

Supplementary Materials

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Supplementary Fig. S1 Scatter plots analysis. (A) *CTSH*. (B) *MAP1LC3B*. (C) *MRPS7*. (D) *PPFIA1*. (E) *RCN2*. (F) *RPS9*. (G) *S100B*. (H) *SH3PXD2A*.

Supplementary Fig. S2 Leave-one-out analysis. (A) *CTSH*. (B) *MAP1LC3B*. (C) *MRPS7*. (D) *PPFIA1*. (E) *RCN2*. (F) *RPS9*. (G) *S100B*. (H) *SH3PXD2A*.

Supplementary Table S1. Genes associated with COPD after FDR correction.

Gene	Outcome	Method	nSNP	Beta	SE	P-value	FDR	OR (95%CI)
<i>IRF1</i>	COPD	Wald ratio	1	-0.460	0.089	2.17E-07	8.90E-04	0.631 (0.531-0.751)
<i>APEH</i>	COPD	Wald ratio	1	-0.127	0.026	8.69E-07	1.78E-03	0.881 (0.838-0.927)
<i>TCF19</i>	COPD	Inverse variance weighted	2	-0.117	0.025	1.90E-06	2.59E-03	0.889 (0.847-0.933)
<i>GPX1</i>	COPD	Wald ratio	1	0.294	0.063	3.03E-06	3.10E-03	1.342 (1.186-1.519)
<i>RCN2</i>	COPD	Inverse variance weighted	3	0.242	0.053	3.98E-06	3.17E-03	1.274 (1.149-1.412)
<i>BAG5</i>	COPD	Wald ratio	1	0.176	0.039	5.08E-06	3.17E-03	1.192 (1.106-1.286)
<i>CTSH</i>	COPD	Inverse variance weighted	8	0.081	0.018	5.42E-06	3.17E-03	1.084 (1.047-1.123)
<i>P4HA2</i>	COPD	Wald ratio	1	-0.340	0.075	6.37E-06	3.26E-03	0.711 (0.614-0.825)
<i>ASH2L</i>	COPD	Wald ratio	1	-0.239	0.054	1.17E-05	5.30E-03	0.788 (0.708-0.876)
<i>DNAH17</i>	COPD	Wald ratio	1	-0.544	0.129	2.40E-05	8.98E-03	0.581 (0.451-0.747)
<i>MAP1LC3B</i>	COPD	Inverse variance weighted	4	-0.097	0.023	2.41E-05	8.98E-03	0.908 (0.868-0.950)
<i>TAP1</i>	COPD	Wald ratio	1	0.322	0.077	2.81E-05	9.58E-03	1.380 (1.187-1.604)
<i>IST1</i>	COPD	Wald ratio	1	-0.278	0.067	3.62E-05	1.14E-02	0.757 (0.664-0.864)
<i>CCNL1</i>	COPD	Inverse variance weighted	2	0.099	0.024	5.00E-05	1.46E-02	1.104 (1.053-1.158)
<i>PIK3C3</i>	COPD	Inverse variance weighted	2	-0.109	0.027	6.83E-05	1.78E-02	0.897 (0.850-0.946)
<i>HLA-DRB1</i>	COPD	Wald ratio	1	0.508	0.128	6.96E-05	1.78E-02	1.662 (1.294-2.135)
<i>RPS9</i>	COPD	Inverse variance weighted	5	-0.073	0.019	8.78E-05	2.11E-02	0.930 (0.897-0.964)
<i>MRPS7</i>	COPD	Inverse variance weighted	9	0.069	0.018	1.05E-04	2.38E-02	1.071 (1.035-1.109)
<i>CLU</i>	COPD	Wald ratio	1	-0.418	0.109	1.25E-04	2.69E-02	0.658 (0.532-0.815)
<i>SI00B</i>	COPD	Inverse variance weighted	5	0.056	0.015	1.42E-04	2.91E-02	1.058 (1.028-1.089)
<i>HLA-DRA</i>	COPD	Inverse variance weighted	2	-0.209	0.056	1.66E-04	3.25E-02	0.811 (0.728-0.905)
<i>ZMYM5</i>	COPD	Wald ratio	1	-0.406	0.109	1.85E-04	3.33E-02	0.667 (0.539-0.825)
<i>SH3PXD2A</i>	COPD	Inverse variance weighted	9	-0.082	0.022	1.87E-04	3.33E-02	0.921 (0.883-0.962)
<i>RPA3</i>	COPD	Wald ratio	1	-0.255	0.069	2.23E-04	3.72E-02	0.775 (0.677-0.887)
<i>PPFIA1</i>	COPD	Inverse variance weighted	8	-0.083	0.023	2.32E-04	3.72E-02	0.920 (0.880-0.962)
<i>ARL3</i>	COPD	Inverse variance weighted	2	0.160	0.044	2.44E-04	3.72E-02	1.174 (1.077-1.278)
<i>LNPEP</i>	COPD	Inverse variance weighted	2	-0.090	0.025	2.50E-04	3.72E-02	0.914 (0.871-0.959)
<i>ARHGAP5</i>	COPD	Inverse variance weighted	2	0.257	0.070	2.54E-04	3.72E-02	1.294 (1.127-1.485)
<i>ERBB2</i>	COPD	Inverse variance weighted	2	0.344	0.096	3.30E-04	4.66E-02	1.411 (1.169-1.702)
<i>CDT1</i>	COPD	Wald ratio	1	0.538	0.150	3.48E-04	4.75E-02	1.712 (1.275-2.300)

