Title: Identification of chemicals targeting dementia genes and pathways in the Comparative Toxicogenomics Database

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Abstract

Introduction: Dementia is a public health challenge and exposures likely contribute to risk, though many have not been evaluated. We screened chemicals for enrichment with dementia genes and related pathways.

Methods: We obtained gene lists from the Comparative Toxicogenomics Database for 1,008 chemicals and nine dementia-related pathways (e.g., Alzheimer's disease, tauopathies). We tested pairwise chemical-dementia gene enrichment using Fisher's exact tests and proportional reporting ratios (PRR), accounting for multiple comparisons with false discovery rate (FDR<$1x10^{-6}$).

Results: Of the chemicals tested, 742 (73.6%) were enriched for at least one dementia pathway and 15 with all nine pathways, including benzo(a)pyrene, ethanol, paraquat, and particulate matter. We observed 295 chemicals enriched for Alzheimer's disease, including sodium arsenite (PRR = 57.9) and 305 enriched for tauopathies, including bisphenol A (PRR=37.7).

Discussion: We identified chemicals enriched for dementia pathways, suggesting broad classes of chemicals contribute to dementia.

Keywords: Dementia, Alzheimer's disease, exposome, neurotoxicology, data-mining, chemical exposures

1. Introduction

Dementia, characterized by progressive loss of neurons with accompanying deterioration of cognitive functions related to memory, language and behavior, is a significant public health challenge.[1,2] In the United States alone, the cost of treating individuals with these disorders was $321 billion in 2022, with that figure predicted to rise above $1 trillion by 2050.[3,4] Dementia subtypes include Alzheimer's disease and frontotemporal lobe dementia, and the majority of persons living with dementia have multiple pathologies, termed mixed dementia.[5] Important hallmarks of dementia include pathological protein aggregation, neuroinflammation, and aberrant proteostasis.[6] In addition, emerging evidence suggests that cellular stress, including endoplasmic reticulum (ER) stress and prolonged activation of the Integrated Stress Response pathway, play important roles in the etiology of dementia.[7,8] Identifying factors that contribute to shared dementia pathologies and to distinct dementia subtypes is critical for prevention.

While genetic factors play a role and risk loci for dementia subtypes including Alzheimer's disease have been identified,[9] increasing evidence points to environmental factors in the etiology of dementia.[10] Components of air pollution, including particulate matter less than 2.5 microns in diameter (PM2.5) and nitric oxide, are associated with poorer executive function and memory.[11] Pesticide exposure has also been linked to dementia risk in human cohorts,[12] and support from animal and cell models demonstrates common forms including chlorpyrifos and dichlorodiphenyltrichloroethane (DTT) increase amyloid-β protein levels.[13,14] Elevated exposures to metals (e.g., lead, cadmium, and manganese) are associated with cognitive decline in human epidemiology studies and elevated levels of molecular hallmarks such as aggregates of amyloid-β protein and tau neurofibrillary tangles in the brain, ER stress, oxidative stress, and neuroinflammation in animal models.[15] Identifying additional environmental toxicants that contribute to disease risk and characterization of the cellular and molecular mechanisms involved in dementia development could reveal important therapeutic targets and new strategies for public health interventions.

Humans are exposed to a diverse array of chemicals throughout life, and only a small proportion of these have been thoroughly assessed for neurotoxic effects. The "exposome" refers to the totality of environmental exposures, including physical, biological, chemical and social factors, that an individual encounters throughout life.[16] The chemical component of the exposome is vast and complex. As of January 30, 2025, the Environmental Protection Agency's (EPA's) Toxic Substances Control Act (TSCA) Inventory lists

86,741 chemicals, with 42,293 of these in active use in the United States as of 2025.[17] Globally, more than 350,000 chemicals and chemical mixtures have been registered for use and production.[18] It is not feasible to thoroughly screen such high numbers of chemicals using traditional laboratory experimental toxicology methods. Alternative approaches, such as data-mining and bioinformatic analysis of publicly available data, can identify chemicals and molecular pathways for targeted further study. Additionally, such approaches can provide important information for designing and interpreting epidemiology studies on environmental contributions to dementia.

The Comparative Toxicogenomics Database (CTD) provides expert curation of millions of interactions between chemicals, genes, and diseases reported in the scientific literature.[19] The CTD offers a unique opportunity to assess a broad array of chemicals (15,167 chemicals contained in the CTD as of August 6, 2025) for known interactions with genes relevant for dementia, many of which are part of the human exposome.[19] In this study, we identified chemicals with documented associations with genes that overlap with dementia risk and the associated molecular/cellular pathways (**Figure 1**). We expect these findings will provide a list of confirmed and novel chemicals to prioritize for future toxicology and epidemiology studies aimed at understanding environmental impacts on dementia.

2. Methods

2.1 Background human gene list

Datasets were sourced from the CTD.[19] We downloaded all genes (unique gene symbols) associated with the species *Homo sapiens* (human) from the CTD (date of download August 6, 2025). These 46,478 genes were used as the background gene list for enrichment testing.

2.2 Chemical gene lists

We used an agnostic approach for chemical selection, due to the large number of chemicals that have not yet been assessed for an association with dementia and associated molecular/cellular pathways. For all chemicals in the CTD database (n=15,167), we downloaded the list of curated chemical-gene interactions (date of download August 6, 2025, **Supplemental Table 1**). We excluded chemicals with sparse gene annotations (less than 50 genes annotated), resulting in 1,008 chemicals included in the study. We used a flowchart to show chemicals considered for study inclusion (**Supplemental Figure 1**).

2.3 Chemical categorization

For the chemicals meeting our inclusion criteria, we developed a chemical categorization scheme that built on categories defined by Nguyen, et al. (based on chemical biomarker data reported in the National Health and Nutrition Examination Survey)[20] and chemical categories annotated in the Medical Subject Headings (MeSH) terms provided by CTD. Each chemical was assigned to one of 25 categories based on chemical use (e.g., "Pesticides, Pesticide Synergists and Cholinesterase Inhibitors"), public health or nutritional relevance (e.g., "Vitamins and Dietary Components") or molecular structure (e.g., "Heterocyclic Compounds"). The full list of chemical categories and the distribution of the number of genes annotated to chemicals in each category are shown in **Table 1**. Chemical categories were used to provide context and examine patterns in the results.

