing for 1 day to let the protein and adjuvant precipitate, and the supernatant was pipetted into the 15 mL glass tube. 0.5g lead acetate and 1mL acetonitrile was used to clean the precipitation, and the supernatants were combined. Then 3mL trichloromethane was added to the supernatant to perform the LLE procedure as the buffer solutions.

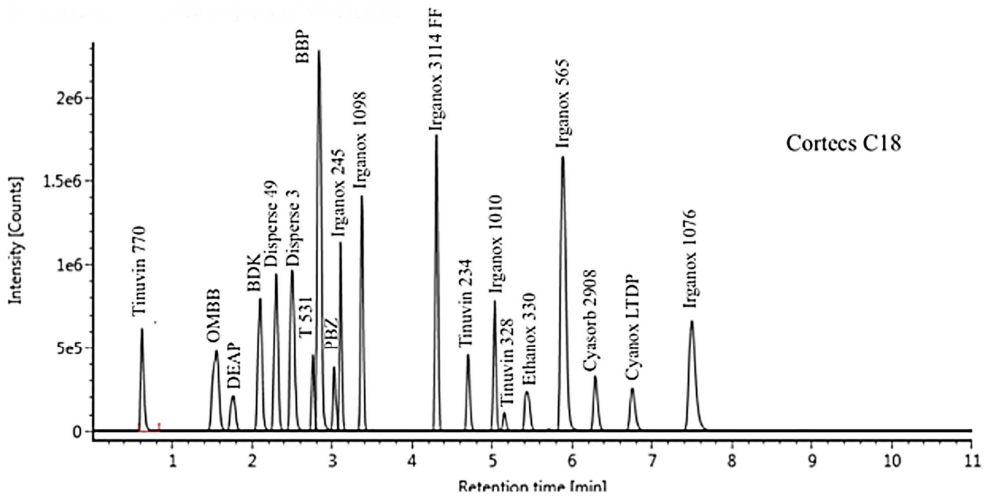

Figure S1 Chromatogram of 20 additives separated on Cortecs C18 column

Table S1 The information of UNIFI library for polymer additives by UPLC-QTOF MS

No.	Name	Formula	RT	F1	F2	F3	Classification	F1	F2	F3	Origin
1	1,2,2,6,6-Pentamethyl-4-piperidinol[a]	C10H21NO	0.6	72.0808	116.107	154.159	light stabilizer	C4H10N	C6H14NO	C10H20N	Cytec
2	2,2-Diethoxyacetophenone (DEAP) [a]	C12H16O3	1.77	105.0335	135.0441	163.039	photoinitiator	C7H5O	C8H7O2	C9H7O3	BASF
3	2,2-dimethoxy-2-phenylacetophenone (BDK) [a]	C16H16O3	2.12	119.0491	152.0468	180.0781	photoinitiator	C8H7O	C8H8O3	C10H12O3	BASF
4	2-Ethylhexyl 8-(3-octyl-2-oxiranyl)octanoate[a]	C26H50O3	4.78	263.2369	281.2475	299.2581	plasticizer	C18H31O	C18H33O2	C18H35O3	BASF
5	2-Ethylhexyl diphenyl phosphate (EHDPP) [a]	C20H27O4P	3.44	77.0386	185.0362	251.0468	flame retardant	C6H5	C8H10O3P	C12H12O4P	Dr. Ehrenstorfer
6	2-Hydroxy-2-methyl propiophenone (photoinitiator1173) [a]	C10H12O2	1.13	77.0386	105.0335	149.0597	photoinitiator	C6H5	C7H5O	C9H9O2	BASF
7	2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (photoinitiator2959) [a]	C12H16O4	0.85	95.0491	179.1067	207.1016	photoinitiator	C6H7O	C11H15O2	C12H15O3	BASF
8	2-isopropylthioxanthone (2-ITX)	C16H14OS	1.98	105.0335	151.0576	224.0654	photoinitiator	C7H5O	C9H11S	C15H12S	BASF
9	2-Mercaptobenzimidazole (MB) [a]	C7H6N2S	0.81	93.0573	106.0525	118.0525	antioxidant	C6H7N	C6H6N2	C7H6N2	Huangyan
10	3-formylbenzoic acid[b]	C8H6O3	0.68	77.0397	105.0346		synthetic intermediate	C6H5	C7H5O		Dr. Ehrenstorfer
11	4-(dimethylamino)-benzoicaciethylester (EDAB)[a]	C11H15NO2	2.06	107.073	134.06	151.0628	photoinitiator	C7H9N	C8H8NO	C8H9NO2	BASF
12	4-Benzoylbiphenyl (PBZ) [a]	C19H14O	3.04	77.0386	105.0335	181.0648	photoinitiator	C6H5	C7H5O	C13H9O	BASF
13	4-methyl benzophenone (4-MBP) [a]	C14H12O	2.12	77.0386	91.0542	105.0335	photoinitiator	C6H5	C7H7	C7H5O	BASF
14	8-methylnonyl tridecyl phthalate	C31H52O4	5.43	149.0233	289.1798	307.1904	plasticizer	C8H5O3	C18H25O3	C18H27O4	BASF
15	Accelerator CZ[a]	C13H16N2S2	3.05	83.0855	165.978	183.0045	accelerant	C6H11	C7H4NS2	C7H7N2S2	Huangyan
16	Accelerator DM[a]	C14H8N2S4	3.42	123.0137	166.9858	197.95	accelerant	C6H5NS	C7H5NS2	C7H4NS3	Huangyan
17	Accelerator M[a]	C7H5NS2	1.2	92.0495	109.0106	135.0137	accelerant	C6H6N	C6H5S	C7H5NS	Huangyan
18	Acid Violet 43[a]	C21H14NNaO6S	2.67	262.0169	328.0968	392.0587	dye	C12H8NO4S	C21H14NO3	C21H14NO5S	Dr. Ehrenstorfer
19	a-Hydroxycyclohexylphenylketone	C13H16O2	1.82	105.0335			photoinitiator	C7H5O			BASF