Supplementary Table S2. Pleiotropy and heterogeneity analysis of EDC-related genes with causal effects on COPD.

Gene	Pleiotropy		Heterogeneity			
	Egger_intercept	P-value	IVW Q	P-value	MR Egger Q	P-value
<i>PIK3C3</i>	NA	NA	0.209	0.648	NA	NA
<i>ARHGAP5</i>	NA	NA	0.277	0.599	NA	NA
<i>CTSH</i>	-0.013	0.277	10.673	0.154	8.622	0.196
<i>SH3PXD2A</i>	-0.001	0.984	10.766	0.215	10.765	0.149
<i>LNPEP</i>	NA	NA	0.041	0.839	NA	NA
<i>RCN2</i>	0.052	0.609	0.924	0.630	0.427	0.513
<i>MRPS7</i>	-0.003	0.822	8.119	0.422	8.056	0.328
<i>PPFIA1</i>	-0.006	0.857	4.362	0.737	4.327	0.633
<i>TCF19</i>	NA	NA	1.143	0.285	NA	NA
<i>ARL3</i>	NA	NA	0.764	0.382	NA	NA
<i>MAP1LC3B</i>	-0.058	0.324	2.067	0.559	0.387	0.824
<i>ERBB2</i>	NA	NA	0.189	0.664	NA	NA
<i>SI00B</i>	-0.080	0.112	6.143	0.189	1.191	0.755
<i>CCNL1</i>	NA	NA	1.084	0.298	NA	NA
<i>RPS9</i>	-0.014	0.202	3.185	0.527	0.534	0.911
<i>HLA-DRA</i>	NA	NA	1.184	0.277	NA	NA

Supplementary Table S3. Results of colocalization analysis for EDC-related genes in COPD.

