The Mab009 data product

Original number of samples	1,050
Number of samples (per 26.02.2024)	1,045
Number of unique participants	1,043
Biological sample type	Whole blood
Participant type(s)	MoBa mothers
Collection timepoint	Gestational week ~17
Case-control selection criteria	Cerebral palsy, autism spectrum disorder, epilepsy
Biomarker type(s)	Toxic/non-essential metals and essential elements
Original reference article	Skogheim *et al*. 2021
Analytical method(s)	ICP-SFMS
Related MoBaBIO product(s)	Mab010
FHI Project number(s)	PDB2322

The project that generated these data

Prenatal exposure to toxicants and childhood neurodevelopmental disorders and cognitive functions (NEUROTOX)

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The purpose of this study was to study whether exposure to environmental toxicants in pregnancy increases the risk for child neurological and neurodevelopmental disorders; attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), cerebral palsy (CP) or epilepsy, as well as cognitive deficits and language difficulties. Parallel analyses make it possible to evaluate whether environmental toxins have a general effect on brain development *in utero*, or whether they affect specific functions.

The present study/data is a part of **phase 2 of the NeuroTox study** (PDB1606/2322), aiming to investigate prenatal exposure to PFAS and inorganic contaminants and a wider range of neurologic and neurodevelopmental conditions in children. Data attainment was done in 2 phases; **Phase I** consisted of PDB 1606 with attainment of maternal toxicant data for NPR-ADHD cases and MoBa controls, as well as participants from the ADHD-study. **Phase II** (this dataset) consisted of PDB 2322, in which maternal toxicant data for ASD, Epilepsy and CP case groups and additional MoBa controls were attained. See Table 1 for a data overview.

Table 1: Overview of toxicant data and populations in the NeuroTox project (PDB1606/2322)

				Complete NeuroTox dataset	
NeuroTox	**PDB nu**	**Biomarker results, N**	**Mab**	**Diagnostic case groups**	**ADHD-study**
Phase I	1606	PFAS (plasma) N=2334	Mab008	Sub-population 1: ~ 700 ADHD cases ~700 controls	Sub-population 2: ~900 ADHD-study participants
		Metals/elements (whole blood), N=1872[a]	Mab007		
Phase II	2322	PFAS (plasma), N=1099	Mab010	~400 ASD cases ~300 Epilepsy cases ~170 CP cases ~300 additional controls[b] ~100 ADHD cases[c]	
		Metals/elements (whole blood), N=1045[a]	Mab009		

[a] For metals/element, NeuroTox utilized available data from the Norwegian Environmental Biobank (PDB1440) for participants that overlapped with NeuroTox participants. Thus, N with measured metals/elements are fewer than for PFAS data.
[b] To be added to controls from phase 1 (PDB1606).
[c] These ADHD cases are additional to those available from PDB1606, as they overlapped with ASD, Epilepsy and/or CP cases in the present dataset. These extra cases can be added to ADHD cases from PDB1606.

Study population

The original Mab009 biomarker data source is based on whole blood samples from **1,048 mothers**.

The study population was selected based on a case-control study design using the same eligible population defined using version 8 of the self-reported questionnaires in MoBa, and same selection criteria as in PDB1606 (Mab008). Cases are in this dataset defined as MoBa mothers of children who had received a medical diagnosis through linkage to Norwegian Patient Registry (NPR) (and additional sources) of cerebral palsy (CP; ICD-10 codes G80.0, G80.1, G80.2, G80.3, G80.4, G80.8 or G80.9), epilepsy (ICD-10 codes G40.0, G40.1, G40.2, G40.3, G40.4, G40.5, G40.6, G40.7, G40.8 or G40.9) or ASD (ICD-10 codes F84.0, F84.1, F84.5, F84.8 or F84.9). The eligible for cases were identified via NPR linkage and/or clinical assessments via MoBa sub-studies of these conditions:

- the Autism Birth Cohort (ABC) Study (PDB141)
- the Cerebral Palsy study (CP-study; MOBAND) (PDB1352)
- the Epilepsy in Young Children (EPYC) Study (PDB1195)

We also identified eligible ADHD cases with ≥2 registrations of ICD-10 F90 in the NPR (linkage from January 2018; diagnoses 2008-2017) using the linkage from PDB1223.

