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Environmental pollutants in blood donors: The multicentre Norwegian donor study

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Abstract

Objectives: The aim of this study was to measure blood concentrations of environmental pollutants in Norwegian donors and evaluate the risk of pollutant exposure through blood transfusions.

Background: Transfused blood may be a potential source of exposure to heavy metals and organic pollutants and presents a risk to vulnerable patient groups such as premature infants.

Methods/Materials: Donors were randomly recruited from three Norwegian blood banks: in Bergen, Tromsø and Kirkenes. Selected heavy metals were measured in whole blood using inductively coupled plasma mass spectrometry (ICP-MS), and perfluoroalkyl substances (PFAS) were measured in serum by ultrahigh-pressure liquid chromatography coupled with a triple-quadrupole mass spectrometer (UHPLC-MS/MS).

Results: Almost 18% of blood donors had lead concentrations over the limit suggested for transfusions in premature infants (0.09 μmol/L). About 11% of all donors had mercury concentrations over the suggested limit of 23.7 nmol/L. Cadmium was higher than the limit, 16 nmol/L, in 4% of donors. Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations were over the suggested limit of 0.91 ng/mL in 68% and 100% of the donors, respectively. PFAS concentrations and heavy metal concentrations increased with donor's age.

Conclusion: A considerable percentage of donors had lead, PFOS and PFOA concentrations over the suggested limits. In addition, at each study site, there were donors with high mercury and cadmium concentrations. Selecting young donors for transfusions or measurements of pollutants in donor blood may be a feasible approach to avoid exposure through blood transfusions to vulnerable groups of patients such as premature infants.

KEYWORDS

cadmium, donor blood, lead, mercury, PFAS

1 | INTRODUCTION

Environmental pollutants are ubiquitous and represent a global threat to both animals and humans.[1-5] The potential for harm is especially great in periods of life with rapid growth and development, such as during pregnancy and childhood. In infants, even low concentrations, transferred from the mother during pregnancy or by later exposure, may disturb neurological and cognitive development and lead to permanent disabilities.[6]

Various measures have been taken to limit human exposure to environmental pollutants. These include restriction of lead in gasoline, paint and consumer products by replacing mercury-containing devices with mercury-free alternatives (eg, in thermometers), by food advisories, by restricting the use of cadmium in electronics and pigments, by secure waste handling and by other actions to limit emissions to the environment.[7-10] However, the possible transfer of pollutants via blood transfusions has not been the focus.

During blood transfusions, pollutants present in the donor's blood are transferred to the recipients. Transfused blood, as well as blood components, may represent a substantial source of environmental pollutant exposure for the recipients, particularly for vulnerable groups such as premature infants who receive multiple blood transfusions.[11-14] Blood transfusions were shown to increase heavy metal concentrations in premature infants.[15]

Previous published studies have shown that a considerable percentage of blood donors have lead concentrations that may cause concern.[16,17] As a result, in some medical institutions, lead testing is required before transfusions.[18-20]

Although exposure to lead and other heavy metals has been addressed, exposure to organic pollutants through donor blood is less studied. There are few studies of perfluoroalkyl substances (PFAS) in blood donors.[21-24] These studies did not specifically address the risk of PFAS exposure via blood transfusions to premature infants. Animal studies showed unfavourable effects of prenatal PFAS exposure, such as low birthweight, enlarged liver, impaired lung and kidney development and lipid metabolism changes.[25,26] Reduced fetal growth was also demonstrated in humans after exposure to mixtures of pollutants such as PFAS, phthalates, lead, mercury, cadmium, thallium and arsenic.[27] Studies of prenatal PFAS exposure in humans showed unfavourable health effects, such as lower birthweight but greater weight and adiposity later in life,[28-30] increased risk of impaired neuropsychological development in early childhood[31] and increased number of respiratory tract infections in the first 10 years of life.[32]

The aim of this multicentre study was to measure blood concentrations of lead, cadmium, mercury and PFAS in Norwegian blood donors and to evaluate the potential risk for pollutant exposure through blood transfusions with special focus on premature infants.

2 | MATERIALS AND METHODS

2.1 | Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway. All the participants gave written informed consent for participation in the study.