Gene	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
<i>TCF19</i>	0.00%	0.00%	0.00%	0.39%	99.61%
<i>MAP1LC3B</i>	0.00%	0.65%	0.00%	1.69%	97.66%
<i>SH3PXD2A</i>	0.00%	1.33%	0.00%	1.66%	97.01%
<i>ASH2L</i>	0.00%	0.44%	0.00%	5.40%	94.16%
<i>CCNL1</i>	0.00%	3.56%	0.00%	2.74%	93.69%
<i>DNAH17</i>	0.00%	2.01%	0.00%	5.38%	92.61%
<i>CDT1</i>	0.01%	8.64%	0.00%	0.41%	90.94%
<i>ARL3</i>	0.00%	9.82%	0.00%	2.75%	87.43%
<i>IST1</i>	0.00%	0.79%	0.00%	16.01%	83.20%
<i>ZMYM5</i>	0.00%	23.70%	0.00%	2.30%	73.99%
<i>IRF1</i>	0.00%	0.01%	0.00%	26.74%	73.25%
<i>APEH</i>	0.00%	0.45%	0.00%	27.25%	72.29%
<i>LNPEP</i>	0.00%	0.98%	0.00%	26.83%	72.19%
<i>RPA3</i>	0.00%	6.25%	0.00%	21.79%	71.96%
<i>TAP1</i>	0.00%	23.02%	0.00%	5.56%	71.42%
<i>GPX1</i>	0.00%	0.59%	0.00%	33.59%	65.82%
<i>RCN2</i>	0.00%	10.36%	0.00%	26.97%	62.67%
<i>ERBB2</i>	0.00%	7.20%	0.00%	37.44%	55.37%
<i>BAG5</i>	0.00%	0.15%	0.00%	55.62%	44.24%
<i>PIK3C3</i>	0.00%	1.14%	0.00%	58.20%	40.66%
<i>P4HA2</i>	0.00%	0.05%	0.00%	82.19%	17.76%
<i>MRPS7</i>	0.00%	83.12%	0.00%	5.76%	11.13%
<i>S100B</i>	0.00%	68.88%	0.00%	25.31%	5.81%
<i>RPS9</i>	0.00%	91.95%	0.00%	2.64%	5.41%
<i>ARHGAP5</i>	0.00%	76.68%	0.00%	19.08%	4.24%
<i>HLA-DRA</i>	0.00%	0.06%	0.00%	97.80%	2.14%
<i>PPFIA1</i>	0.00%	87.44%	0.00%	11.30%	1.26%
<i>CLU</i>	0.00%	0.00%	0.00%	99.25%	0.75%
<i>HLA-DRB1</i>	0.00%	0.00%	0.00%	100.00%	0.00%
<i>CTSH</i>	0.00%	0.00%	0.00%	100.00%	0.00%