Cases and *control* mother-child pairs were selected using the following **criteria**:

- Non-withdrawals from MoBa
- Singleton pregnancies
- Child born in 2001 or later
- Available records from the Medical Birth Registry of Norway (MBRN)
- Mother's questionnaire 1 available (week 17)
- No child serious malformation or affected by Down's syndrome (except for the CP case group)
- Available maternal plasma and whole blood sampled during the routine ultrasound assessment (K1) approximately 17-18th week of pregnancy (for CP cases: available maternal plasma or whole blood).

Controls were comprised of a randomly-selected sample from MoBa of the same eligible group as cases, and frequency matched to cases by child sex and year of birth.

Available biomarker measures (variable names in bold)

Essential elements:

Cobalt (**Co**)
Copper (**Cu**)
Magnesium (**Mg**)

Manganese (**Mn**)
Molybdenum (**Mo**)
Potassium (**K**)
Selenium (**Se**)
Sodium (**Na**)
Zinc (**Zn**)

Toxic/non-essential metals:

Arsenic (**As**)
Cadmium (**Cd**)
Cesium (**Cs**)
Lead (**Pb**)
Mercury (**Hg**)
Thallium (**Tl**)

Other metadata variables

- Rack
- Position

Definition of cases and controls in the dataset

There are two case/control variables that are provided with the Mab009 dataset, **CaseControlGrpAlt1** and **CaseControlGrpAlt2**. Each of these subcategorizes cases and controls into the specific selection groups to which they belong and from which they were derived for inclusion in this study. A variable key with associated descriptions is provided below.

CaseControlGrpAlt1 (Retrieval ID: 956)

- Case_ASD: *Mother-child pairs where the child was diagnosed with ASD.*
- Case_CP: *Mother-child pairs where the child was diagnosed with CP.*
- Case_Epilepsy: *Mother-child pairs where the child was diagnosed with Epilepsy.*
- Control: *Mother-child pairs that were randomly selected from MoBa, frequency matched ASD, CP and Epilepsy case groups on child sex and birth year*.
- Case-ADHDNPR: *Mother-child pairs where the child was registered with ≥ 2 ADHD diagnoses.*

Variable describing the overlap between groups:

- Case_ASD (+ Case_ADHDNPR)
- Case_ASD + Case_CP

- Case_ASD + Case_CP (+ Case_ADHDNPR)
- Case_ASD + Case_CP + Case_Epilepsy
- Case_ASD + Case_CP + Case_Epilepsy (+ Case_ADHDNPR)
- Case_ASD + Case_Epilepsy
- Case_ASD + Case_Epilepsy (+ Case_ADHDNPR)
- Case_ASD + Control
- Case_ASD + Control (+ Case_ADHDNPR)
- Case_CP (+ Case_ADHDNPR)
- Case_CP + Case_Epilepsy
- Case_CP + Case_Epilepsy (+ Case_ADHDNPR)
- Case_CP + Case_Epilepsy + Control
- Case_CP + Control
- Case_Epilepsy (+ Case_ADHDNPR)
- Case_Epilepsy + Control
- Case_Epilepsy + Control (+ Case_ADHDNPR)
- Control (+ Case_ADHDNPR)

CaseControlGrpAlt2

- Case_Neurotox*: Mother-child pair where child had at least one diagnoses (ASD, CP or Epilepsy).*
- Control: *Mother-child pairs that were randomly selected from MoBa, frequency matched ASD, CP and Epilepsy case groups on child sex and birth year*
- Control (+ Case_Neurotox): *Mother-child pairs where the child had at least one diagnosis (ASD, CP or Epilepsy) and was selected as a control*

Biological sampling and processing

Whole blood samples were collected from mothers at 17-18 weeks' gestation into 3 mL trace-free sampling tubes, and shipped from the collecting hospital overnight to MoBa's biobank at the Norwegian Institute of Public Health (NIPH). The samples most often arrived at the biobank within 1–2 days of blood donation, and were placed in long-term storage at a temperature of −80 °C.
For more information on biological sampling, processing and storage, please refer to the original reference articles for NIPH's biobank by Rønningen *et al*. 2006 and Paltiel *et al.* 2014.

Analytical methodology

Data on heavy metals and essential elements were measured using **inductively coupled plasma–sector field mass spectrometry (ICP-SFMS)** after microwave-assisted sample decomposition. For more information on the analytical method used in this study, refer to the original reference articles by Rodushkin *et al*. 2000 and Rodushkin *et al*. 2004.

