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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection

Provide a description of all commercial, open source and custom code used to collect the data in this study, specifying the version used OR state that no software was used.

Data analysis

For bulk RNA-seq, Salmon 1.8.0. was used to align reads to the mm10 genome and quantify transcript abundance as transcripts per million (TPM) values. Documentation for Salmon is available at https://combine-lab.github.io/salmon/. The R package tximport version 1.26.1, available at https://bioconductor.org/packages/release/bioc/html/tximport.html, was used to convert TPM values into gene-TPM abundance matrices. DESeq2 version 1.38.3 was used to identify differentially expressed genes.

Gene set enrichment analysis was performed using the GSEA (v4.2) application which can be downloaded at https://www.gsea-msigdb.org/gsea/index.jsp

ToxPrint enrichment analysis was performed using the publicly available ToxPrint feature set (https://toxprint.org/) and the Chemotyper visualization application (https://chemotyper.org/). Chemical sets of interest were assigned as the "positive" chemical set and remaining chemicals were the "negative" chemical set. The Fisher's exact test was used to calculate odds ratios and p-values.

Analysis of the US National Health and Nutrition Examination Survey data was performed using R version 4.2.2 and R Studio version 2023.06.2 +561 . NHANES data cycles 2013-2014, 2015-2016, and 2017-2018 were imported using the R package "nhanesA" version 0.7.4. Density plots were generated with the R package "ggplot2" version 3.4.3. Multivariable logistic regression analyses were performed using the R package "survey" version 4.2.1 and included strata, cluster, and weight variables. Covariates used in logistic regression analyses include urinary creatinine, sex, age, race/ethnicity, ratio of family income to poverty, education level of the household reference person, mother's age, and mother smoked while pregnant. Age, urinary creatinine, and ratio of family income to poverty were modeled as continuous variables while

sex, race/ethnicity, education level of the household reference person, mother's age, and mother smoked while pregnant were included as discrete covariates. Visualization of logistic regression analyses were done using the package "gtsummary" version 1.7.2.9000.

Graphpad Prism version 10.1.1 was utilized for all statistical analyses except for NHANES complex sample logistic regression.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Publicly available data were downloaded from the US National and Nutrition Examination Survey website (https://wwwn.cdc.gov/Nchs/Nhanes/)
The publicly available genome mm10 (GENCODE) was utilized for RNA sequencing analysis.
Data availability: Primary screening results are available in Supplementary Table 1 and will be included in a future public release of the US EPA ToxCast database. RNA-seq datasets generated in this study have been deposited in Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) and are accessible under accession code GSE244500.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample size calculation was performed. Sample sizes were estimated based on previous literature.
Data exclusions	No data were excluded
Replication	At least 3 biological replicates were utilized for all experiments and are described for each data panel when applicable. For human cortical organoid experiments, individual organoids were considered biological replicates and were generated from 4 independent batches. Biological replicates for in vitro experiments were not included in this manuscript if they did not meet the quality control standards that ensure each system is performing as expected. In vivo studies were performed using multiple litters and no data were excluded.
Randomization	For mouse studies, animals were randomly assigned to control or experimental groups on postnatal day 5. For cellular studies, wells and organoids were randomly selected to receive control or experimental conditions. Automated cell counting was performed to quantify immunohistochemistry and immunocytochemistry images
Blinding	For immunohistochemistry, whole slide scan images were taken using the same exposure settings. Analysis was performed by a blinded investigator using the image analysis tool QuPath, v0.4.0 (https://qupath.github.io/) for automated cell counting. Immunocytochemistry images were obtained using an automated PerkinElmer Operetta High-Content Imaging System. Image analysis was performed using the Columbus Image Data Storage and Analysis System with automated scripts that applied identical parameters to every

image analyzed.

Pharmacokinetics was performed by a blinded investigator. Covariate selection for logistic regression was not performed by a blinded investigator but was performed based on literature review.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

anti-O1 (CCF Hybridoma core)
anti-O4 (CCF Hybridoma core)
anti-MBP (Abcam, ab7349, clone 12)
anti-SOX10 (R&D, AF2864,)
anti-APC CC1 (Millipore, MABC200, clone CC-1)
anti-NEUN (CST, 24307)
anti-SOX2 (Thermo Fisher, MAB2018, clone 245610)
Donkey anti-Rat IgG (H+L) Alexa Fluor 488 (Thermo Fisher, A21208)
Donkey anti Mouse IgG(H+L) Alexa Fluor 647 (Thermo Fisher, A31571)

Validation

O1, O4, and MBP antibodies were validated against mouse proteins. CC1, SOX10, SOX2, and NeuN antibodies were validated against human proteins. The MBP antibody is validated for immunohistochemistry by Abcam. The SOX10 and SOX2 antibodies are verified for immunohistochemistry by R&D. The CC1 antibody has been validated by Saikali, P. et al. (2007. J Neurosci. 27(5):1220-1228) for immunohistochemistry according to Millipore. The NeuN antibody has been approved for use in immunohistochemistry by Cell Signaling Technology.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

The human embryonic stem cell line H7 (female) was purchased from WiCell (WA07). The human induced pluripotent stem cell line CWRU22 was generated previously from a healthy male donor.

Authentication

None

Mycoplasma contamination

Human embryonic cell lines are regulatory tested for mycoplasm. All cell lines including primary cell cultures tested negative.

Commonly misidentified lines
(See ICLAC register)

We did not use commonly misidentified lines.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals

Studies used C57Bl/6 mice purchased from Charles Rivers Laboratory. Mice were housed in a temperature and humidity-controlled environment, with 12 h: 12 h light:dark cycle. Mice had ad libitum access to rodent chow and water and experimental mice were housed with dams until tissue collection. For mixed primary OPC and astrocyte isolations, males and females were used for all studies and sacrificed at P2-3. Males and females were used for all studies evaluating the effects of developmental exposure to environmental chemicals and sacrificed at P15.

Wild animals

Wild animals were not involved in this study

Reporting on sex

For primary cell culture experiments, sex differences were not analyzed as primary astrocyte and oligodendrocyte progenitor cells

Reporting on sex	isolations were pooled from mixed populations of male and female P2-3 mice. For developmental testing (P4-P15) of chemical exposures, mice were randomly assigned within a litter to vehicle or one of two chemical groups.
Field-collected samples	This study did not involve field-collected samples.
Ethics oversight	Procedures were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, and were approved by the Case Western Reserve University Institutional Animal Care and Use Committee (IACUC).

Note that full information on the approval of the study protocol must also be provided in the manuscript.