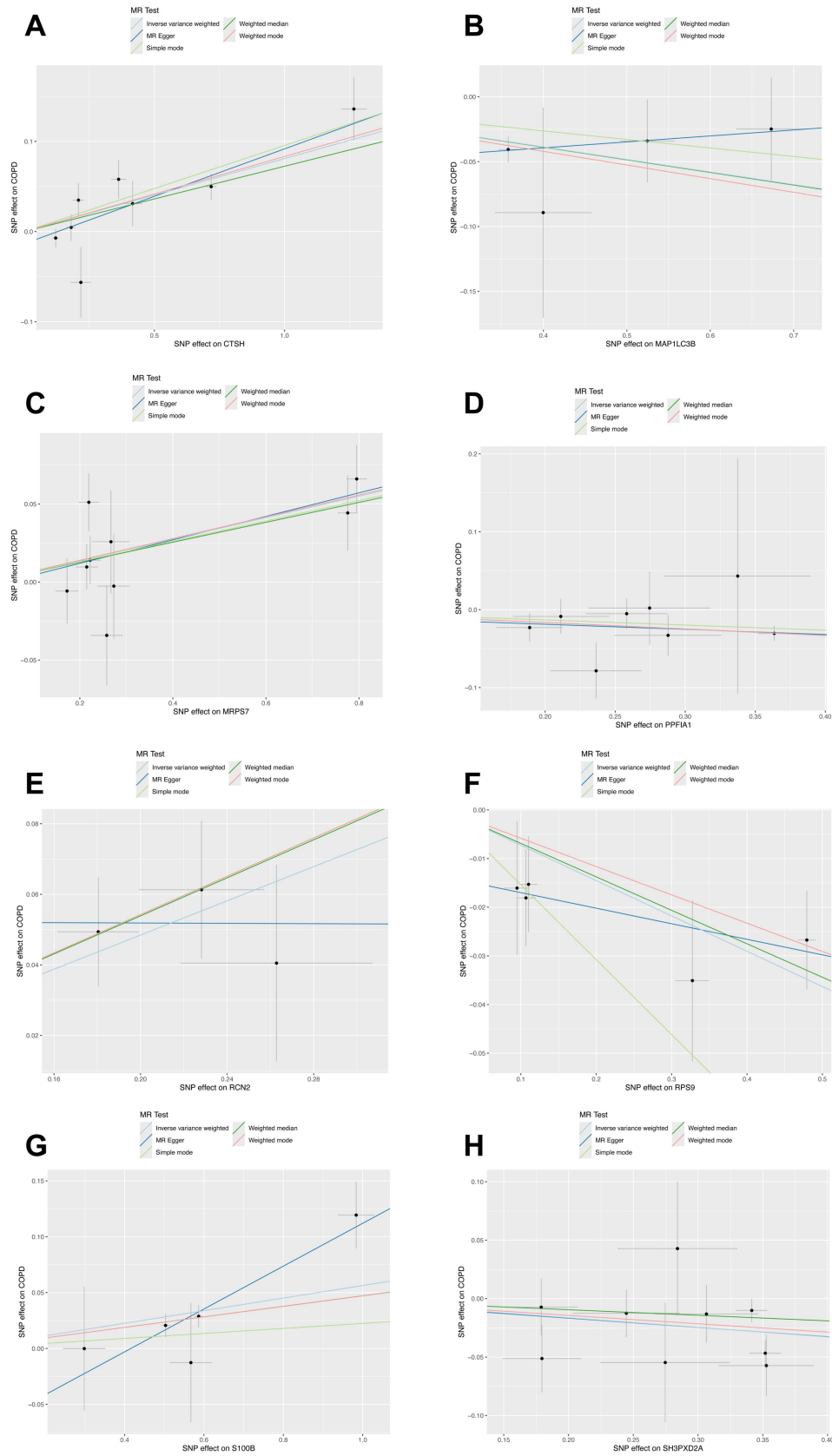
Supplementary Table S4. Interaction between EDCs and colocalized genes associated with COPD.