2.4 Dementia gene lists

Based on the known etiology and identified molecular/cellular hallmarks of dementia,[6,21-24] we considered 12 disease terms or biological processes annotated in the CTD as relevant for evaluation: "Alzheimer Disease" (MESH: D000544), "Frontotemporal Dementia" (MeSH: D057180), "Tauopathies" (i.e., abnormal accumulation of tau proteins in the brain,[25] a hallmark of AD; MeSH: D024801), "Lewy Body Disease" (MeSH: D020961), "Proteostasis Deficiences" (MeSH: D057165), "Lysosomal Storage Diseases, Nervous System" (MeSH: D020140), "TDP-43 Proteinopathies" (i.e., mislocalization of the Transactive response DNA binding protein of 43 kDa, characteristic of neurodegenerative diseases, including dementia,[26] MeSH: D057177), "Neuroinflammatory Diseases" (MeSH: D000090862), "Response to Unfolded Protein" (GO:0006986), "Response to ER Stress" (GO:0034976), "Integrated Stress Response Signaling" (GO:0140467) and "Microglial Cell Activation" (GO:0001774). For each term, we downloaded the corresponding CTD gene list (date of download August, 6 2025, **Supplemental Table 2**). We excluded sparsely annotated terms and restricted our disease/pathways to those with a minimum gene set size of 35. We used a flowchart to show dementia terms considered for study inclusion (**Supplemental Figure 1**).

2.5 Testing chemical gene lists for enrichment with dementia and pathways

Analyses were performed using R statistical software (version 4.4.1).[27] The code used to conduct these analyses and generate figures is publicly available (https://github.com/bakulskilab/CTD-dementia). We calculated univariate descriptive statistics for our chemical analytic sample including median, 25th percentile,

75th percentile, and interquartile range (IQR). Chemical count and percent were calculated by chemical category. Quartiles were calculated for gene annotations within a chemical category. We visualized the overlap of gene signatures in our dementia disease list pathways in an upset plot.

For our primary analyses, we generated pairwise 2 x 2 descriptive tables for chemical gene annotations by disease genes annotations. Based on these observed frequencies, we conducted enrichment tests between each chemical gene annotation and each dementia pathway gene annotation using Fisher's exact tests. In situations where an observed 2 x 2 table returned a cell count of zero, we applied Laplace smoothing methodology, which adds one to each cell count.[28] We accounted for multiple comparisons with the Benjamini-Hochberg method to calculate false discovery rate (FDR) adjusted p-values.[29] We considered FDR < 0.05 to be nominally associated, and a threshold of FDR < $x10^{-6}$ to be significantly associated. To determine the direction and magnitude of association, we calculated the proportional reporting ratio (PRR) with the 95% confidence interval (CI). A PRR value greater than one indicates enrichment (more overlapping genes than expected by chance), a PRR less than one indicates depletion (fewer overlapping genes than expected by chance), a PRR equal to one indicates neither. We visualized results across all dementia pathways using scatter plots of the magnitude of association and level of significance. Within each pathway, we ranked associations by smallest FDR. To consider results across pathways, we summed the ranked associations. In table format we presented the summed rank, number of genes annotated per chemical, rank within the disease list, PRR, and FDR. To visualize the results at the top ranked chemicals, we used heatmaps of PRR values by disease pathway and a forest plot of PRR values by disease pathway. To assess enrichment by chemical category, we viewed the number and percent of chemicals enriched by chemical category and disease list.

2.6 Assessing chemicals impacting key genes involved in neurodegenerative disease etiology

To gain insight into chemicals that impact key genes involved in the etiology of dementia, we quantified the number of curated chemical-gene interactions for five key genes involved in neurodegenerative disease etiology[6]: *APOE* (Apolipoprotein E), *APP* (amyloid-beta precursor protein), *MAPT* (microtubule associated protein tau), *PSEN1* (Presenilin-1) and *PSEN2* (Presenilin-2). All five of these genes and their protein products play important roles in the formation of the amyloid-beta plaques, one of the key pathological hallmarks of Alzheimer's disease and genetic polymorphisms for these genes are associated with development of Alzheimer's disease.[30-34]

3. Results

3.1 Chemical gene annotations

After filtering on the number of gene annotations, 1,008 chemicals from 25 chemical categories were included in the analysis (**Supplemental Figure 1A**). The chemical category containing the greatest number of chemicals was “heterocyclic compounds” (n = 210, 20.8%), including fluorescein-5-isocyanate, salinomycin and quinoline, and these chemicals were annotated to a median of 134 genes (IQR = 354) (**Supplemental Table 1**). The categories with the smallest number of chemicals were “fluorine, chlorine, or bromine compounds” (n = 9, 0.8%), including sodium fluoride, which were annotated to a median of 103 genes (IQR = 73), and “fluorocarbons” (n = 9, 0.8%), including perfluorohexanesulfonic acid, which were annotated to a median of 515 genes (IQR = 1,481).

3.2 Disease gene annotations

After applying filters for minimum number of gene annotations, nine disease lists were included in analysis (**Supplemental Figure 1B**). “Response to ER Stress” had the largest gene set size (n = 348), while “Neuroinflammatory Diseases” had the smallest (n = 35). Across all disease pathways, the majority of genes were unique to a pathway (**Supplemental Figure 2**). The “Response to ER Stress” pathway had the most unique genes (i.e., genes not annotated to any of the other dementia disease terms, n = 199, 57.2%), while “Tauopathies” had the fewest (n = 3, 2.7%). The largest intersection (n = 22 genes) between gene lists was observed between “Response to ER Stress” (7.0%), “Response to Unfolded Protein” (12.8%), and “Integrated Stress Response” (19.6%).

3.3 Overall chemical gene associations with dementia pathways

In general, we observed extensive associations between the chemical gene lists and genes in the dementia pathways (**Figure 2**, **Supplemental Table 3**). Those associations were more likely to be enriched (PRR>1, in red in Figure 2) with more overlap than we would expect by chance, rather than depleted (PRR<1, in blue in Figure 2) with less overlap than we would expect by chance. When looking at pairwise associations between each chemical (n = 1,008) and disease list tested (n = 9), the greatest numbers of chemicals were significantly associated (FDR < $1x10^{-6}$) with the terms “Alzheimer's disease” (n = 509) and “Tauopathies” (n = 511), while “Neuroinflammatory Diseases” had the least amount of associations in our chemical set (n = 75). If considering a nominal association (FDR < 0.05), we observed that between 90.3% (“Tauopathies”, n = 910 chemicals) and

66.1% ("Integrated Stress Response", n = 666 chemicals) of the chemicals tested (n = 1,008), were associated with a dementia pathway.

Out of the 1,008 chemicals tested, 396 (39.3%) were nominally enriched (FDR<0.05) across all nine dementia terms. Fifteen chemicals (1.5%) were enriched at FDR < 10^{-6} across all nine dementia terms (**Supplemental Table 4**). The top chemicals by summed rank across all nine disease lists included structurally diverse xenobiotic environmental toxicants like benzo(a)pyrene, bisphenol A, cadmium, and arsenic, as well as endogenous compounds like glucose and estradiol (**Table 2, Supplemental Figure 3**). The greatest percentage (21.6%) of chemicals enriched across all nine dementia pathways was found in the chemical category of heterocyclic compounds (**Supplemental Table 5**).