	(photoinitiator 184) [a]										
20	Antioxidant 201 (GW-201) [a]	C11H23NO2	0.61	102.0913	123.1168	184.1696	antioxidant	C5H12NO	C9H15	C11H22NO	Jiyi
21	Antioxidant 616[b]	C32H44O2	4.14	163.1128	347.2017	403.2643	antioxidant	C11H15O	C24H27O2	C28H35O2	Jiyi
22	Antioxidant NBC[a]	C18H36N2NiS4	4.11	116.0528	172.1154	128.1434	antioxidant	C5H10NS	C9H18NS	C8H18N	Huangyan
23	Antioxidant RD[a]	C12H15N	2.5	118.0651	132.0808	159.1043	antioxidant	C8H8N	C9H10N	C11H13N	Huangyan
24	Arachidic acid[b]	C20H40O2	4.85	293.285			lubricant	C20H37O			Dr. Ehrenstorfer
25	Behenic acid[b]	C22H44O2	5.39	321.3163			detergent	C22H41O			Dr. Ehrenstorfer
26	Benzoic acid[b]	C7H6O2	0.82				preservative				Dr. Ehrenstorfer
27	Benzophenone	C13H10O	1.98	77.0386	105.0335		photoinitiator	C6H5	C7H5O		BASF
28	Benzyl 2-Ethylhexyl Phthalate (OBP) [a]	C23H28O4	3.62	91.0542	149.0233	257.0808	plasticizer	C7H7	C8H5O3	C15H13O4	Jiyi
29	Benzyl 4-methylpentyl phthalate[a]	C21H24O4	3.28	149.0233	91.0542	233.1172	plasticizer	C8H5O3	C7H7	C14H17O3	Jiyi
30	Benzyl butyl phthalate (BBP) [a]	C19H20O4	2.84	91.0542	149.0233	205.0859	plasticizer	C7H7	C8H5O3	C12H13O3	Jiyi
31	Bis(2-butoxyethyl) Ester (DBEP)[a]	C20H30O6	2.86	101.0961	149.0233	249.1121	plasticizer	C6H13O	C8H5O3	C16H17O5	Jiyi
32	Bis(2-ethylhexyl) isophthalate (DOIP) [a]	C24H38O4	4.22	279.1591	149.0233	167.0339	plasticizer	C16H23O4	C8H5O3	C8H7O4	Jiyi
33	Bis(4-methylcyclohexyl) phthalate[a]	C22H30O4	3.8	97.1012	149.0233	167.0339	plasticizer	C7H13	C8H5O3	C8H7O4	Jiyi
34	Bis(4-methylpentyl) phthalate[a]	C20H30O4	3.69	149.0233	163.039	233.1178	plasticizer	C8H5O3	C9H7O3	C14H17O3	Jiyi
35	Bis(6-ethyl-14-methylpentadecan-7-yl)phthalate[a]	C44H78O4	8.56	413.2686	301.1434	283.2632	plasticizer	C26H37O4	C18H21O4	C18H35O2	Jiyi
36	Bis(8-methylnonyl) phthalate[a]	C28H46O4	4.78	149.0233	289.1798	307.1904	plasticizer	C8H5O3	C18H25O3	C18H27O4	Jiyi
37	Bis(oxiran-2-ylmethyl) cyclohex-4-ene-1,2-dicarboxylate (711) [a]	C14H18O6	1.1	79.0542	153.0546	181.0859	lubricant	C6H7	C8H9O3	C10H13O3	Jiyi
38	Butyl cyclohexyl benzene-1,2-dicarboxylate[a]	C18H24O4	3.16	149.0233	205.0859	223.0965	plasticizer	C8H5O3	C12H13O3	C12H15O4	Jiyi
39	Butyl isodecyl phthalate[a]	C22H34O4	3.95	141.1638	205.0859	149.0233	plasticizer	C10H21	C12H13O3	C8H5O3	Jiyi
40	Butyl octyl phthalate[a]	C20H30O4	3.75	205.0859	149.0233	261.1485	plasticizer	C12H13O3	C8H5O3	C16H21O3	BASF
41	Butylated hydroxytoluene (BHT)[b]	C15H24O	3.47	203.1441			antioxidant	C14H19O			BASF
42	Cinnamic acid[b]	C9H8O2	3.28	103.0553			heat stablier	C8H7			Dr. Ehrenstorfer
43	Cresyl Diphenyl Phosphate (CDP) [a]	C19H17O4P	2.78	91.0542	247.0519	215.0256	plasticizer	C7H7	C12H8O4P	C12H8O2P	Cytec