ChemicalName	nCount	Target
bisphenol A	16	<i>APEH, ARL3, ASH2L, CCNL1, CDT1, DNAH17, ERBB2, GPX1, IRF1, IST1, LNPEP, MAP1LC3B, RCN2, RPA3, SH3PXD2A, TCF19</i>
Copper Sulfate	14	<i>APEH, ARL3, ASH2L, CCNL1, CDT1, DNAH17, ERBB2, GPX1, MAP1LC3B, RCN2, RPA3, SH3PXD2A, TCF19, ZMYM5</i>
sodium arsenite	14	<i>APEH, ASH2L, CCNL1, CDT1, DNAH17, ERBB2, GPX1, LNPEP, MAP1LC3B, RCN2, RPA3, SH3PXD2A, TCF19, ZMYM5</i>
triphenyl phosphate	11	<i>ARL3, CCNL1, DNAH17, ERBB2, IRF1, IST1, LNPEP, MAP1LC3B, SH3PXD2A, TAP1, TCF19</i>
Benzo(a)pyrene	10	<i>CDT1, ERBB2, GPX1, IRF1, LNPEP, MAP1LC3B, RPA3, SH3PXD2A, TAP1, TCF19</i>
Cadmium Chloride	9	<i>APEH, ARL3, CDT1, DNAH17, ERBB2, GPX1, MAP1LC3B, RPA3, TCF19</i>
Quercetin	9	<i>CDT1, ERBB2, GPX1, LNPEP, MAP1LC3B, RPA3, SH3PXD2A, TAP1, TCF19</i>
bisphenol AF	9	<i>APEH, ARL3, GPX1, IRF1, IST1, LNPEP, MAP1LC3B, RCN2, SH3PXD2A</i>
tris(1,3-dichloro-2-propyl)phosphate	9	<i>ARL3, CCNL1, IRF1, MAP1LC3B, RCN2, RPA3, SH3PXD2A, TCF19, ZMYM5</i>
2,2',4,4'-tetrabromodiphenyl ether	8	<i>APEH, ASH2L, CCNL1, DNAH17, GPX1, IST1, LNPEP, RCN2</i>
Formaldehyde	8	<i>APEH, CCNL1, GPX1, IRF1, LNPEP, MAP1LC3B, TAP1, TCF19</i>
methylmercuric chloride	8	<i>ASH2L, CCNL1, GPX1, IST1, LNPEP, MAP1LC3B, TCF19, ZMYM5</i>
Coumestrol	7	<i>ARL3, CDT1, ERBB2, MAP1LC3B, RPA3, TCF19, ZMYM5</i>
Thiram	7	<i>APEH, CCNL1, GPX1, MAP1LC3B, RCN2, TCF19, ZMYM5</i>
bisphenol F	7	<i>APEH, ERBB2, IST1, LNPEP, MAP1LC3B, RCN2, SH3PXD2A</i>
cobaltous chloride	7	<i>APEH, ARL3, ERBB2, MAP1LC3B, RPA3, TCF19, ZMYM5</i>
Zinc	6	<i>CCNL1, CDT1, IRF1, MAP1LC3B, RCN2, TAP1</i>
perfluorooctanoic acid	6	<i>ERBB2, GPX1, MAP1LC3B, RCN2, RPA3, TAP1</i>
1-Methyl-3-isobutylxanthine	5	<i>APEH, ERBB2, IRF1, IST1, SH3PXD2A</i>
Acrylamide	5	<i>APEH, GPX1, MAP1LC3B, SH3PXD2A, TCF19</i>
Arsenic	5	<i>ERBB2, GPX1, IRF1, MAP1LC3B, TAP1</i>
Dichlorodiphenyl Dichloroethylene	5	<i>CDT1, DNAH17, MAP1LC3B, TAP1, TCF19</i>
Tetrachlorodibenzodioxin	5	<i>CCNL1, ERBB2, IRF1, RCN2, SH3PXD2A</i>
Triclosan	5	<i>CDT1, GPX1, IRF1, LNPEP, MAP1LC3B</i>