2.2 | The study population

Blood donors who were accepted for donation were randomly selected to participate in the present study. Donors were recruited from three Norwegian blood banks: in Bergen, Tromsø and Kirkenes. The rationale for this design was to recruit a representative sample of Norwegian blood donors from three different geographical regions in Norway: the Arctic region Finnmark (Kirkenes), Northern Norway (Tromsø) and Western Norway (Bergen). During the study, all the blood donors routinely attending the blood banks were consecutively invited to participate in the study, and only one person refused to participate. No exclusion criteria were applied. As it was planned in advance, 201 donors were recruited from Bergen, 101 donors from Tromsø and 50 donors from Kirkenes, for a total of 352 participants. The difference in number of the participants from different sites reflects the relative size of the population in these areas. Age, gender and number of previous blood donations were registered.

2.3 | Analysis of heavy metals

Lead, mercury and cadmium were measured in whole blood using inductively coupled plasma mass spectrometry (ICP-MS) on Perkin Elmer DRC-e in standard mode (Table Table S1) at the Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen. Limits of quantification (LOQs) for lead, mercury and cadmium were 0.0267 μmol/L, 3.25 nmol/L and 1.615 nmol/L, respectively. Limits of quantification were defined as five times the within-day analytical SD. Limits of detection (LODs) were 0.0160 μmol/L for lead, 1.95 nmol/L for mercury and 0.969 nmol/L for cadmium.

The between-run analytical coefficients of variation (CVa) for cadmium, mercury and lead were 4.4%, 2.9% and 4.2%, respectively. All analyses complied with UKNEQAS for trace elements (Royal Surrey County Hospital, Guildford, UK) and Seronorm Trace Elements Whole Blood (Sero AS, Billingstad, Norway) acceptable range.

2.4 | Analysis of PFAS

Perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorononane sulfonate (PFNS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA) and perfluorodecanoate (PFDA) were analysed in serum by ultrahigh-pressure liquid chromatography triple-quadrupole mass-spectrometry (UHPLC-MS/MS, Waters, Milford, MA, USA) at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø. The LODs were set as concentrations calculated by the Targetlynx software for each individual sample (LOD*i*) and each individual PFAS with a signal to noise ratio of 3, divided by the related sample amount. Mean LODs (SD) were 0.030 ng/mL (0.048 ng/mL) for PFOS, 0.112 ng/mL (0.037 ng/mL) for PFOA, 0.011 ng/mL (0.006 ng/mL) for PFHxS, 0.014 ng/mL (0.005 ng/mL) for PFNA and 0.015 ng/mL (0.007 ng/mL) for PFDA. LOQs for PFAS were defined as three times their LODs. For quality assurance, four blank samples, four SRM 1958 (NIST, Gaithersburg, Maryland) and three bovine serum samples (Sigma Aldrich, Steinheim, Germany) were prepared and analysed within each batch of

96 samples in order to control for background and carry-over effects. Details on sample preparation and instrumental analyses were described earlier.[33] All the quality controls were within the acceptance limits. CVa was <10% for all measured PFAS. All PFAS analyses were within the acceptable ranges of the international quality control programme: the Arctic Monitoring and Assessment (AMAP) Ring Test for Persistent Organic Pollutants in Human Serum (organised by the Laboratoire de toxicologie, Institut National de Santé Publique du Quebec, Canada).

2.5 | Estimation of tolerable intravenous doses

2.5.1 | Lead

The maximum concentration for lead in donor blood given to small children was set to 0.15 μmol/L (0.031 μg/mL) by Rhainds and Delage,[19] and this limit was later used by various centres.[18,20,34] However, Bearer et al estimated an even lower limit of acceptable lead concentration of 0.09 μmol/L for intravenous exposure in infants with extreme low birthweight.[11] This threshold was based on the assumption of 10% lead absorption in the gastrointestinal tract and the provisional tolerable weekly intake (PTWI) of 25 μg/kg from the 1996 World Health Organisation (WHO) guidelines for drinking water quality.[35] Given that only 10% of lead is absorbed from the gastrointestinal system, a daily permissible dose would be 0.36 μg/kg; for a donor unit of 20 mL/kg blood transfusion, the concentration must be less than 0.018 μg/mL or 0.09 μmol/L.