44	Cyanox 1790[b]	C42H57N3O6	4.05	232.1343	318.1459	508.2817	antioxidant	C14H18NO2	C16H20N3O4	C29H38N3O5	Cytec
45	Cyanox LTDP[a]	C30H58O4S	6.76	161.0267	143.0161	329.2145	antioxidant	C6H9O3S	C6H7O2S	C18H33O3S	Cytec
46	Cyanox1760 (antioxidant 300)[b]	C22H30O2S	3.2	163.1128	179.09	194.0771	antioxidant	C11H15O	C11H15S	C11H14OS	Cytec
47	Cyasorb 1164[a]	C33H39N3O2	9.95	132.0808	248.1645	136.0393	light stabilizer	C9H10N	C15H22NO2	C7H6NO2	Cytec
48	Cyasorb 2908[a]	C31H54O3	6.26	57.0699	233.1536	177.091	light stabilizer	C4H9	C15H21O2	C20H41O	Cytec
49	Cyasorb 3638[a]	C22H12N2O4	3.57	146.0237	250.0499		light stabilizer	C8H4NO2	C15H8NO3		Cytec
50	Cyasorb 3853[a]	C27H53NO2	3.22	58.0651	140.1434	123.1168	light stabilizer	C3H8N	C9H18N	C9H15	Cytec
51	Decyl octyl ester[a]	C26H42O4	4.74	149.0233	261.1485	289.1798	plasticizer	C8H5O3	C16H21O3	C18H25O3	Jiyi
52	Diamino diphenyl sulfone[a]	C12H12N2O2S	0.67	92.0495	156.0114		curing agent	C6H6N	C6H6NO2S		Jiyi
53	Diamyl Phthalate (DAP) [a]	C18H26O4	3.36	149.0233	163.039		plasticizer	C8H5O3	C9H7O3		Jiyi
54	Dibutyl Maleate (DBM) [a]	C12H20O4	2.35	99.0077	155.0703	170.0937	plasticizer	C4H3O3	C8H11O3	C9H14O3	Jiyi
55	Dibutyl phthalate (DBP) [a]	C16H22O4	2.89	205.0859	149.0233	163.039	plasticizer	C12H13O3	C8H5O3	C9H7O3	Jiyi
56	Dibutyl Sebacate (DBS) [a]	C18H34O4	3.67	139.1117	185.1172	259.1904	plasticizer	C9H15O	C10H17O3	C14H27O4	Jiyi
57	Dicumyl peroxide (DCP) [a]	C18H22O2	3.52				vulcanizer				Jiyi
58	Dicyclohexyl phthalate (DCHP) [a]	C20H26O4	3.41	149.0233	231.1016	249.1121	plasticizer	C8H5O3	C14H15O3	C14H17O4	Jiyi
59	Diethyl phthalate (DEP) [a]	C12H14O4	1.59	161.0233	149.0233	177.0546	plasticizer	C9H5O3	C8H5O3	C10H9O3	Jiyi
60	Diheptan-3-yl phthalate[a]	C24H44O4	4.08	129.0182	213.1121	315.2166	plasticizer	C5H5O4	C11H17O4	C17H31O5	Jiyi
61	Dihexyl Phthalate (DNHP) [a]	C20H30O4	3.73	149.0233	233.1172	163.039	plasticizer	C8H5O3	C14H17O3	C9H7O3	Jiyi
62	Diisobutyl phthalate (DIBP) [a]	C16H22O4	2.83	163.039	149.0233	205.0859	plasticizer	C9H7O3	C8H5O3	C12H13O3	Jiyi
63	Dinonyl Phthalate (DINP) [a]	C26H42O4	4.74	275.1642	163.039	149.0233	plasticizer	C17H23O3	C9H7O3	C8H5O3	Jiyi
64	Dioctyl ester (DNOP) [a]	C24H38O4	4.36	113.1325	149.0233	261.1485	plasticizer	C8H17	C8H5O3	C16H21O3	Jiyi
65	Dioctyl isophthalate[a]	C24H38O4	4.22	149.0233	167.0339	279.1591	plasticizer	C8H5O3	C8H7O4	C16H23O4	Jiyi
66	Dioctyl phthalate (DOP) [a]	C24H38O4	4.22	149.0233	167.0339	279.1591	plasticizer	C8H5O3	C8H7O4	C16H23O4	Jiyi
67	Dioctyl sebacate[a]	C26H50O4	4.91	139.1117	297.2424	185.1172	plasticizer	C9H15O	C18H33O3	C10H17O3	Jiyi
68	Diphenyl guanidine (D) [a]	C13H13N3	0.64	77.0386	92.0495	119.0604	accelerant	C6H5	C6H6N	C7H7N2	BASF