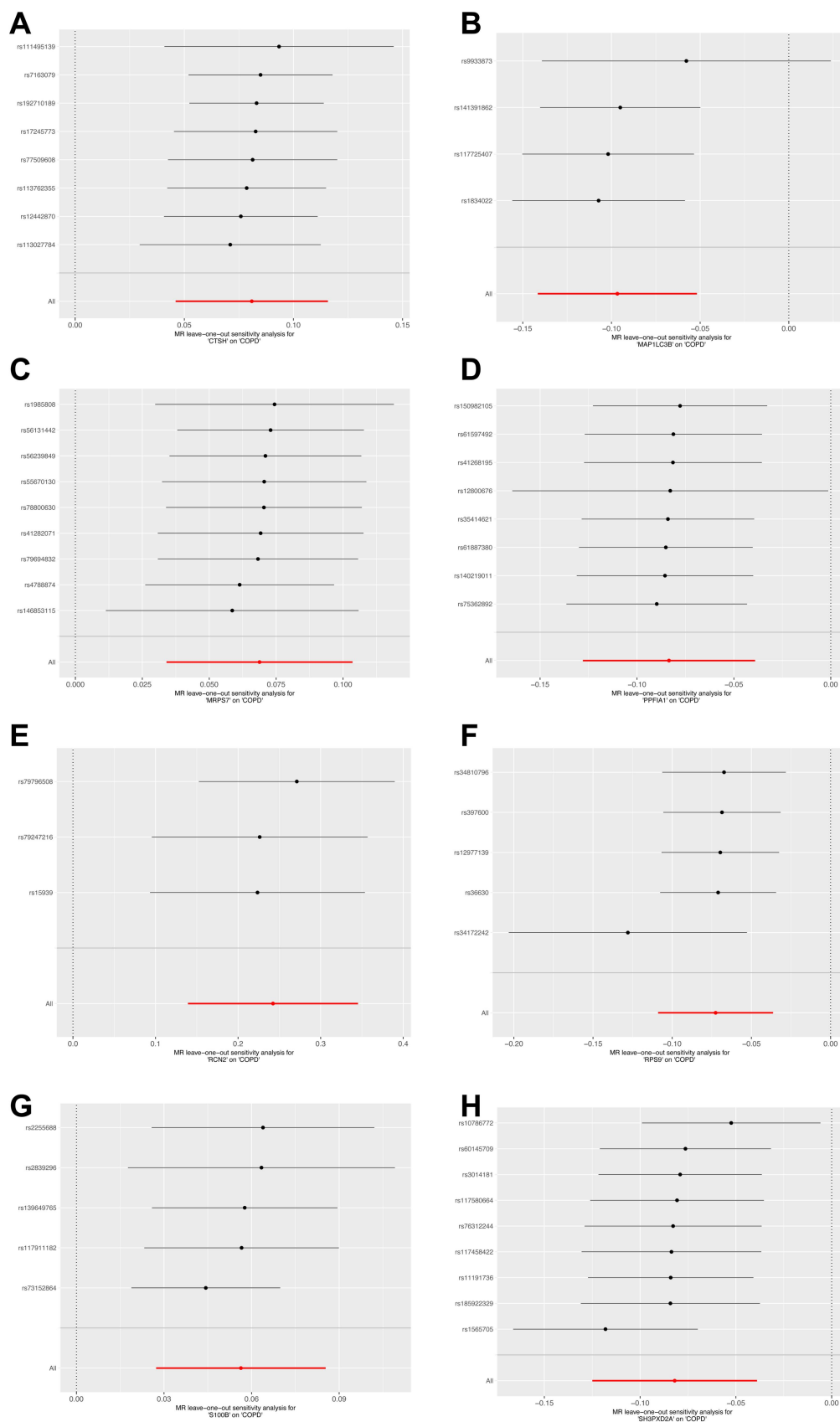
bisphenol B	5	<i>APEH, LNPEP, MAP1LC3B, RCN2, SH3PXD2A</i>
potassium chromate(VI)	5	<i>ASH2L, CCNL1, CDT1, LNPEP, MAP1LC3B</i>
tetrabromobisphenol A	5	<i>APEH, ASH2L, DNAH17, IST1, RCN2</i>
2,4,6-tribromophenol	4	<i>ASH2L, DNAH17, IST1, RCN2</i>
Cadmium	4	<i>APEH, ERBB2, GPX1, TCF19</i>
Ethanol	4	<i>ASH2L, IRF1, MAP1LC3B, SH3PXD2A</i>
Genistein	4	<i>ARL3, CDT1, ERBB2, GPX1</i>
Lead	4	<i>ERBB2, GPX1, MAP1LC3B, SH3PXD2A</i>
bisphenol S	4	<i>APEH, LNPEP, RCN2, SH3PXD2A</i>
decabromobiphenyl ether	4	<i>ASH2L, DNAH17, IST1, RCN2</i>
hexabrominated diphenyl ether 153	4	<i>ASH2L, DNAH17, IST1, RCN2</i>
pentabrominated diphenyl ether 100	4	<i>ASH2L, DNAH17, IST1, RCN2</i>
2-methyl-4-isothiazolin-3-one	3	<i>CCNL1, DNAH17, MAP1LC3B</i>
Paraquat	3	<i>GPX1, IRF1, MAP1LC3B</i>
Vehicle Emissions	3	<i>GPX1, MAP1LC3B, TAP1</i>
beta-Naphthoflavone	3	<i>ERBB2, IRF1, LNPEP</i>
nickel sulfate	3	<i>CDT1, IRF1, TAP1</i>
Apigenin	2	<i>ERBB2, MAP1LC3B</i>
Atrazine	2	<i>CDT1, ZMYM5</i>
Diethylhexyl Phthalate	2	<i>ARL3, TAP1</i>
Disulfiram	2	<i>MAP1LC3B, SH3PXD2A</i>
Emodin	2	<i>GPX1, RCN2</i>
Endosulfan	2	<i>ERBB2, ZMYM5</i>
Lithium Chloride	2	<i>APEH, ERBB2</i>
Nicotine	2	<i>APEH, GPX1</i>
Sodium Selenite	2	<i>GPX1, MAP1LC3B</i>