3.4 Chemical gene enrichment with individual dementia pathways

Of the chemicals associated with "Alzheimer's Disease" genes, we observed 58.1% (295 chemicals) were enriched, meaning that they had more overlapping genes than would be expected by chance at FDR<10^{-6} (**Supplemental Table 5**). Among the enriched chemicals, 16.3% were chemicals from the heterocyclic compounds category and 12.2% were metals or metalloids. The chemicals most significantly enriched with "Alzheimer's Disease" genes based on FDR were glucose (PRR = 4.2), sodium arsenite (PRR = 57.9), and chlorpyrifos (PRR = 2.8). We saw that 70% of vitamins and dietary components tested were associated with "Alzheimer's Disease".

For the "Response to ER Stress" pathway, 33.8% of associations were enriched (200 chemicals). Of the enriched chemicals, 17.5% were heterocyclic compounds and 7.5% were personal care and consumer products. The most significantly enriched chemicals were sodium arsenite (PRR=39.9), valproic acid (PRR=40.6), and particulate matter (PRR=17.2).

We found 193 chemicals associated with the "Integrated Stress Response" pathway and all were enriched (none were depleted). The most significantly enriched chemicals were benzyloxycarbonylleucyl-leucyl-leucine aldehyde (PRR=4.9), triphenyl phosphate (PRR=24.1.0), and abrine (PRR=22.0). We saw 42.1% of all selenium compounds tested were enriched for the "Integrated Stress Response" pathway.

For the "Microglial Cell Activation" pathway, we observed 213 chemical associations and 80.8% of those associations were enriched. The most significantly enriched chemicals were tretinoin (PRR=32.4), nickel (PRR=14.7), and tetradecanoylphorbol acetate (PRR=5.1). We observed 42.9% of all elements and minerals

tested and 33.3% of all complex mixtures tested were enriched for genes in the “Microglial Cell Activation” pathway.

We observed 75 chemicals associated with the “Neuroinflammatory Diseases” pathway, and similar to the “Integrated Stress Response” pathway, all were enriched. Of the enriched chemicals, 17% were heterocyclic compounds and 12% were biologic factors. The most significantly enriched chemicals were tetradecanoylphorbol acetate (PRR=6.8), nickel (PRR=18.2), and metformin (PRR=4.5).

For the “Proteostasis Deficiencies” pathway, we observed 414 chemical associations and 55.8% of associations were enriched (231 chemicals). The most significantly enriched chemicals were resveratrol (PRR=15.6), acetylcysteine (PRR=3.7), and benzo(a)pyrene (PRR=67.3). We saw 60% of all vitamins and dietary components tested, 45.8% of complex mixtures tested, and 37.5% of pesticides tested were enriched for genes in the “Proteostasis Deficiencies” pathway.

Of the 404 chemical associations with the “Response to Unfolded Proteins” pathway, 56.9% were enriched. The most significantly enriched chemicals were tunicamycin (PRR=8.2), sodium arsenite (PRR=61.2), and cadmium chloride (PRR=28.4). Similar to the results from the “Proteostasis Deficiencies” pathway, for “Response to Unfolded Proteins”, we observed that 60% of all vitamins and dietary components tested, 45.8% of complex mixtures tested, and 36.8% of selenium compounds were enriched for genes in the “Response to Unfolded Proteins” pathway.

For the “Tauopathies” pathway, we observed 511 associations and 59.7% of those chemicals were enriched for genes in the “Tauopathies” pathway. The most significantly enriched chemicals were sodium arsenite (PRR=57.5), glucose (PRR=4.0), and bisphenol A (PRR=37.7). We observed 70% of all vitamins and dietary components tested, 42.9% of complex mixtures, and 42.1% of selenium compounds tested were enriched for genes in the “Tauopathies” pathway.

We observed 476 chemicals associated with the “TDP-proteinopathies” pathway, and 67.4% of these associations were enriched. The most significantly enriched chemicals were acetylcysteine (PRR=3.8), resveratrol (PRR=14.9), and curcumin (PRR=3.6). We saw 60% of all vitamins and dietary components tested, 42.9% of elements and minerals, and 41.7% of complex mixtures tested were enriched for genes in the “TDP-proteinopathies” pathway.

3.5 Key Alzheimer’s disease genes impacted by chemicals

We examined five key genes involved in neurodegenerative disease etiology (*APOE*, *APP*, *MAPT*, *PSEN1*, and *PSEN2*) for appearance in chemical gene annotations (**Table 3**). *APP* was observed in the gene annotations for 163 chemicals (16%), including glucose and lead. The presenilin genes were least represented in chemical gene annotations. *PSEN1* was observed in 52 chemical gene lists (5% of chemicals tested) and *PSEN2* was observed in 42 gene lists (4% of chemicals tested). The full list of chemical-gene annotations for the five key Alzheimer's disease genes is shown in **Supplemental Table 6**.

4. Discussion

Dementia is a highly impactful and debilitating disorder. Emerging evidence continues to point to environmental exposures as a modifiable risk factor for developing dementia.[35-41] However, the large number of environmental toxicants that are found in the modern human exposome, as well as gaps in our understanding of cellular and molecular mechanisms of toxicity, make prioritizing chemicals for public health interventions essential. We screened a large and diverse set of chemicals for gene enrichment with dementia genes using the CTD and observed 742 chemicals were associated with at least one dementia pathway, and 15 were associated with all nine dementia pathways (2-(2-amino-3-methoxyphenyl)-4H-1-benzopyran-4-one, benzo(a)pyrene, capsaicin, ethanol, glucose, glutathione, lipopolysaccharides, metformin, paraquat, particulate matter, quercetin, rosiglitazone, SB 203580, tetradecanoylphorbol acetate, and tretinoin). This study provides important insights into chemical classes that warrant further mechanistic evaluation regarding their relationship to dementia and contributes to our understanding of how the environment may drive dementia risk.