69	Diphenyl Phthalate[a]	C20H14O4	2.51	77.0386	197.0597	225.0546	plasticizer	C6H5	C13H9O2	C14H9O3	Jiyi
70	Dipropyl Phthalate[a]	C16H18O6	2.27	209.0808	149.0233	121.0284	plasticizer	C11H13O4	C8H5O3	C7H5O2	Jiyi
71	Disperse Brown 1[a]	C16H15Cl3N4O4	2.65	185.0476	197.0476	228.066	dye	C8H10N2OCl	C9H10N2OCl	C10H13N2O2Cl	Dr. Ehrenstorfer
72	Disperse Orange 1[a]	C18H14N4O2	3.32	169.0886	181.076	273.126	dye	C12H11N	C12H9N2	C18H15N3	Dr. Ehrenstorfer
73	Disperse Red 17[a]	C17H20N4O4	2.24	164.107	269.1033	314.1373	dye	C10H14NO	C14H13N4O2	C16H18N4O3	Dr. Ehrenstorfer
74	Disperse Yellow 1[a]	C12H9N3O5	3.32	258.0509	228.0529	149.022	dye	C12H8N3O4	C12H8N2O3	C6H3N3O2	Dr. Ehrenstorfer
75	Disperse Yellow 3[a]	C15H15N3O2	2.53	253.121	150.0788	107.0491	dye	C15H15N3O	C8H10N2O	C7H7O	Dr. Ehrenstorfer
76	Disperse Yellow 49[a]	C21H22N4O2	2.32	238.1339	223.1104	164.0706	dye	C15H16N3	C14H13N3	C9H10N1O2	Dr. Ehrenstorfer
77	Ditridecyl phthalate[a]	C34H58O4	8.49	331.2268	149.0233	163.039	plasticizer	C21H31O3	C8H5O3	C9H7O3	Jiyi
78	Dodacyl mercaptan (DDM) [a]	C13H14N2	0.61	92.0495	106.0651	182.0964	modifier	C6H6N	C7H8N	C13H12N	Dr. Ehrenstorfer
79	Dodecanoic acid[b]	C12H24O2	3.36		181.1598		lubricant		C12H21O		Dr. Ehrenstorfer
80	Ethanox 330[a]	C54H78O3	5.38	513.3727	351.2682	219.1743	antioxidant	C36H49O2	C25H35O	C15H23O	Albemarle
81	Heneicosanoic acid[b]	C21H42O2	5.11		307.3006		synthetic intermediate		C21H39O		Dr. Ehrenstorfer
82	Henraiaconranoic acid[b]	C31H62O2	6.38		447.4571		synthetic intermediate		C31H59O		Dr. Ehrenstorfer
83	Heptadecanoic acid[b]	C17H34O2	4.19	209.1911	225.2224		synthetic intermediate	C14H25O	C15H29O		Dr. Ehrenstorfer
84	Hexabromocyclododecane (HBCD)[b]	C12H18Br6	3.78	78.9189	158.9815		flame retardant	Br	C6H8Br		Dr. Ehrenstorfer
85	Hexacosanic acid[b]	C26H52O2	7.19		255.233		fatty acid		C16H31O2		Dr. Ehrenstorfer
86	Hexamethylenetetramine (H) [a]	C6H12N4	0.6	85.076	98.0713	112.0869	accelerant	C4H9N2	C4H8N3	C5H10N3	BASF
87	Hexyl 8-methylnonyl phthalate[a]	C24H38O4	4.22		149.0233	273.1121	plasticizer		C8H5O3	C16H17O4	Jiyi
88	Irgafos 168[a]	C42H63O3P	9.78	385.2291	441.2917		antioxidant	C24H34O2P	C28H42O2P		BASF

89	Irganox 1010[a]	C73H108O12	4.91	205.1598	739.4427	957.6097	antioxidant	C14H21O	C43H63O10	C58H85O11	BASF
90	Irganox 1076[a]	C35H62O3	7.44	267.2693	311.2956		antioxidant	C18H35O	C20H39O2		BASF
91	Irganox 1098[a]	C40H64N2O4	3.41	100.1121	248.1645	507.3581	antioxidant	C6H14N	C15H22NO2	C32H47N2O3	BASF
92	Irganox 1135[b]	C25H42O3	4.13			363.2894	antioxidant			C23H39O3	BASF
93	Irganox 245[b]	C34H50O8	3.1	235.134	367.2126	409.2232	antioxidant	C14H19O3	C20H31O6	C22H33O7	BASF
94	Irganox 565[a]	C33H56N4OS2	5.94	118.9732	231.0984	289.1369	antioxidant	C2H3N2S2	C10H19N2S2	C16H21N2OS	BASF
95	Irganox HP-136[a]	C24H30O2	3.84	245.1536	323.2369		antioxidant	C16H21O2	C23H31O		BASF
96	Irganox 1035[b]	C38H58O6S	3.99	205.054	277.1809	423.2211	antioxidant	C8H13O4S	C17H25O3	C23H35O5S	BASF
97	Irganox 3114 FF[a]	C48H69N3O6	4.31	219.1743			antioxidant	C15H23O			BASF
98	Irganox MD 1024[a]	C34H52N2O4	3.28	441.2748	385.2122	329.1496	antioxidant	C26H37N2O4	C22H29N2O4	C18H21N2O4	BASF
99	Isodecyl octyl phthalate(ODP)[a]	$C_{26}H_{42}O_4$	4.57	163.039	149.0233	261.1485	plasticizer	C9H7O3	C8H5O3	C16H21O3	Jiyi
100	Itaconic acid[b]	C5H6O4	0.73	85.0295	96.9931		synthetic intermediate	C4H5O2	C4HO3		Dr. Ehrenstorfer
101	Linoleic acid[b]	C18H32O2	3.94				synthetic intermediate				Dr. Ehrenstorfer
102	Melamine[a]	C3H6N6	0.6	85.0509	68.0243	110.0461	curing agent	C2H5N4	C2H2N3	C3H4N5	Dr. Ehrenstorfer
103	Metanil Yellow[a]	C18H14N3NaO3S	1.85	167.073	181.076	272.1182	dye	C12H9N	C12H9N2	C18H14N3	Dr. Ehrenstorfer
104	N-(p-toluene-sulphonylamido-N'-phenylene diamine) (TPPD) [a]	C19H18N2O2S	1.9	93.0573	107.0604	183.0917	antioxidant	C6H7N	C6H7N2	C12H11N2	BASF
105	N,N,O-triglycidyl-p-aminophenol (AFG-90) [a]	C15H19O4N	0.97	220.0968	234.1125	260.1281	lubricant additive	C12H14NO3	C13H16NO3	C15H18NO3	BASF
106	N,N'-bis(2,2,6,6-tetramethyl-4-piperidinyl)-6-hexanediamine(HMBTAD) [a]	C24H50N4	0.6	140.1434	239.2482	282.2904	light stabilizer	C9H18N	C15H31N2	C17H36N3	BASF
107	N,N-Methylene-bis-acrylamide[a]	C7H10N2O2	0.73	84.0444	100.0267		cross-linking	C4H6NO	C3H4N2O2		Chemtura