2.5.2 | Mercury

Whole-blood concentration of mercury in a general population is usually <50 nmol/L (< 10 ng/mL).[36] The US Environmental Protection Agency (EPA) estimated a maximum daily intake of mercury that is not likely to cause harmful effects during a lifetime, known as a reference dose (RdF) for dietary methyl mercury of 0.1 μg/kg/day.[37,38] Assuming that about 95% of methylmercury is absorbed from the gastrointestinal tract, the acceptable limit for mercury will be 0.095 μg/kg/day or 23.7 nmol/L (4.75 ng/mL) for the donor unit of 20 mL/kg.

2.5.3 | Cadmium

In 2011, the European Food Safety Authority (EFSA) defined 2.5 μg/kg/week (22.25 nmol/kg/week) as the tolerable weekly intake of cadmium, which provides an estimate of a tolerable daily intake (TDI) of 0.357 μg/kg/day (3.18 nmol/kg/day).[39]

Based on the conservative assumption that only 10% of the oral dosage is absorbed, the intravenous tolerable dose would be 0.32 nmol/kg. For a 20 mL/kg transfusion, this corresponds to a whole-blood cadmium concentration of 16 nmol/L (1.80 ng/mL).

2.5.4 | Selected PFAS

In the 2008 report from the EFSA, the TDI for PFOS was defined as 150 ng/kg/day.[40] However, in 2015, the Danish EPA established a TDI of 30 ng/kg per day for PFOS and a TDI of 100 ng/kg per day for PFOA.[41] PFAS are readily absorbed after dietary exposure with the highest gastrointestinal uptake estimated as 91%.[42] Taking into consideration the 91% absorption and 20 mL/kg transfusion, a daily acceptable venous dose for PFOS 1.37 ng/mL and for PFOA 4.55 ng/mL was estimated. In 2016, the US EPA issued a reference dose (RfD) of 20 ng/kg per day, valid both for PFOS and PFOA.[41] If we use this threshold to calculate a daily acceptable venous dose, it will be 0.91 ng/mL for 20 mL/kg transfusion for both PFOS and PFOA. In 2018, the EFSA proposed new tolerable weekly intake (TWI) oral doses for PFOS and PFOA: 13 and 6 ng/kg/week, respectively.[41] If we consider only one transfusion of 20 mL/kg blood per week, then the tolerable venous dose for PFOS will be 0.59 ng/mL and for PFOA 0.27 ng/mL (the limit will be lower if the number of transfusions increases). The TDIs for other PFAS, such as PFHxS, PFNA and PFDA, are not established yet. Therefore, we chose a young and relatively healthy general Norwegian population without occupational exposure to PFAS for the comparison. The 97.5 percentile of serum PFHxS, PFNA and PFDA concentrations measured in Norwegian adolescents (15-19 years old) from the Fit Futures study were applied as thresholds: 7.66 ng/mL for PFHxS, 1.61 ng/mL for PFNA and 0.79 ng/mL for PFDA.[43]

2.6 | Statistical analyses

Statistical analyses were performed using the SPSS programme (IBM Corp. IBM SPSS Statistics for Windows, Version 24.0., IBM Corp., Armonk, New York). To reduce possible bias of left-censored data analyses, we have used the actual values below the LOQs for both PFAS and heavy metal concentrations. Chi-square test was used for comparisons of proportions. Spearman correlation was performed to evaluate associations between various PFAS and heavy metals. A two-tailed *t*-test was used to compare age and number of blood donations between the study sites. Heavy metals and PFAS concentrations were not normally distributed according to distribution plots, skewness estimates, QQ-plots and the Kolmogorov-Smirnov test. Therefore, the non-parametric Mann-Whitney *U* test was used for comparisons between the different study sites. All the heavy metals and PFAS concentrations were $\log_{10}$-transformed before the statistical analyses because of the skewed distribution. We have checked the homoscedasticity and normality of residuals distribution by graphic inspection of residuals and linearity of the relations between the variables using the Passing-Bablok test and found that log-transformed concentrations satisfy these assumptions. Multiple linear regression analyses were performed for log-transformed concentrations of heavy metals and PFAS as continuous variables to evaluate associations with age, gender and number of blood donations. Beta-coefficients were

back-transformed as 10^{β} to evaluate the associations between the independent variables and concentrations of pollutants. All statistical tests were two-sided. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

General characteristics of the study population are shown in Table 1. Blood donors in Kirkenes were slightly older than in Bergen and Tromsø and had a higher percentage of women. Age and gender distribution in the entire study population was similar to another study of the Norwegian donors, with approximately 50% of donors being women.[44] The study population included blood donors of all ages from three geographic areas in Norway (Arctic, Northern Norway and Western Norway). The study population included both newly recruited blood donors with few blood donations and experienced blood donors with numerous blood donations up to and more than 60 donations. The mean number of blood donations was similar for all study sites. We assume that the study population was fairly representative of the general Norwegian blood donor population.