By assessing 25 broad categories of chemicals, we demonstrated that chemicals with diverse molecular structures and uses have the potential to impact molecular pathways involved in the development of dementia. These findings build on recent human epidemiology chemical exposure-wide association studies of cognition among older adults.[42,43] Here, we found that chemicals like cadmium, lead, and ozone were significantly enriched with genes in the disease term "Alzheimer's Disease", consistent with human epidemiology studies showing associations between exposure to these chemicals and risk for dementia.[15,44] Chemicals with gene annotations enriched for "Alzheimer's Disease" are used in a variety of widespread industrial or agricultural processes, such as plasticizers (diethylhexyl phthalate) or pesticides (glyphosate), leading to exposures for workers in certain manufacturing industries,[45] agriculture[46] as well as consumers of certain products[47] and

residents near farms[48] or manufacturing facilities.[49] Traditionally, workers in these industries are comprised of disadvantaged groups with less access to education, a known risk factor for dementia, which may highlight a hidden mechanism that contributes to the high prevalence of dementia in lower educated populations.[50] Importantly, exposures to these chemicals can occur via multiple pathways, including food and drink consumption, personal care products, residential location, the workplace, and during recreation, that contribute to an individual's total environmental exposure. Overall, we observed that chemicals across all 25 categories assessed were enriched for one or more dementia pathways, highlighting the diversity of molecular structures, chemical uses and potential exposure pathways for chemicals that may influence dementia risk. Of the chemical categories assessed, "environmental pollutants and complex mixtures", including environmental contaminants like tobacco smoke, particulate matter, and coal ash, had the highest percentage of chemicals enriched for dementia pathway genes, consistent with studies showing that exposures to these pollutants can adversely impact cognition and increase risk for cognitive decline and dementia.[51-54]

Our study provides insight into potential mechanisms underlying associations between environmental exposures and dementia, including disruptions in protein homeostasis, activation of cell stress pathways, and activation of neuroinflammation. Protein homeostasis encompasses the controlled synthesis, folding, post-translational modification, and degradation of proteins, all of which are necessary for proper brain and neurological functions.[55] Proteinopathies in the context of neurodegenerative disorders involve the accumulation of certain proteins in the brain due to dysfunctions in protein homeostasis.[56] We identified chemicals in the CTD that were enriched with genes involved in proteinopathies that are consistent with dementia ("Tauopathies", "TDP-43 Proteinopathies" and "Proteostasis Deficiences"). Toxicants can disrupt protein homeostasis through multiple mechanisms such as by altering redox status of cells, leading to free radical stress, which can interfere with protein folding[57,58] or in the case of metals, binding to protein functional groups.[59] These effects have been demonstrated with toxicants including metals and pesticides,[57] but our findings suggest that a broader range of chemicals including polycyclic aromatic hydrocarbons like benzo(a)pyrene and pyrazolanthrone, fluorinated compounds like perfluorooctanoic acid, chemicals contained in consumer products like bisphenol A, and endogenous chemicals like glucose (as in cases of high blood sugar[60]) can disrupt protein homeostasis in neurons, thereby contributing to the etiology of dementia.

Consistent with these findings, we showed that diverse sets of chemicals were enriched with genes involved in cellular stress responses pathways. These response pathways are activated in response to stressful events and can affect protein homeostasis or inflammation ("Integrated Stress Response", "Response to ER Stress", and "Response to Unfolded Protein"). The Integrated Stress Response is an adaptive cellular pathway that serves to restore homeostasis in response to stressful stimuli or conditions including amino acid deprivation, viral infections and reactive oxygen species.[61] While cytoprotective when activated in the short term, prolonged or high intensity stress can cause the Integrated Stress Response pathway to promote cell death via apoptosis.[60,61] A main signaling event in Integrated Stress Response activation is the phosphorylation of the alpha subunit of the eukaryotic initiator factor 2 (eIF2α).[61] Studies using mouse models of neurodegenerative disease have shown that prolonged eIF2α phosphorylation is associated with cognitive deficits.[7] Our findings suggest that a significant number of environmental toxicants could activate or otherwise dysregulate the Integrated Stress Response pathway and contribute to dementia. Importantly, humans may be chronically exposed to some of the chemicals we assessed, such as air pollutants or drinking water contaminants like volatile organic chemicals or heavy metals. If chemicals additively or synergistically activate the Integrated Stress Response pathway in a prolonged manner under chronic exposure conditions, these exposures could lead to significant impacts on the development of neurodegenerative diseases. Future studies should seek to understand the net effect of the exposome on the Integrated Stress Response pathway in neurons in the context of dementia, particularly for the Integrated Stress Response-enriched toxicants identified in this study. In addition, these insights could be leveraged for future *in vitro* or *in vivo* mixture toxicology studies that seek to understand the cumulative impact of multiple chemicals on dementia-relevant pathways.

Prolonged activation of stress pathways like the Integrated Stress Response, and phosphorylated eIF2α in particular, can lead to neuroinflammation.[7] We identified chemicals in the CTD that were enriched for pathways related to neuroinflammation ("Neuroinflammation", "Microglial Activation"). Neuroinflammation can lead to the death of neurons and damage to brain tissue.[62] Studies have shown increased inflammation in brain regions including the inferior and middle temporal gyri, left amygdala, and inferior parietal lobes in Alzheimer's disease cases compared to controls.[62] Our study demonstrated that chemicals across classes including "environmental pollutants and complex mixtures", "personal care", "consumer products", "therapeutic agents", "pharmacologic

actions and specialty use chemicals", and "selenium compounds" impact genes involved in neuroinflammation and microglial activation.

Our top hit chemicals by summed rank included xenobiotic environmental pollutants like benzo(a)pyrene, bisphenol A, and arsenic compounds (e.g., sodium arsenite), consistent with epidemiology and animal studies linking these chemicals to neurodegenerative effects.[63-66] Interestingly, top hit chemicals also included non-xenobiotic chemicals like glucose and estradiol (the main estrogen hormone in the human body). Higher blood glucose[67] and estrogen therapy[68,69] have both been associated with dementia in human studies. However, in the case of estrogen use, potential protective effects have also been observed.[70] We also observed that an array of chemicals impact key neurodegenerative hallmark genes (*APOE*, *APP*, *PSEN1*, *PSEN2,* and *MAPT)*. While previous studies have shown that toxicants including bisphenol A,[71] lead,[72] benzo(a)pyrene,[63] and ochratoxin A[73] can alter expression of these genes, we identified additional chemicals that could impact their expression. A relatively low percentage of the chemicals assessed (4-16%) impacted each of these hallmark genes, suggesting that many environmental toxicants may contribute to dementia risks through alternate gene-chemical interactions that require additional research.

In addition to environmental toxicants, we identified several vitamins or other dietary factors that were enriched with dementia pathways, e.g., ascorbic acid (vitamin C), vitamin E, and selenium. Importantly, we note that the scope of our study was limited to identifying statistical associations between chemicals and dementia-relevant genes and the direction of chemical effects on gene expression was not specified.[19] Thus, enrichment with dementia pathways for these dietary factors could indicate these compounds interacting with dementia pathways in a protective manner, and additional work is needed to determine the direction of associations. While this would support previous human and animal studies suggesting that maintaining adequate levels of, or supplementation with, certain dietary factors and/or vitamins can be protective against dementia[74-76] and/or cognitive impairment, findings from other meta-analyses or clinical trials have been mixed or negative, highlighting the need for further study.[77,78] Overall, our findings serve to further highlight the complexity of the human exposome and its impact on dementia risk. Future *in vitro* or *in vivo* mechanistic studies could draw on these findings to design studies of relevant chemical mixtures to clarify the influence toxicants, nutrient and therapeutic compounds have on dementia risk within the context of the human exposome.