							agent				
108	Naugard 445(antioxidant 405) [a]	C30H31N	4.05	119.0855	196.1121	375.1982	antioxidant	C9H11	C14H14N	C28H25N	Chemtura
109	n-Hexyl decyl phthalate[a]	$C_{24}H_{38}O_4$	4.36	233.1172	149.0233	163.039	plasticizer	C14H17O3	C8H5O3	C9H7O3	Jiyi
110	Nonadecanoic acid[b]	C19H38O2	4.63	253.2537	280.2772		fatty acid	C17H33O	C19H36O		Dr. Ehrenstorfer
111	Nylostab S-EED[a]	C26H42N4O2	0.56	231.1128	287.1754	370.2489	stabilizer	C13H15N2O2	C17H23N2O2	C22H32N3O2	Chemtura
112	Octacosanoic acid[b]	C28H56O2	8.76	281.2486			synthetic intermediate	C18H33O2			Dr. Ehrenstorfer
113	Octadecanoic acid[b]	C18H36O2	4.42	239.238	265.2537		heat stabilizer	C16H31O	C18H33O		Dr. Ehrenstorfer
114	Oleic acid[b]	C18H34O2	4.15				lubricant				Dr. Ehrenstorfer
115	o-Methyl-benzoyl Benzoate(OMBB) [a]	C15H12O3	1.58	105.0335	209.0597		photoinitiator	C7H5O	C14H9O2		BASF
116	Palmitic acid[b]	C16H32O2	4.09	237.2224			lubricant	C16H29O			Dr. Ehrenstorfer
117	Pentacosanoic acid[b]	C25H50O2	6.64				fatty acid				Dr. Ehrenstorfer
118	Pentadecanoic acid[b]	C15H30O2	3.87	223.2062			fatty acid	C15H27O			Dr. Ehrenstorfer
119	Perfluorooctanoic Acid (PFOA)[b]	C8HF15O2	2.41	168.9894	218.9862	368.9766	emulgator	C3F7	C4F9	C7F15	Dr. Ehrenstorfer
120	Phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide (photoinitiator 819) [a]	C26H27O3P	3.37	147.0804	257.0726	299.0832	photoinitiator	C10H11O	C15H14O2P	C17H16O3P	BASF
121	2-Benzyl-2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-1-butanone (photoinitiator 369) [a]	C23H30N2O2	0.59	176.1434		322.1802	photoinitiator	C12H18N		C21H24NO2	BASF
122	Ethyl 4-Dimethylaminobenzoate (EDB) [a]	C11H14NO2	2.05	107.073	134.06	150.055	photoinitiator	C7H9N	C8H8NO	C8H8NO2	BASF
123	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO) [a]	C22H21O2P	2.7	119.0855	147.0804		photoinitiator	C9H11	C10H11O		BASF
124	Pyridinium dichromate[a]	C9H19NO	0.6	81.0699	102.0913	123.1168	light stabilizer	C6H9	C5H12NO	C9H15	Dr. Ehrenstorfer
125	Rionox MD-697 (Naugard XL-1)[b]	C40H60N2O8	3.56	205.1598	277.1809	417.2395	antioxidant	C14H21O	C17H25O3	C23H33N2O5	Chemtura
126	Sodium dodecyl sulfate[a]	C12H25NaO4S	2.74	149.0267		232.1128	emulgator	C5H9O3S		C11H20O3S	Dr. Ehrenstorfer
127	Solvent Blue 35[a]	C22H26N2O2	4.08	307.1441	294.1363	251.0815	dye	C19H19N2O2	C18H18N2	C15H11N2O2	Dr. Ehrenstorfer

									O2		
128	Solvent Red 1[a]	C17H14N2O2	3.48	248.0944	156.0444	123.0679	dye	C16H12N2O	C10H6NO	C7H9NO	Dr. Ehrenstorfer
129	Sudan Orange G[a]	C12H10N2O2	4.11	93.0573	122.0237	198.0788	dye	C6H7N1	C6H4N1O2	C12H10N2O1	Dr. Ehrenstorfer
130	Sudan I[a]	C16H12N2O					dye				Dr. Ehrenstorfer
131	Sudan Red 7B[a]	C24H21N5	5.03	274.1339	198.1026	183.0917	dye	C18H16N3	C12H12N3	C12H11N2	Dr. Ehrenstorfer
132	Antioxidant T531[a]	C16H13N	2.76	92.0495	128.0621	142.0651	antioxidant	C6H6N	C10H8	C10H8N	BASF
133	Terephthalic acid[b]	C8H6O4	0.83	121.0295			synthetic intermediate	C7H5O2			Dr. Ehrenstorfer
134	Tetrabromobisphenol A (TBBPA)[b]	C15H12Br4O2	2.91	168.9295	288.8869	443.8002	flame retardant	C6H2OBr	C9H7OBr2	C14H7O2Br3	Dr. Ehrenstorfer
135	Tetracosanoic acid[b]	C24H48O2	6.13	349.3476			synthetic intermediate	C24H45O			Dr. Ehrenstorfer
136	Tetradecanoic acid[b]	C14H28O2	3.77	210.1989			defoamer	C14H26O			Dr. Ehrenstorfer
137	Tetramethyl thiuram disulfide (TMTD) [a]	C6H12N2S4	1.13	88.0215	119.9936	195.9378	accelerant	C3H6NS	C3H6NS2	C4H6NS4	
138	Tinuvin 144[a]	C42H72N2O5	0.61	154.159	219.1743	532.3997	light stabilizer	C10H20N	C15H23O	C32H54NO5	BASF
139	Tinuvin 1577[a]	C27H27N3O2	7.07	104.0495	136.0393	220.1332	light stabilizer	C7H6N	C7H6NO2	C13H18NO2	BASF
140	Tinuvin 1988[a]	C13H14O5	1.51	59.0128	161.0597	219.0652	light stabilizer	C2H3O2	C10H9O2	C12H11O4	BASF
141	Tinuvin 234[a]	C30H29N3O	4.69	119.0855	292.1444	370.1914	light stabilizer	C9H11	C18H18N3O	C24H24N3O	BASF
142	Tinuvin 292-1 (m/z508) [a]	C30H56N2O4	0.61	72.0808	123.1168	356.2795	light stabilizer	C4H10N	C9H15	C20H38NO4	BASF
143	Tinuvin 292-2 (m/z369) [a]	C21H39NO4	1.04	123.1168	199.1329	154.159	light stabilizer	C9H15	C11H19O3	C10H20N	BASF
144	Tinuvin 312[a]	C18H20N2O3	3.1	109.0522	148.0757	137.0835	light stabilizer	C6H7NO	C9H10NO	C8H11NO	BASF
145	Tinuvin 326[a]	C17H18ClN3O	4.9	225.0088	267.0194	283.0507	light stabilizer	C12H4N3Cl	C14H6N3OCl	C15H10N3OCl	BASF
146	Tinuvin 327[a]	C20H24ClN3O	5.23	57.0699	119.0487	149.0961	light stabilizer	C4H9	C6H5N3	C10H13O	BASF