Concentrations of lead, mercury and cadmium in donor blood are shown in Table 2. Overall, 4.5% of all blood donors had lead levels higher than the highest suggested limit for lead concentration in the

TABLE 1 General characteristics of the study population: The Norwegian donor study

	Bergen n = 201	Tromsø n = 101	Kirkenes n = 50	Entire study n = 352
Age range, y	19-72	20-66	19-66	19-72
Mean age, y (SD)	43.1 (15.6)	41.4 (12.3)	46.1 (11.1)[a]	43.0 (14.2)
Mean blood donations (SD)	26.2 (31.2)	26.7 (25.3)	25.2 (20.9)	26.2 (28.2)
Women	47.8%	51.5%	64.0%[b]	51.1%
0-1 blood donations	13.9%	7.9%	6.1%	11.1%
2-10 blood donations	33.8%	30.7%	26.5%	31.9%
11-20 blood donations	12.0%	17.8%	14.3%	13.9%
21-40 blood donations	15.4%	17.9%	38.8%	19.4%
41-60 blood donations	10.0%	11.9%	8.2%	10.3%
>60 blood donations	14.9%	13.9%	6.1%	13.4%

Note: Two-tailed *t*-test, Chi-squared test.
[a]*P* < .05 compared with Tromsø.
[b]*P* < .05 compared with Bergen.

TABLE 2 Concentrations of heavy metals in blood (μmol/L and nmol/L): The Norwegian donor study

	Bergen n = 201	Tromsø n = 101	Kirkenes n = 50	Entire study n = 352
Lead, mean (SD), μmol/L	0.068 (0.05)	0.057 (0.03)	0.081 (0.08)	0.067 (0.05)
Lead, median, μmol/L	0.055	0.049	0.062[a]	0.055
Lead, range, μmol/L	<LOD-0.586	<LOD-0.159	<LOD-0.439	<LOD-0.586
Lead >0.15 μmol/L	5.8%	2.0%	6.0%	4.5%
Lead >0.09 μmol/L	10.9%	20.9%[b]	20.0%	17.9%
Mercury, mean (SD), nmol/L	13.2 (13.5)	12.6 (9.2)	8.73 (6.0)	12.4 (11.7)
Mercury, median, nmol/L	10.2	11.0	7.38[a,b]	9.49
Mercury, range, nmol/L	<LOD-129	<LOD-39.6	<LOD-31.3	<LOD-129
Mercury >50 nmol/L	2.0%	0.0%[b]	0.0%[b]	1.1%
Mercury >23.7 nmol/L	11.9%	11.9%	2.0%[a,b]	10.5%
Cadmium, mean (SD), nmol/L	3.65 (4.04)	2.43 (2.22)	4.94 (4.72)	3.48 (3.80)
Cadmium, median, nmol/L	2.41	1.89[b]	2.92[a]	2.30
Cadmium, range, nmol/L	<LOD-34.6	<LOD-16.8	<LOD-21.5	<LOD-34.6
Cadmium >16 nmol/L	2.5%	1.0%	4.0%	2.3%

Note: Mann–Whitney *U* test, Chi-squared test.
[a]*P* < .05 compared with Tromsø.
[b]*P* < .05 compared with Bergen.

donor blood (0.15 μmol/L = 0.031 μg/mL), whereas almost 18% of blood donors had lead concentrations over the alternative limit of 0.09 μmol/L (0.018 μg/mL) suggested for transfusions in premature infants. Lead concentrations over the limit of 0.09 μmol/L were significantly more often measured in Tromsø donors than in Bergen donors. We evaluated age as a possible criterion to select blood with the lowest lead concentrations. Our calculations showed that the optimal age cut-off is 22 years or younger, and 0% of donors in this age group had lead concentrations over the limit 0.09 μmol/L (0.018 μg/mL). If we used the age cut-off of 40 years or younger, there were 5.2% donors with lead blood levels over this limit. In the age group of over 40 years, a high lead concentration was found in 28% of donors.