One important advantage of the methods used in this study is the ability to broadly screen a large number of chemicals for dementia-relevant associations compared to standard *in vitro* or *in vivo* toxicology models. Moreover, our methods allowed us to screen chemicals for multiple mechanisms of toxicity at once, including cellular stress responses, proteinopathies and neuroinflammation. Limitations of this study should also be noted. Our screening efforts have covered a considerable range of chemicals, however these represent only a portion of the chemicals (1,008/15,167; 6.6%) within the CTD and in use globally. Significant gaps in our understanding of the broader chemical landscape and associations with dementia risk remain and require further research. Toxicology data from the CTD is not tissue or cell type-specific, meaning that some of the assessed associations may not be relevant for neurons or other cell types that make up the human brain. However, cell stress and inflammation pathways are observed across a wide array of cell types.[77] In addition, doses of chemicals may vary across studies annotated in the CTD and dose-responses for chemical-gene associations are not discernable using the method employed in this study. Finally, we tested chemicals for interactions with genes only. Thus, direction and magnitude of gene expression changes caused by chemical exposures was not assessed. To address these limitations, future studies could use *in vitro* or *in vivo* models to confirm associations between chemicals and the dementia pathways, prioritizing the genes identified in this study. For example, studies using microglial cell models in high-throughput testing systems could screen plausible mixtures of these chemicals for activation or other relevant inflammation markers or assess additive, synergistic or counteracting effects of multiple chemicals on endoplasmic reticulum stress or integrated stress response pathways in neuron or microglial cell models. Additionally, functional assays, including enzyme-linked immunosorbent assays (ELISAs) targeting dementia pathology,[79] electrophysiological assays that capture loss of synaptic function,[80] and assays of mitochondrial dysfunction and oxidative stress (e.g., quantification of Aβ-Binding Alcohol Dehydrogenase[81] or lipid peroxidation[82]) would be useful expansions on the gene expression data described here.

In conclusion, this hypothesis generating screening study indicates that a diverse array of chemicals overlap with molecular and cellular pathways consistent with the development of dementia. These chemicals may act through cellular mechanisms including activation of cellular stress pathways and/or neuroinflammation. Given the significant challenges of understanding the cumulative impact of the exposome

on the risk for dementia, these findings provide important information that can inform future epidemiology and toxicology studies seeking to understand the link between environmental exposures and dementia.

Acknowledgements: This research was supported by the National Institute on Aging (R01 AG067592, R01 AG070897, P30 AG072931) and the National Institute of Environmental Health Sciences (P42 ES017198).

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Table 1. Descriptive statistics for the included chemical sample Number of chemicals per chemical category and distribution of genes per chemical category.

Chemical category	Count of chemicals per category	Genes annotated per chemical category				
	Overall, N = 1,008	Min	Quartile 1	Median	Quartile 3	Max
Biological Factors	48	50	88	134	407	10,844
Carboxylic acids	30	50	76	183	532	4,801
Elements and Minerals	14	72	83	198	674	4,692
Environmental Pollutants and Complex Mixtures	24	51	231	406	2,613	11,387
Fluorine, Chlorine or Bromine compounds	9	57	82	103	155	2,864
Fluorocarbons	9	52	62	151	1,543	2,366
Heterocyclic Compounds	210	50	73	139	427	6,918
Hormones, Hormone Substitutes, Steroids and Hormone Antagonists	39	50	82	200	419	7,305
Hydrocarbons: Chlorinated, Acyclic, Aromatic, Halogenated, Cyclic, Other	37	52	84	133	369	5,889
Metals and Metal Compounds	88	54	95	237	1,082	13,975
Nucleic Acids, Nucleotides, Nucleosides, Amino Acids, Peptides, and Proteins	37	51	71	142	349	4,320
Organophosphorus compounds	16	61	178	588	862	7,361
Other: Selenium Compounds, Onium Compounds, Gases, Free Radicals, Coordination Complexes, Noxae, Boron Compounds	19	53	76	148	571	4,082
Other Nitrogen-Containing Compounds: Amides, Amidines, Amines, Azo, Hydrazines, Isocyanates, Triazines, Nitriles, Nitro and Nitroso Compounds	51	50	73	125	193	7,569
Other Organic Chemicals: Ethers, Alcohols, Aldehydes, Ketones, Lactones, Quinones, Carbohydrates, Lipids, Organosilicon	106	51	68	128	303	15,333
Personal Care, Consumer Products, Therapeutic Agents, Pharmacologic Actions and Specialty Use Chemicals	48	54	85	234	1,113	11,657
Pesticides, Pesticide Synergists and Cholinesterase Inhibitors	16	50	75	254	573	3,032

Phthalic Acids and Plasticizers	11	54	63	76	186	2,414
Polychlorinated Biphenyls and Flame Retardants	21	59	154	412	962	5,661
Polycyclic Aromatic Hydrocarbons	46	50	79	117	248	16,489
Phytoestrogens, Alkaloids, and Terpenes	69	51	73	152	484	6,961
Sulfur compounds	16	51	120	210	1,368	3,875
Vitamins and Dietary Components	10	68	77	808	1,433	2,456
Volatile Organic Compounds	10	50	64	143	583	1,902
Other	24	52	91	147	422	2,115

[1]Median

Chemical count (%) per chemical category are shown in the second column. Minimum, quartile 1, median, quartile 3, and maximum gene annotations were calculated within a chemical category.