147	Tinuvin 328[a]	C22H29N3O	5.19	71.0855	252.1131	322.1914	light stabilizer	C5H11	C15H14N3O	C20H24N3O	BASF
148	Tinuvin 329[a]	C20H25N3O	4.31	253.121	212.0818	120.0556	light stabilizer	C15H15N3O	C12H10N3O	C6H6N3	BASF
149	Tinuvin 360[a]	C41H50N6O2	4.43	383.1377	439.2129	495.2629	light stabilizer	C22H17N5O2	C27H27N4O2	C30H33N5O2	BASF
150	Tinuvin 400-1(m/z654.4276) [a]	C41H55N3O4	8.51	472.2231	392.2795	210.0761	light stabilizer	C28H30N3O4	C23H38NO4	C10H12NO4	BASF
151	Tinuvin 400-2(m/z640.4113) [a]	C40H53N3O4	6.61	398.1863		337.2737	light stabilizer	C25H24N3O2		C21H37O3	BASF
152	Tinuvin 622[a]	C17H31NO4	3.66				light stabilizer				BASF
153	Tinuvin 770 [a]	C28H52N2O4	0.62			123.1168	antioxidant			C9H15	BASF
154	Tinuvin PED [a]	C13H11N3O	3.29	79.0542	107.0491	120.0556	antioxidant	C6H7	C7H7O	C6H6N3	BASF
155	Tri(2-ethylhexy)phosphate [a]	C24H51O4P	4.68			321.2189	plasticizer			C16H34O4P	Dr. Ehrenstorfer
156	Triallyl isocyanurate (TAIC) [a]	C12H15N3O3	1.56	84.0444	165.0659	224.1394	accelerant	C4H6NO	C8H9N2O2	C11H18N3O2	Dr. Ehrenstorfer
157	Tributyl phosphate [a]	C12H27O4P	2.75	193.0624	207.0781	237.125	plasticizer	C7H14O4P	C8H16O4P	C10H22O4P	Dr. Ehrenstorfer
158	tricosanoic acid[b]	C23H46O2	5.75	284.2721			fatty acid	C18H36O2			Dr. Ehrenstorfer
159	Triethyl phosphate [a]	C6H15O4P	1.02	97.9763	136.0284	153.0311	plasticizer	H3O4P	C4H9O3P	C4H10O4P	Jiyi
160	Triphenyl phosphate (TPP, TPhP) [a]	C18H15O4P	2.51	94.0413	138.9943	233.0362	flame retardant	C6H6O	C12H11O2	C12H10O3P	Dr. Ehrenstorfer
161	Tripropyl phosphate [a]	C9H21O4P	1.9	97.9763		194.0702	plasticizer	H3O4P		C7H15O4P	Jiyi
162	Tripropylamine [a]	C9H21N	0.65	58.0651	73.0886	100.1121	synthetic intermediate	C3H8N	C4H11N	C6H14N	Dr. Ehrenstorfer
163	Tri-p-tolyl phosphate[a]	C21H21O4P	3.23	91.0542	261.0675	279.0781	plasticizer	C7H7	C14H14O3P	C14H16O4P	BASF
164	Tris(1,3-Dichloro-2-Propyl)Phosphate (TDCP) [a]	C9H15Cl6O4P	2.45	98.9842	136.9998	208.9532	flame retardant	H4O4P	C3H6O4P	C3H8O4PCl2	Dr. Ehrenstorfer
165	Tris(2-butoxyethyl) phosphate (TBEP) [a]	C18H39O7P	2.96	107.9607	124.9998		plasticizer	CHO4P	C2H6O4P		Dr. Ehrenstorfer
166	Tris(2-carboxyethyl)phosphine (TCEP) [a]	C6H12Cl3O4	1.16	124.9998	160.9765	222.9688	flame	C2H6O4P	C2H7O4PCl	C4H10O4PCl	Dr. Ehrenstorfer