TABLE 3 Associations of heavy metal blood concentrations with age, gender and number of blood donations: The Norwegian donor study (n = 352)

	Gender (men vs women)		Age (y)		Number of blood donations	
Heavy metals[a]	*β*	*P*-value	*β*	*P*-value	*β*	*P*-value
Lead	1.18	.002	1.02	<.0001	1.00	.69
Mercury	1.15	.093	1.03	<.0001	1.00	.41
Cadmium	0.77	<.0001	1.02	<.0001	1.00	.10

Note: Presented β-coefficients were back-transformed as 10^{β}.
[a]Multiple linear regression models with log10-transformed heavy metal concentrations as dependent variables and gender, age and number of blood donations as covariates.

TABLE 4 Concentrations of selected PFASs in blood (ng/mL): The Norwegian donor study

	Bergen n = 201	Tromsø n = 101	Kirkenes n = 50	Entire study n = 352
PFOS, mean (SD)	5.71 (3.34)	6.31 (3.68)	5.35 (4.47)	5.83 (3.62)
PFOS, median	4.88	5.27	4.71[a]	4.91
PFOS, range	1.46-23.8	1.30-19.8	1.75-32.3	1.30-32.3
PFOS > 12.8 ng/mL[b]	4.0%	5.9%	4.0%	4.5%
PFOS > 1.37 ng/mL	100%	99.0%	100%	99.7%
PFOS > 0.91 ng/mL	100%	100%	100%	100%
PFOS > 0.59 ng/mL	100%	100%	100%	100%
PFOA, mean (SD)	1.41 (0.76)	1.20 (0.56)	1.04 (0.37)	1.30 (0.67)
PFOA, median	1.26	1.08[c]	0.94[c]	1.16
PFOA, range	0.48-4.97	0.42-4.15	0.43-2.25	0.42-4.97
PFOA > 4.9 ng/mL[b]	0.5%	0%	0%	0.3%
PFOA > 4.55 ng/mL	1.0%	0%	0%	0.6%
PFOA > 0.91 ng/mL	72.6%	65.3%	56.0%	68.2%
PFOA > 0.27 ng/mL	100%	100%	100%	100%
PFHxS, mean (SD)	0.87 (1.01)	0.83 (0.63)	0.59 (0.40)	0.82 (0.85)
PFHxS, median	0.64	0.62	0.49[a,c]	0.62
PFHxS, range	0.15-10.4	0.21-3.72	0.22-2.67	0.15-10.4
PFHxS > 7.66 ng/mL[b]	0.5%	0%	0%	0.3%
PFNA, mean (SD)	0.60 (0.36)	0.62 (0.30)	0.61 (0.39)	0.61 (0.34)
PFNA, median	0.52	0.52	0.51	0.52
PFNA, range	0.15-2.61	0.17-1.70	0.21-2.66	0.15-2.66
PFNA >1.61 ng/mL[b]	1.5%	2.0%	2.0%	1.7%
PFDA, mean (SD)	0.27 (0.17)	0.33 (0.21)	0.27 (0.19)	0.29 (0.19)
PFDA, median	0.23	0.25[c]	0.21	0.24
PFDA, range	0.04-1.16	0.07-1.27	0.08-1.21	0.04-1.27
PFDA >0.79 ng/mL[b]	2.0%	4.0%	2.0%	2.6%

Note: Mann–Whitney *U* test. Chi-squared test.
[a]*P* < .05 compared with Tromsø.
[b]97.5 percentile concentration in a young population from Tromsø area (The Fit Futures study).
[c]*P* < .05 compared with Bergen.

TABLE 5 Associations of selected PFAS serum concentrations with age, gender and number of blood donations

	Gender (men vs women)		Age (y)		Number of blood donations	
PFAS[a]	*β*	*P*-value	*β*	*P*-value	*β*	*P*-value
PFOS	1.75	<.0001	1.02	<.0001	.99	<.0001
PFOA	1.14	.006	1.01	<.0001	.995	<.0001
PFHxS	1.84	<.0001	1.01	<.0001	.99	<.0001
PFNA	1.15	.008	1.02	<.0001	.998	.018
PFDA	1.04	.52	1.02	<.0001	.998	.04

Note: The Norwegian donor study (n = 352).
[a]Multiple linear regression models with log10-transformed PFAS concentrations as dependent variables and gender, age and number of blood donations as covariates. Presented β-coefficients were back-transformed as 10^{β}.