The published studies from Mab009 (and Mab007) also utilized subsets of data on blood concentrations of metals/elements in pregnant MoBa mothers from the Norwegian Environmental Biobank (PDB1440, see Mab011). These samples were analysed at the Department of Occupational and Environmental Medicine at Lund University, Sweden, using comparable analytical methods as the ALS Laboratory group, as described in Caspersen *et al.* 2019, however, these analyses did not include magnesium, caesium, potassium or sodium. For these analyses, the same standard reference material (Seronorm Trace Elements whole blood L-1, SERO AS, Billingstad, Norway) were analysed and these can be used to adjust for inter-laboratory variations in metal/element concentrations in addition to intra-laboratory variations across analytical rounds.

Measurement units:

Cobalt, Copper, Manganese, Molybdenum, Selenium, Zinc, Arsenic, Cadmium, Cesium, Lead, Mercury, Thallium: µg/L

Magnesium, Potassium, Sodium: mg/L

Limit of quantification (LOQ):

Arsenic (As): 1 µg/L
Cadmium (Cd): 0.05 µg/L
Cesium (Cs): 0.05 µg/L
Cobalt (Co): 0.05 µg/L
Copper (Cu): 1 µg/L
Lead (Pb): 0.5 µg/L
Magnesium (Mg): 0.2 mg/L
Manganese (Mn): 0.5 µg/L
Mercury (Hg): 0.2 µg/L
Molybdenum (Mo): 0.2 µg/L
Potassium (K): 0.5 mg/L
Selenium (Se): 5 µg/L
Sodium (Na): 0.5 mg/L
Thallium (Tl): 0.05 µg/L
Zinc (Zn): 10 µg/L

Total Hg and total As were measured, which included both inorganic and organic forms.

Concentrations above LOQ were reported for most metals/elements, except for arsenic, cadmium, mercury and lead where concentrations above limit of detection (LOD) were reported. LOD was approximately one third of the LOQ.

Published articles using Mab009

Note: This section also includes publications that used Mab007, as these datasets were often combined and analyzed together

This section also includes articles related to study design, sampling, and data collection.

- Weyde KVF, Winterton A, Surén P, Andersen GL, Vik T, Biele G, Knutsen HK, Thomsen C, Meltzer HM, Skogheim TS, Engel SM, Aase H, Villanger GD. Association between gestational levels of toxic metals and essential elements and cerebral palsy in children. Front Neurol. 2023.
- Weyde KVF, Olsen AK, Duale N, Kamstra JH, Skogheim TS, Caspersen IH, Engel SM, Biele G, Xia Y, Meltzer HM, Aase H, Villanger GD. Gestational blood levels of toxic metal and essential element mixtures and associations with global DNA methylation in pregnant women and their infants. Sci Total Environ. 2021 Sep 15;787:147621.
- Skogheim TS, Weyde KVF, Engel SM, Aase H, Surén P, Øie MG, Biele G, Reichborn-Kjennerud T, Caspersen IH, Hornig M, Haug LS, Villanger GD. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environ Int. 2021 Jul;152:106468.

Restrictions for use

None currently known.

Acknowledgements recommended for use

We recommend that any use of these data in analyses that are presented in peer-review publications acknowledges the original articles describing sampling and data collection:

Weyde KVF, Olsen AK, Duale N, Kamstra JH, Skogheim TS, Caspersen IH, Engel SM, Biele G, Xia Y, Meltzer HM, Aase H, Villanger GD. Gestational blood levels of toxic metal and essential element mixtures and associations with global DNA methylation in pregnant women and their infants. Sci Total Environ. 2021 Sep 15;787:147621.

Skogheim TS, Weyde KVF, Engel SM, Aase H, Surén P, Øie MG, Biele G, Reichborn-Kjennerud T, Caspersen IH, Hornig M, Haug LS, Villanger GD. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environ Int. 2021 Jul;152:106468.

Disclaimer

The data in Mab009 that are available for use are provided by MoBa on an *as is* basis as they were received from the generating laboratory and have not been curated or quality controlled prior to release. FHI does not provide any guarantees related to data quality and assurance of the original dataset. We reserve the right to periodically remove samples from the dataset belonging to participants who have retracted their consent to participate in this cohort study, and may alter the contents of the associated documentation accordingly.