Appendix A

Table 1

KEGG pathway database enrichments for IQOS-exposed vs. control groups

Predicted expression direction	Enriched term	Enrichment score	Number of enriched genes	Adjusted p-value
Down	Amyotrophic lateral sclerosis	-1.7568	254	0.008**
Down	Cell cycle	-1.7539	82	0.014*
Down	Proteasome	-1.7532	33	0.028*
Down	Spinocerebellar ataxia	-1.7434	102	0.010*
Down	Glutathione Metabolism	-1.7297	53	0.025*
Down	Parkinson's disease	-1.6909	171	0.008**
Down	Platinum drug resistance	-1.6641	61	0.048*
Down	Drug metabolism	-1.6604	62	0.048*
Down	Hepatocellular carcinoma	-1.6289	130	0.017*
Down	Huntington disease	-1.612	209	0.008**
Down	Protein processing in the endoplasmic reticulum	-1.5905	120	0.031*
Down	Prion disease	-1.5813	178	0.014*
Down	Pathways of neurodegeneration	-1.5565	336	0.008**

Predicted expression direction	Enriched term	Enrichment score	Number of enriched genes	Adjusted p-value
Down	Alzheimer's disease	-1.5322	258	0.011*
Down	Metabolic pathways	-1.2618	1160	0.017*

Note: Table displaying the key enriched pathways, enrichment scores, number of enriched genes, and adjusted p-value from the KEGG or Kyoto Encyclopedia of Genes and Genomes database based on the IQOS-exposed vs. control datasets. The enrichment score indicates how many genes are overrepresented in a particular biological pathway or process. Higher enrichment scores suggest a greater significance of the gene set in the biological process or condition being studied. *$p < .05$. **$p < .01$.

Table 2

KEGG pathway database enrichments for IQOS-exposed vs. CS-exposed groups

Predicted expression direction	Enriched term	Enrichment score	Number of enriched genes	Adjusted p-value
Down	Metabolism of xenobiotics by cytochrome P450	-2.0292	53	0.001**
Down	Chemical carcinogenesis	-1.9719	57	0.001**
Down	Osteoclast differentiation	-1.9383	94	0.001**
Down	Arachidonic acid metabolism	-1.9306	62	0.004**
Down	Steroid hormone biosynthesis	-1.9049	58	0.004**
Down	Lipid and atherosclerosis	-1.8861	157	0.001**
Down	Ovarian steroidogenesis	-1.8766	42	0.005**
Down	Chemical carcinogenesis	-1.8413	156	0.001**
Down	C-type lectin receptor signaling pathway	-1.8336	83	0.006**
Down	Proteasome	-1.8259	34	0.007**
Down	Salmonella infection	-1.8199	194	0.001**
Down	Apoptosis	-1.8179	106	0.004**

Predicted expression direction	Enriched term	Enrichment score	Number of enriched genes	Adjusted p-value
Down	Toll-like receptor signaling pathway	-1.8171	73	0.007**
Down	IL-17 signaling pathway	-1.8153	70	0.007**
Down	Glutathione metabolism	-1.8119	54	0.007**
Down	Metabolism of xenobiotics by cytochrome P450	-1.7663	125	0.005**
Down	Phagosome	-1.7553	41	0.012*
Down	Amino sugar and nucleotide sugar metabolism	-1.7534	30	0.013*
Down	Tryptophan metabolism	-1.7513	39	0.012*
Down	Mineral absorption	-1.7458	84	0.011*
Down	TNF signaling pathway	-1.7393	63	0.012*
Down	Rheumatoid arthritis	-1.739	104	0.009**
Down	Lysosome	-1.7228	95	0.011*
Down	Biosynthesis of cofactors	-1.719	31	0.018*
Down	Biosynthesis of nucleotide sugars	-1.7063	136	0.007**
Down	Tuberculosis	-1.7059	152	0.006**

Predicted expression direction	Enriched term	Enrichment score	Number of enriched genes	Adjusted p-value
Down	Chemical carcinogenesis	-1.6982	101	0.012*
Down	Yersinia infection	-1.6926	170	0.005**
Down	Epstein-Barr virus infection	-1.6879	110	0.012*
Down	Fluid shear stress and atherosclerosis	-1.6871	49	0.022*
Down	Cytosolic DNA-sensing pathway	-2.0292	53	0.001**

Note: Table displaying the key enriched pathways, enrichment scores, number of enriched genes, and adjusted p-value from the KEGG or Kyoto Encyclopedia of Genes and Genomes database based on the IQOS-exposed vs. CS-exposed datasets. The enrichment score indicates how many genes are overrepresented in a particular biological pathway or process. Higher enrichment scores suggest a greater significance of the gene set in the biological process or condition being studied. *$p < .05$. **$p < .01$.