Mercury concentrations were not especially high in blood donors: only 1.1% had mercury concentrations over 50 nmol/L (10 ng/mL). However, 10.5% of all donors had mercury concentrations over the suggested limit for donor blood (23.7 nmol/L = 4.75 ng/mL). Donors from Tromsø and Bergen had significantly higher concentrations of mercury compared with the donors from Kirkenes. Median and mean cadmium concentrations were highest in Kirkenes donors (2.92 and 4.94 nmol/L, respectively), of which 4% had concentrations higher than the suggested limit for donor blood (16 nmol/L = 1.80 ng/mL).

Table 3 shows that lead, mercury and cadmium blood concentrations are significantly positively associated with age. The results of the regression analyses show that a 1-year increase in age was associated with a 2% increase of lead and cadmium concentrations and with a 3% increase of mercury concentration. There was no significant association between the number of blood donations for lead, mercury and cadmium. Men had significantly higher concentrations of lead than women, whereas women had higher concentrations of cadmium.

Lead, mercury and cadmium blood concentrations were significantly correlated with each other (Table S2). Lead and mercury concentrations were significantly correlated with serum PFAS concentrations (Table S2).

Concentrations of individual PFAS that were measured in donor serum with a detection frequency of 100% are shown in Table 4. PFAS concentrations in general were not high in this donor population compared to the 97.5 percentile concentrations derived from the Fit Futures study of the young general population from Tromsø.[43] Only 0.3% to 4.5% of the donors were above 97.5 percentile concentrations of different PFAS measured in the Fit Futures study of teenagers.[43] However, 100% of all donors had PFOS concentrations over the estimated limits of 0.91 and 0.59 ng/mL for the donor blood. About 68% of all donors had PFOA concentrations above the limit of 0.91 ng/mL in blood based on the US EPA RfD for oral intake of 20 ng/kg per day.

If the 2018 EFSA TWI limit for PFOA was applied, then 100% of donors had PFOA concentrations over the limit. Even though these doses of PFOS and PFOA were lower than the acute cytotoxic doses (0.1 mg/kg/day), they were over the limits, indicating possible health effects in humans.[41]

Concentrations of selected PFAS increased with age (PFOS, PFOA, PFHxS, PFNA, PFDA) and decreased with number of blood donations (Table 5). Furthermore, it was observed that men had generally higher concentrations of PFOS, PFOA, PFHxS and PFNA than women (Table 5).

4 | DISCUSSION

Several publications are suggesting that measures should be taken in order to limit lead concentrations in donor blood given to premature infants and small children.[12,13,17,45-47] The lead limit of 0.15 μmol/L used in this study and previously published studies was calculated from WHO's PTWI and adjusted for bioavailability and other factors.[19] The limit of 0.15 μmol/L for lead was used by several studies[18,34]; however, a lower limit of 0.09 μmol/L was suggested for transfusions in premature infants.[11] The lead threshold of 0.09 μmol/L was discussed in the recent publication in the Nature Pediatric Research[35]; no safe concentration of lead was identified, and WHO had not re-issued the PTWI for lead. The exposure limit based on the PTWI of 25 μg/kg/week was associated with a significant decrease of IQ in children.[35] The meta-analyses of epidemiological data by the Joint FAO/WHO Expert Committee on Food Additives showed that a chronic dietary lead exposure of 0.6 μg/kg/day (4.2 μg/kg/week) corresponded to a 1 IQ point decrease in children.[48]

Lead concentrations in our study were lower than in blood donors from other countries: median concentration of 0.055 μmol/L (range 0.019-0.586 μmol/L) compared with 0.082 μmol/L (range 0.011-2.90 μmol/L) in Canadian donors.[17] In our study, 4.5% of the blood donors had a blood lead concentration above the limit of 0.15 μmol/L compared to 15.5% in other studies.[17] Between 10% and 20% of donors at all of our study sites had lead concentrations over the limit of 0.09 μmol/L, resulting in the risk of lead exposure to premature infants and potential harmful effects.