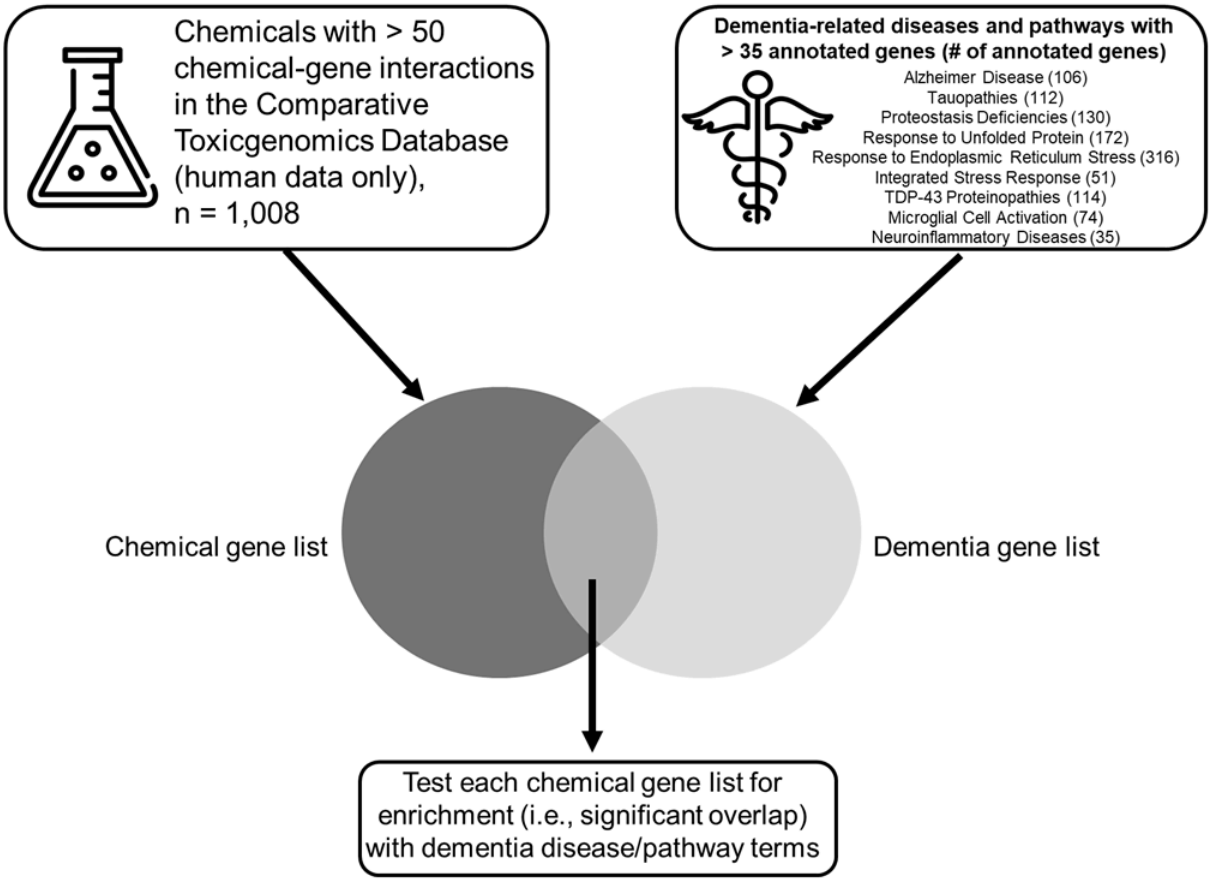

Figure 1. Summary of method and criteria for chemical and dementia disease gene lists used for enrichment testing. Chemicals with > 50 annotated chemical-gene interactions in the Comparative Toxicogenomics Database (CTD) were selected for enrichment testing using nine dementia-related disease or pathways terms. Gene lists for all dementia terms were also obtained from the CTD. Enrichment testing was conducted to determine which chemicals had a significantly high number of overlapping genes with each of the dementia gene lists (i.e., more overlapping genes between the chemical and dementia gene lists than would be expected by chance). Significant enrichment identified using FDR < 0.05 (Fisher's exact test).

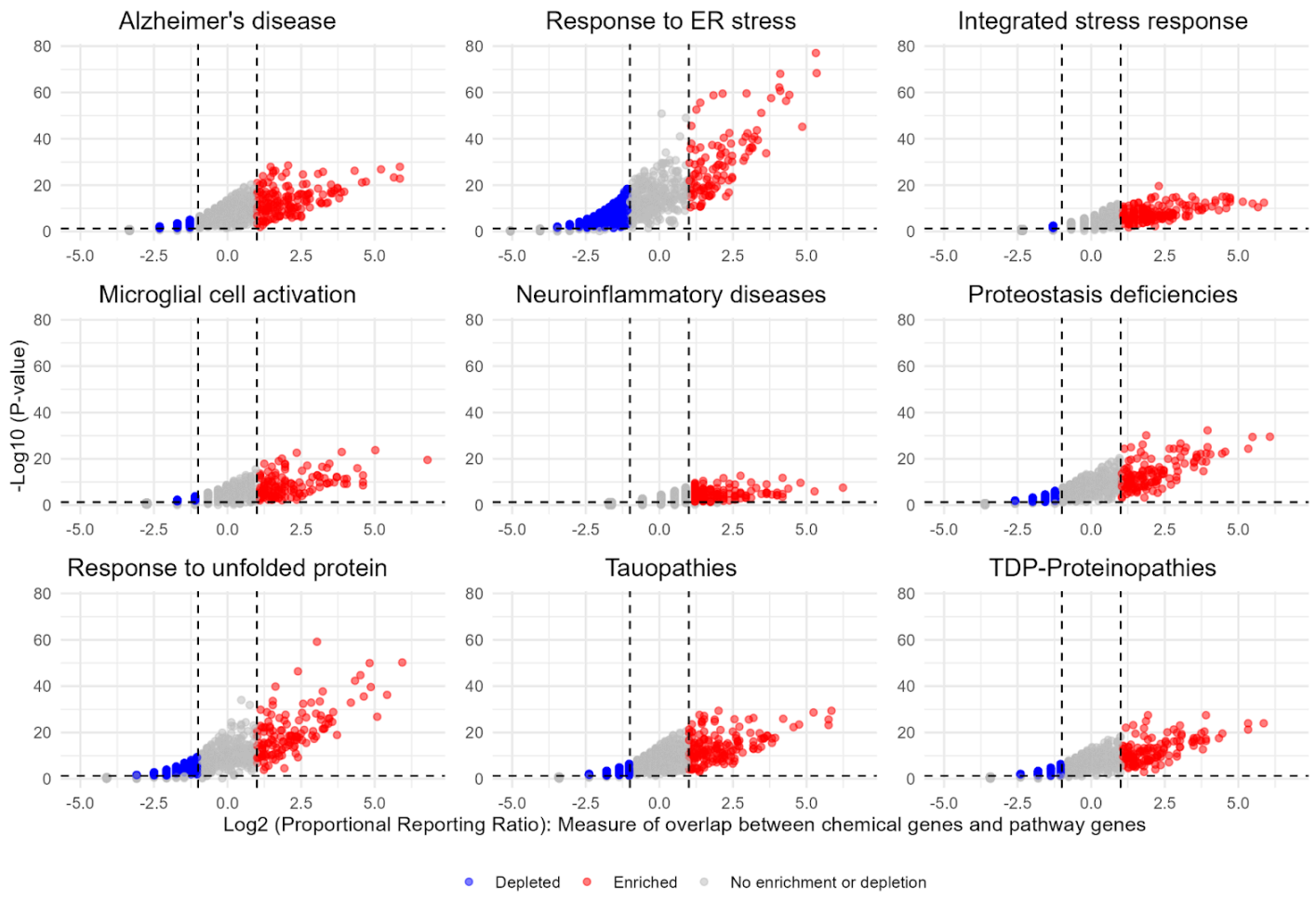

Figure 2. Scatter plots showing enrichment or depletion of chemical gene annotations for nine dementia pathways. Points in red represent enrichment, blue represents depletion, and gray represents no enrichment or depletion. The x-axis is log2 proportional reporting ratio (PRR). The y-axis is -log10 FDR-corrected p-value for Fisher's Exact test for chemical gene annotation enrichment with each dementia pathway.