hydroquinone	2	<i>ARL3, ERBB2</i>
pentabromodiphenyl ether	2	<i>CCNL1, LNPEP</i>
perfluoro-n-nonanoic acid	2	<i>IRF1, TAP1</i>
propionaldehyde	2	<i>CDT1, GPX1</i>
1,2,5,6-dibenzanthracene	1	<i>ERBB2</i>
2,2',4,4',5-brominated diphenyl ether	1	<i>TAP1</i>
2,2,2-trichloroethanol	1	<i>TAP1</i>
2,5,2',5'-tetrachlorobiphenyl	1	<i>CCNL1</i>
2-butenal	1	<i>LNPEP</i>
4-nonylphenol	1	<i>ERBB2</i>
6-OH-BDE-47	1	<i>GPX1</i>
Acetaldehyde	1	<i>CCNL1</i>
Ammonium Chloride	1	<i>MAP1LC3B</i>
Benzene	1	<i>IRF1</i>
Chromium	1	<i>GPX1</i>
Cycloheximide	1	<i>ERBB2</i>
Dieldrin	1	<i>TAP1</i>
Diquat	1	<i>MAP1LC3B</i>
Homocysteine	1	<i>GPX1</i>
Iron	1	<i>MAP1LC3B</i>
Luteolin	1	<i>MAP1LC3B</i>
Mercuric Chloride	1	<i>ZMYM5</i>
Oleic Acid	1	<i>MAP1LC3B</i>
Selenic Acid	1	<i>GPX1</i>
Silver Nitrate	1	<i>GPX1</i>
Sulfur Dioxide	1	<i>GPX1</i>

Zinc Acetate	1	<i>GPX1</i>
Zinc Oxide	1	<i>MAP1LC3B</i>
alpha-Tocopherol	1	<i>GPX1</i>
benz(a)anthracene	1	<i>ERBB2</i>
beta-hexachlorocyclohexane	1	<i>ERBB2</i>
biochanin A	1	<i>GPX1</i>
cupric chloride	1	<i>MAP1LC3B</i>
cyfluthrin	1	<i>GPX1</i>
cyprodinil	1	<i>GPX1</i>
diisononyl phthalate	1	<i>MAP1LC3B</i>
fipronil	1	<i>GPX1</i>
fludioxonil	1	<i>GPX1</i>
fluorotelomer alcohols	1	<i>ERBB2</i>
kaempferol	1	<i>RPA3</i>
lead acetate	1	<i>GPX1</i>
methylparaben	1	<i>IST1</i>
perfluorobutyric acid	1	<i>MAP1LC3B</i>
pyrimethanil	1	<i>GPX1</i>
quinoline	1	<i>RCN2</i>
tris(2-butoxyethyl) phosphate	1	<i>DNAH17</i>



Supplementary Fig. S1 Scatter plots analysis. (A) *CTSH*. (B) *MAP1LC3B*. (C) *MRPS7*. (D) *PPF1A1*. (E) *RCN2*. (F) *RPS9*. (G) *S100B*. (H) *SH3PXD2A*.



Supplementary Fig. S2 Leave-one-out analysis. (A) *CTSH*. (B) *MAP1LC3B*. (C) *MRPS7*. (D) *PPF1A1*. (E) *RCN2*. (F) *RPS9*. (G) *S100B*. (H) *SH3PXD2A*.