Female donors had higher cadmium concentrations than males. There is no industry in Norway with occupational exposure to cadmium that could explain this gender difference. Studies in other European populations showed the same gender difference in cadmium concentrations and possible association with sex hormones in women.[49,50] Another possible explanation of gender differences in cadmium concentrations may be different lifestyle and diet habits. Smoking and diet are known sources of cadmium exposure.[49-51] Population studies showed that Norwegian women smoke at least as much as men.[52,53] Unfortunately, we do not have data on smoking and diet for our study population to test this hypothesis.

All study sites had blood donors with mercury and cadmium concentrations above the suggested limits for donor blood. Mercury

concentrations over the suggested limit of 23.7 nmol/L (4.75 ng/mL) were found in 1 of every 10 donors. Prenatal exposure to mercury was reported to be associated with reduced fetal growth and lower birthweight,[54,55] as well as with adverse effects on neonates' neurobehavioral development, poorer language skills at the age of 5 years[56,57] and with the increased risk of respiratory infections during the first year of life.[58] Mercury and lead are identified as one of the developmental neurotoxicants.[5,59] Cadmium exposure was also reported to be associated with delayed growth in early childhood[60] and with adverse effects on neurodevelopment and cognitive function in children.[61,62] Thus, there is emerging evidence that the exposure of small children to heavy metals may result in cognitive damage.

The present study, as well as previous studies, used heavy metal limits for donor blood based on the oral TDIs. However, there is a limitation in this approach as the current knowledge indicates that there are no safe levels for lead[63,64] or mercury,[65] and for cadmium as well, the limit for tolerable intake has been challenged.[66,67] It has been demonstrated that transfused blood may cause an increase in the levels of lead and mercury[14,15,45,68,69] in the blood of the recipients, and even very small amounts of lead may have negative effects on children.[16,63]

PFOS, PFOA, PFHxS, PFNA and PFDA serum concentrations in the Norwegian donors were not higher than in previous studies of blood donors in Germany, USA and South Korea (Table S3).[21,22,24] Very few donors had concentrations of PFHxS, PFNA and PFDA over the 97.5 percentile concentration of these PFAS in the adolescent Norwegian population. However, the concentrations of the recognised organic pollutants PFOS and PFOA were over the suggested limits for donor blood (based on the 2018 EFSA TWIs) in 100% of donors. It is, however, unknown if few blood transfusions with these concentrations of PFOS and PFOA may cause permanent health damage in infants. The estimation of the acceptable venous concentrations based on the oral TWIs for PFAS is not an optimal approach as the number of transfusions during the week may vary. The long-term health effects of these PFAS concentrations received not as a chronic alimentary exposure, but with few blood transfusions, are not known. Further research in this field is required.

We suggest that measures to limit the exposure of paediatric recipients of blood products to heavy metals and other pollutants should be evaluated by the appropriate regulatory bodies. The present work and several other studies have shown that blood levels of environmental pollutants tend to increase with the individual's age in cross-sectional studies.[17,49,70,71] Selecting young donors for transfusions to infants may therefore be a feasible approach to reduce the risk of adverse health effects. Our data showed that the optimal cut-off for donor's age for selecting blood with the lowest lead concentrations was 22 years or younger; this corresponds with the results from the study of Canadian donors that suggested 23 years as a possible age cut-off.[17] It may also be appropriate to ask donors for known sources of exposure (eg, occupational, special dietary habits, smoking etc.). However, the ultimate precaution would be to measure heavy metal and other pollutant concentrations in donor blood before transfusions to premature infants and other particularly vulnerable patients.

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M.A. was involved in planning the project, supervised the data collection, analysed and interpreted the data and took the lead in writing the manuscript; prof. B.B. designed and directed the project, supervised the blood sample analyses for heavy metals, aided in interpreting the results and made substantial contributions to writing the manuscript; S.H. supervised the serum samples analyses for PFAS and contributed to interpretation of the results and to writing the manuscript; and T.H., M.K. and E.K.K. were involved in planning the project, supervised the data collection and participated in drafting the article and revising it critically. All authors provided critical feedback and contributed to the final manuscript.

CONFLICT OF INTEREST

The authors have no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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