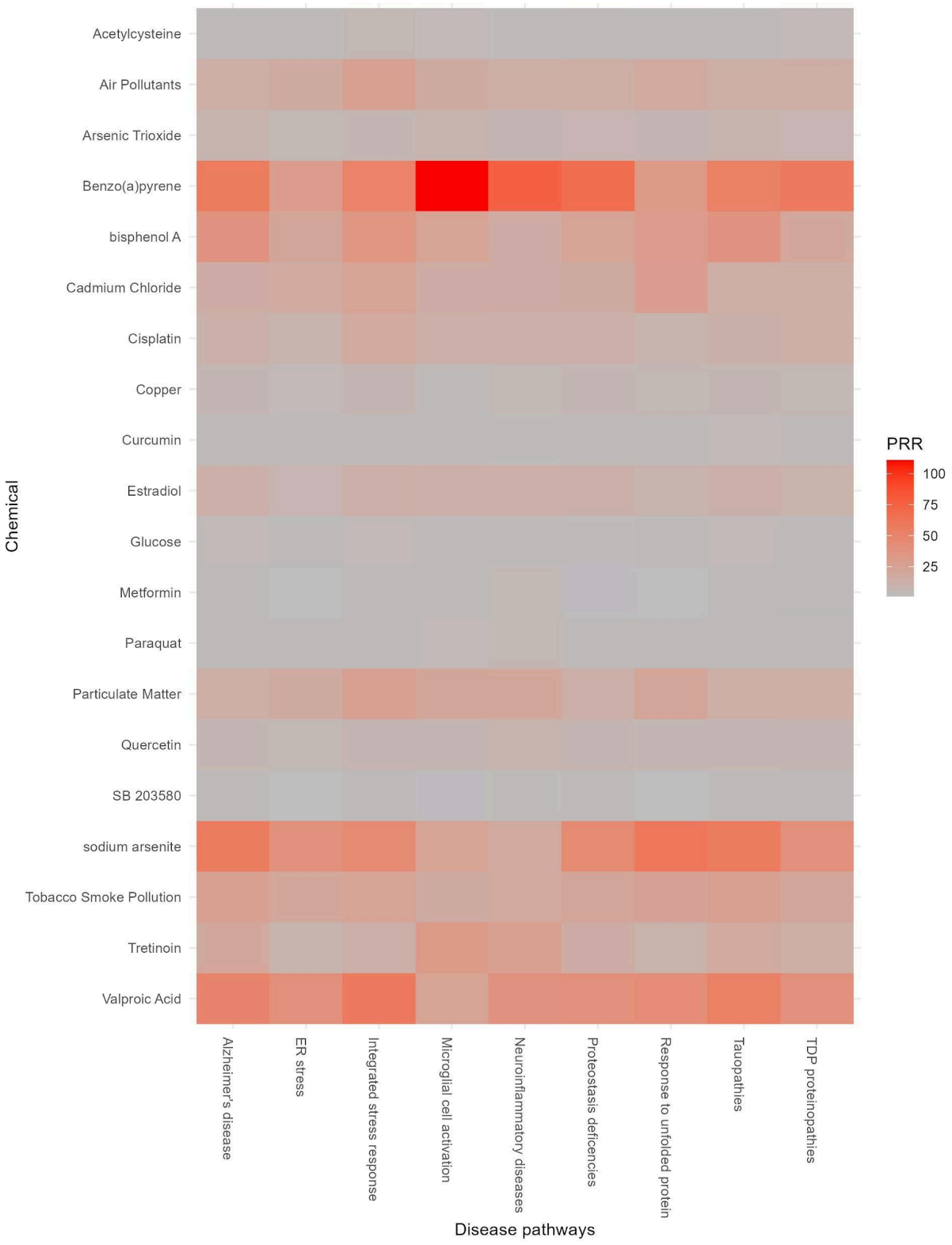

Figure 3. Heatmap of proportional reporting ratio (PRR) gene enrichment of top hits for nine dementia disease/pathways. Rows indicate chemicals tested and columns indicate the disease/pathway tested. The color of the cell indicates the PRR between the given chemical and disease/pathway, with red indicating a PRR closer to 100 and gray indicating a PRR closer to 1.

Table 2. Table of the top 20 chemical gene annotations enriched for dementia pathways based on the summed rank of the minimum significance value.