		P					retardant				
167	Tris（clorisopropyl）Phosphate (TCPP) [a]	C9H18Cl3O4P	1.9	98.9842	174.9921	215.0234	flame retardant	H4O4P	C3H9O4PCl	C6H13O4PCl	Dr. Ehrenstorfer
168	Tris(dimethylaminomethyl)phenol [a]	C15H27N3O	0.67				plasticizer				Dr. Ehrenstorfer
169	Undecanoic acid[b]	C11H22O2	3.12				fatty acid				Dr. Ehrenstorfer
170	Uvinul 120[b]	C29H42O3	4.14	189.1285	205.1598		light stabilizer	C13H17O	C14H21O		BASF
171	Uvinul 3030[a]	C69H48N4O8	3.49	350.1387	812.2755	83.0491	light stabilizer	C21H20NO4	C53H38N3O6	C5H7O	BASF
172	Uvinul 3000 (UV 0)[a]	C13H10O3	1.72	105.0335	137.0233		light stabilizer	C7H5O	C7H5O3		BASF
173	Uvinul 3008 (Cyasorb 531)[a]	C21H26O3	4.18	137.0233	215.0703	105.0335	light stabilizer	C7H5O3	C13H11O3	C7H5O	BASF
174	Uvinul 3040 (UV 9)[a]	C14H12O3	2.46	105.0335	151.039	77.0386	light stabilizer	C7H5O	C8H7O3	C6H5	BASF

a, ionized in positive mode; b, ionized in negative mode; RT, retention times; F1, fragment 1; F2, fragment 2; F3, fragment 3

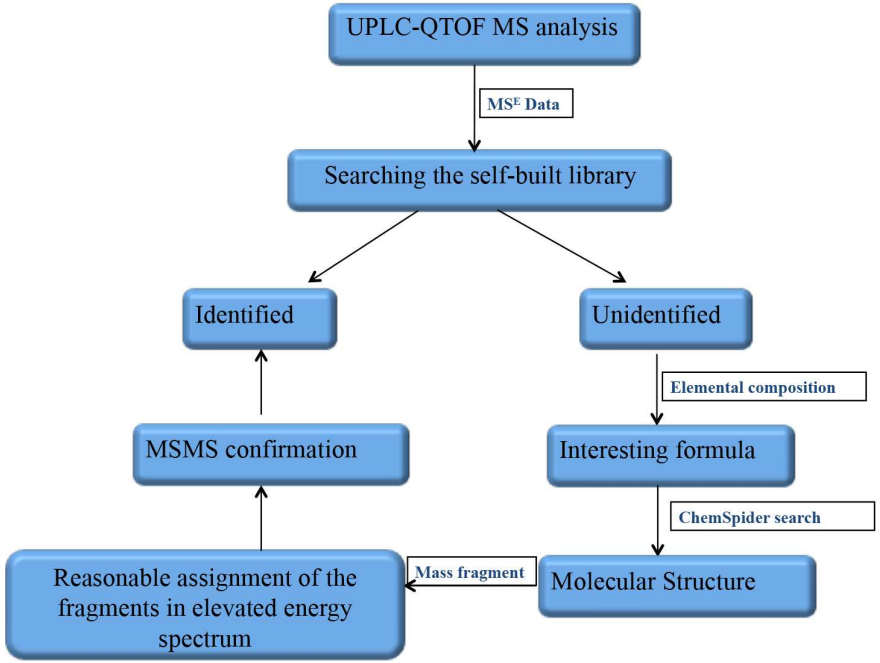

Figure S2 Workflow for identification targeted and non-targeted leachables

Method validation

According to the information provided by the packaging manufacture, Irgafos 168, Irganox 1010, Irganox 1076 and Bis(8-methylnonyl) phthalate were used in the packaging materials. Hence, these additives were selected to assess the sample preparation method. As shown in Table S-1, the achieved limits of detection (LODs) and limits of quantitation (LOQs) of the developed method were in the range from 0.1-0.5 µg/L and 0.2-2.5 µg/L. The liner ranges are from 0.5-50 µg/L with the correlation (R^2) greater than 0.998. Recoveries of the compounds were measured by spiking blank media samples with three additives at three different concentrations (5.0, 10.0, and 20.0µg/L). The recoveries in three media for Irganox 1010, Irganox 1076, Bis (8-methylnonyl) phthalate and Irgafos 168 are 75.86-117.74 %, 77.50-110.90 %, 67.7-117.9 %and 80.06-119.10 %, respectively, with their relative standard deviations (RSDs) lower than 10 % based on the peak areas for six replicate runs (Table S2).

Table S2 Linear ranges, correlation coefficients, mean recoveries, LOQs, and LODs of the 4 additives

Additives	Linear range (ug/L)	Correlation index (R^2)	Recoveries and RSD (%, n=6)			LOD (ug/L)	LOQ (ug/L)
			5µg/L	10µg/L	20µg/L		
A) Irganox 1076	0.5-50	0.998	78.7 (7.3)	77.8 (4.4)	83.0 (5.6)	0.5	2
Irganox 1010	1-50	0.999	105.1 (7.3)	117.7 (2.3)	81.4 (0.9)	0.1	0.2

Bis(8-methylnonyl) phthalate	0.5-50	0.999	97.1 (3.7)	90.1 (3.6)	95.8 (2.4)	0.1	0.4
Irgafos 168	1-50	0.999	118.1 (2.8)	98.5 (1.0)	82.6 (3.6)	0.2	0.5
B) Irganox 1076	0.5-50	0.998	83.3 (7.1)	110.9 (3.6)	85.5 (9.2)	0.5	2.5
Irganox 1010	1-50	0.999	114.1 (6.9)	75.8 (7.7)	107.2 (6.7)	0.1	0.4
Bis(8-methylnonyl) phthalate	0.5-50	0.999	74.0 (3.7)	71.6 (6.4)	67.7 (2.0)	0.1	0.5
Irgafos 168	1-50	0.999	80.0 (8.1)	119.1 (3.2)	99.7 (6.4)	0.2	0.5
C) Irganox 1076	0.5-50	0.998	77.5 (4.1)	81.1 (2.5)	91.5 (6.7)	0.5	2
Irganox 1010	1-50	0.999	82.5 (0.9)	90.9 (9.5)	77.4 (1.5)	0.1	0.4
Bis(8-methylnonyl) phthalate	0.5-50	0.999	85.8 (8.1)	93.1 (1.8)	117.9 (6.9)	0.1	0.5
Irgafos 168	1-50	0.999	110.0 (2.1)	118.2 (2.8)	102.2 (1.2)	0.2	1

A) buffered salt solvent; B) protein solvent; C) vaccine

Table S3 Linear ranges, correlation coefficients, LOQs, and LODs of the other additives identified in samples

Additives	Linear range (μg/L)	Correlation index (R^2)	LOD (μg/L)	LOQ (μg/L)
Dibutyl phthalate (DBP)	2-50	0.998	0.5	2
Irganox 3114 FF	0.5-25	0.997	0.2	0.5
Isodecyl octyl phthalate(ODP)	0.5-25	0.997	0.2	0.5
diallyl phthalate (DAP)	1-50	0.999	0.2	0.5

Analysis procedure and results of VOC in the vaccine by headspace gas chromatography mass spectrometry

An automated headspace sampler (Agilent 7697A, US) equipped with a sample loop volume of 1 mL, a GC system (Agilent 7890A, US) equipped with HP-5MS UI column, and MS system (Agilent 5975C, US), were used for the analysis of volatile components in vaccine. 10 mL vaccine was transferred into the 20mL headspace vial to perform the analysis. The headspace operating conditions were as follows: Vial equilibration time, 15 min; oven temperature, 80 °C; vial pressurisation time, 0.04 min; loop fill time, 0.05min; loop temperature, 9 °C; transfer line temperature, 100 °C. GC operating conditions were as follows: The carrier gas was helium at a flow rate of 1 mL/min; the column temperature program of GC was initially set at 35 °C for 5 min, and gradually increased to 200 °C at 10 °C/min, then kept there for 5 min. For GC–MS detection, electron ionization (EI) system was used with ionization energy at 70 eV. The full scan mass range was m/z 20-400.

As a result, compared with the blank, there's just an air peak at 1.4 min and no obvious volatile organic compound in the vaccine (Figure S-3).

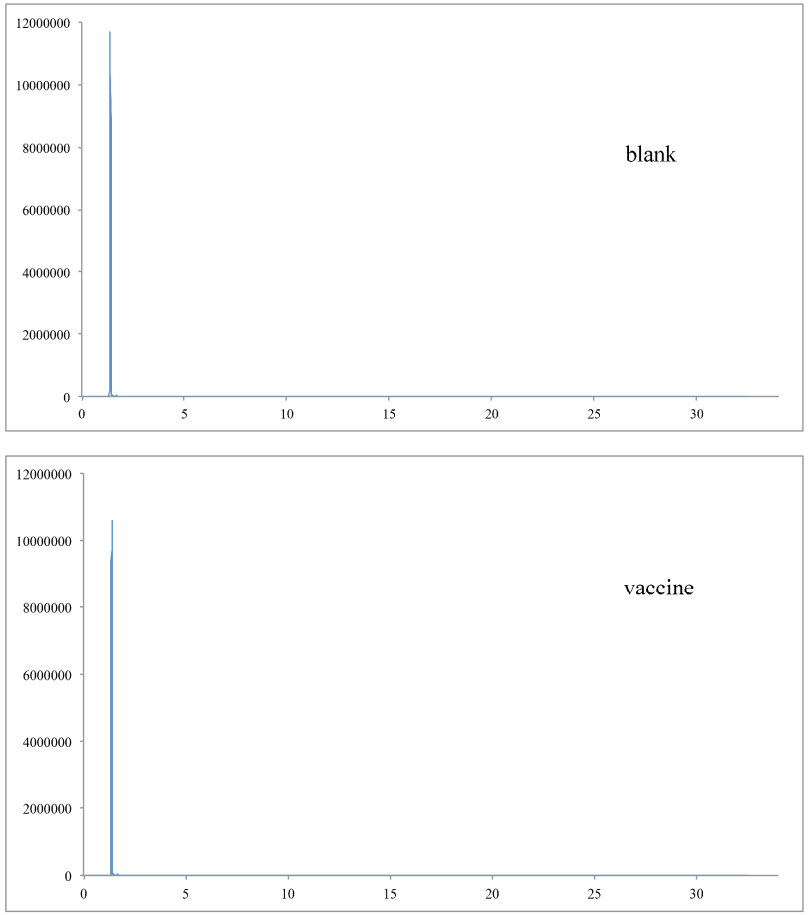

Figure S3 Chromatograms of the blank and vaccine analyzed in headspace gas chromatography-mass spectrometry

Analysis procedure and results of heavy metal ions in the vaccine by ICP-MS

1 mL vaccine was transferred to 1.5 mL centrifuge tube and then centrifuged 5 min under the rotation rate of 2000r/min. Then, we took the supernatant out and added 1 mL HNO_3 into the supernatant at 70□ for 50 min until dry to remove the protein. The redundant was re-dissolved by 4 mL 2% HNO_3 for ICP-MS analysis. The experiment was repeated three times. Each sample was injected twice for ICP-MS analysis. The quantification results were shown in Table S-4.

Table S4 The contents of the heavy metal ions in the vaccine

Heavy metals	Content (μg/L)	RSD (%, n=6)
Zn	1181	6.5
As	3.96	7.6
Sb	0.98	9.8
Pb	27.08	8.9