Summed Rank	Chemical name	Number of genes	Alzheimer's disease		ER stress		Integrated stress response		Microglial cell activation		Neuroinflammatory diseases		Proteostasis deficiencies		Response to unfolded protein		Tauopathies		TDP proteinopathies	
			Rank	FDR	Rank	FDR	Rank	FDR	Rank	FDR	Rank	FDR	Rank	FDR	Rank	FDR	Rank	FDR	Rank	FDR
165.5	Benzo(a)pyrene	16,489	17	$1.4x10^{-23}$	18	$6.3x10^{-46}$	46	$3.2x10^{-11}$	5	$2.9x10^{-20}$	25	$2.7x10^{-08}$	3	$2.9x10^{-30}$	28	$1.6x10^{-27}$	19	$6.5x10^{-24}$	4.5	$1.1x10^{-24}$
189.5	Tretinoin	7,737	6	$5.9x10^{-27}$	37	$1.0x10^{-36}$	72.5	$6.5x10^{-10}$	1	$1.8x10^{-24}$	7	$2.2x10^{-10}$	7	$8.3x10^{-26}$	40	$1.6x10^{-24}$	7	$1.2x10^{-26}$	12	$3.6x10^{-21}$
218.5	Glucose	583	1	$2.9x10^{-29}$	17	$2.6x10^{-46}$	10.5	$9.3x10^{-15}$	32	$3.0x10^{-13}$	47.5	$1.3x10^{-07}$	33	$6.5x10^{-20}$	22	$1.7x10^{-29}$	1.5	$4.1x10^{-30}$	54	$4.9x10^{-15}$
243.5	Particulate Matter	8,808	52	$1.4x10^{-17}$	3	$8.4x10^{-69}$	10.5	$9.3x10^{-15}$	16	$1.0x10^{-16}$	38	$7.2x10^{-08}$	35	$1.1x10^{-19}$	5	$1.8x10^{-45}$	47	$3.7x10^{-18}$	37	$5.0x10^{-17}$
259	Acetylcysteine	594	30	$2.1x10^{-20}$	13	$2.4x10^{-53}$	3.5	$8.7x10^{-16}$	10	$2.8x10^{-18}$	159	$2.2x10^{-05}$	2	$7.1x10^{-31}$	13	$2.5x10^{-34}$	27	$4.1x10^{-21}$	1.5	$3.4x10^{-28}$
262	Valproic Acid	15,333	16	$4.6x10^{-24}$	2	$4.3x10^{-69}$	22	$3.7x10^{-13}$	101	$2.9x10^{-09}$	78	$1.1x10^{-06}$	11	$4.4x10^{-25}$	10	$5.7x10^{-37}$	11	$2.4x10^{-26}$	11	$5.8x10^{-22}$
265.5	Metformin	288	6	$5.9x10^{-27}$	59	$3.0x10^{-30}$	26.5	$9.9x10^{-13}$	12	$2.4x10^{-17}$	3	$2.0x10^{-12}$	38	$1.7x10^{-19}$	94	$2.5x10^{-18}$	5	$6.5x10^{-28}$	22	$8.2x10^{-19}$
271.5	Arsenic Trioxide	3,465	8	$1.7x10^{-26}$	20	$3.0x10^{-43}$	96	$5.1x10^{-09}$	13	$2.7x10^{-17}$	102	$2.9x10^{-06}$	5	$2.4x10^{-27}$	15	$1.3x10^{-33}$	6	$5.2x10^{-27}$	7	$8.7x10^{-24}$
317.5	Cadmium Chloride	9,286	45	$6.9x10^{-18}$	4	$5.9x10^{-63}$	19	$3.1x10^{-13}$	47	$5.6x10^{-12}$	109	$3.5x10^{-06}$	21	$1.0x10^{-22}$	3	$1.1x10^{-50}$	42.5	$2.0x10^{-18}$	27	$6.3x10^{-18}$
332.5	Bisphenol A	11,657	4	$1.5x10^{-27}$	8	$1.1x10^{-59}$	15	$1.4x10^{-13}$	27.5	$1.3x10^{-13}$	225	$7.3x10^{-05}$	16	$8.7x10^{-24}$	8	$2.4x10^{-40}$	3	$2.2x10^{-29}$	26	$2.9x10^{-18}$
333.5	Curcumin	668	14	$2.4x10^{-24}$	12	$2.5x10^{-56}$	62	$1.8x10^{-10}$	27.5	$1.3x10^{-13}$	179	$3.9x10^{-05}$	6	$6.5x10^{-27}$	19	$1.5x10^{-32}$	11	$2.4x10^{-26}$	3	$1.3x10^{-25}$
345	Paraquat	801	105	$1.6x10^{-14}$	30	$1.2x10^{-38}$	54	$9.0x10^{-11}$	18	$3.9x10^{-16}$	10	$5.1x10^{-10}$	17	$1.0x10^{-23}$	25	$1.9x10^{-28}$	77	$3.5x10^{-16}$	9	$1.5x10^{-22}$
366.5	Quercetin	3,759	72.5	$1.9x10^{-16}$	41	$7.7x10^{-35}$	69	$5.0x10^{-10}$	36	$8.0x10^{-13}$	28	$3.6x10^{-08}$	14	$4.6x10^{-25}$	29	$3.2x10^{-27}$	63	$4.7x10^{-17}$	14	$1.2x10^{-20}$
375.5	Cisplatin	7,479	56.5	$3.2x10^{-17}$	19	$1.9x10^{-44}$	18	$2.7x10^{-13}$	40	$9.9x10^{-13}$	112	$4.1x10^{-06}$	20	$6.1x10^{-23}$	57	$3.3x10^{-22}$	38	$1.9x10^{-19}$	15	$2.1x10^{-20}$
380	Tobacco Smoke Pollution	11,387	18	$3.1x10^{-22}$	11	$4.2x10^{-57}$	53	$8.8x10^{-11}$	89.5	$6.8x10^{-10}$	145	$1.5x10^{-05}$	19	$5.7x10^{-23}$	11	$2.9x10^{-36}$	18	$3.6x10^{-24}$	16	$2.8x10^{-20}$
405	Sodium arsenite	13,975	2.5	$1.1x10^{-28}$	1	$8.8x10^{-78}$	25	$8.5x10^{-13}$	64	$1.0x10^{-10}$	301	$2.5x10^{-04}$	4	$3.6x10^{-30}$	2	$5.9x10^{-51}$	1.5	$4.1x10^{-30}$	4.5	$1.1x10^{-24}$
432.5	Estradiol	7,305	41	$2.3x10^{-18}$	40	$2.5x10^{-35}$	60.5	$1.8x10^{-10}$	33	$5.4x10^{-13}$	105	$3.0x10^{-06}$	26	$3.1x10^{-21}$	43	$3.2x10^{-24}$	42.5	$2.0x10^{-18}$	42	$1.3x10^{-16}$

485	Copper	2,657	23	$2.6x10^{-21}$	32	$1.0x10^{-37}$	17	$1.6x10^{-13}$	218	$1.4x10^{-06}$	134	$9.4x10^{-06}$	11	$4.4x10^{-25}$	17	$3.9x10^{-33}$	20	$3.3x10^{-23}$	13	$8.0x10^{-21}$
488.5	Air Pollutants	9,669	98	$4.3x10^{-15}$	5	$1.9x10^{-61}$	16	$1.6x10^{-13}$	45	$4.1x10^{-12}$	161	$2.6x10^{-05}$	36.5	$1.7x10^{-19}$	16	$1.3x10^{-33}$	76	$3.1x10^{-16}$	35	$4.5x10^{-17}$
507.5	SB 203580	281	24	$3.7x10^{-21}$	77	$7.7x10^{-27}$	24	$8.3x10^{-13}$	72	$2.2x10^{-10}$	65.5	$6.8x10^{-07}$	27	$4.5x10^{-21}$	169	$1.4x10^{-13}$	28	$9.7x10^{-21}$	21	$5.5x10^{-19}$

Table 3. Table showing number (%) chemicals in the analytic sample (N=1,008) that impact specific dementia hallmark genes.

Alzheimer's disease Dementia hallmark genes	Number of chemicals	Example chemicals relevant to human exposome
APOE	109 (11%)	Aflatoxin B1, Arsenic, Benzo(a)pyrene, Lead, Perfluorooctane Sulfonic Acid
APP	163 (16%)	Benzene, Bisphenol A, Glyphosate, Perfluorobutanesulfonic Acid, Perfluorooctanoic Acid
PSEN1	52 (5%)	Atrazine, Benzo(a)pyrene, Lead, Particulate Matter, Vehicle Emissions
PSEN2	42 (4%)	Arsenic, Bisphenol A, Cannabidiol, Glyphosate, Valproic Acid
MAPT	113 (11%)	Aflatoxin B1, Arsenic, Methamphetamine, Particulate Matter, Tobacco Smoke Pollution