Is blood a reliable indicator of trace metal concentrations in organs of small mammals?

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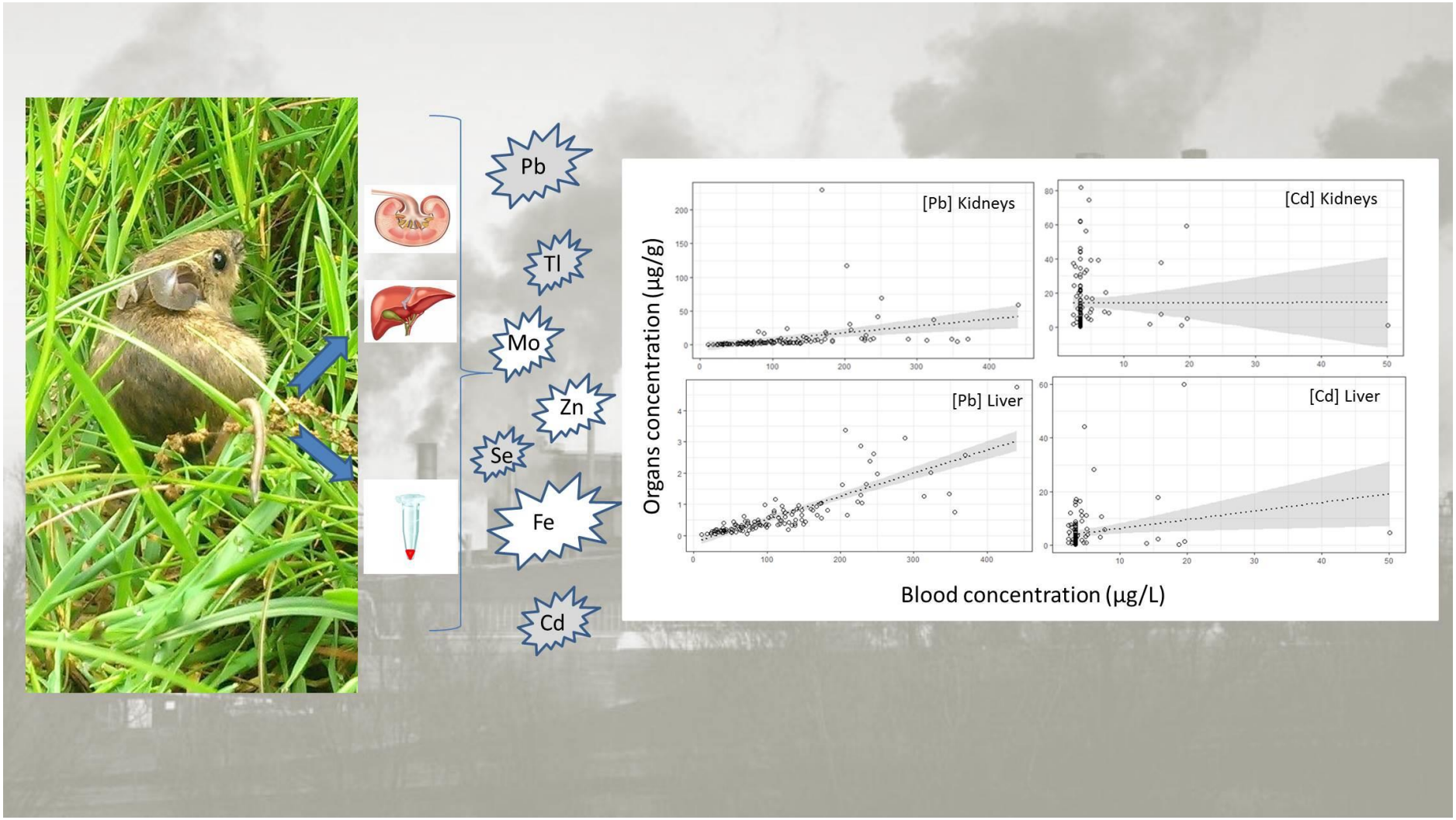
Highlights

- Non-destructive biomonitoring approach is required for scientific and ethical reasons.
- We tested whether blood metal levels can serve as indicator of organ concentrations.
- This hypothesis was confirmed for Pb, Se, and Tl, with accurate modelling.
- For the other 8 investigated metals above the limit of detection, relationships were weak or non-significant.
- More toxicokinetic research is needed to develop the use of blood in ecotoxicology.

Graphical abstract



Abstract

In wildlife ecotoxicology, the rationale for using blood rather than other body fluids or tissues is that sampling blood is a minimally invasive technique, without animal's sacrifices, providing both ethical and scientific benefits. To date, only few data on the relationships between blood and organ metal concentrations are available for small mammals living in contaminated sites. The present work aims at studying the relationships between the concentrations of 18 essential and non-essential metals in blood and their concentrations in the liver and kidneys, two accumulation and target organs, in wood mice from a former lead and zinc smelter named Metaleurop Nord, Northern France. Results from Se, Pb and Tl indicate that blood levels may be used to predict concentrations in organs of small mammals. Conversely, for Cd, Cu, Fe, Mo, Ti and Zn, blood concentrations were poorly or not related to liver and kidney concentrations. On top of accurately predicting concentrations of some metals in target organs, blood can provide important information about physiological and biochemical status of organisms, but further toxicokinetic research would be required to develop the use of blood as low-invasive biomonitoring and ecotoxicological method in wildlife.

1. Introduction

In human, blood tests are often used in health care to determine physiological and biochemical states, giving information about organ function or diseases. In wildlife ecotoxicology, blood has also widely been used to evaluate various parameters of individuals' health (Gorriz et al., 1996; Nunes et al., 2001; Topashka-Ancheva et al., 2003 ; Rogival et al., 2006; Sánchez-Chardi et al., 2008 ; Adham et al., 2011). The rationale for using blood rather than other body fluids or tissues is that sampling blood is a minimally invasive technique that does not necessitate sacrificing individuals, which has obviously both ethical and scientific benefits. There is indeed an increasing will from the large public to perform scientific studies with minimal impacts on the species being studied. Many countries have therefore developed regulation (see e.g. Directive 2010/63/UE) that frame the use of lab and free-ranging animals (mostly vertebrates) used for scientific purposes. Accordingly, current scientific guidelines such as the one from the *American Society of Mammalogists* fully acknowledge those ethical issues and propose appropriate procedures minimizing stress, pain, and, generally speaking, impact on animals (Sikes and the Animal Care and Use Committee of the American Society of Mammalogists, 2016). From a scientific point of view, minimizing impact on studied animal models, particularly avoiding sacrificing individuals, is also crucial to limit disturbance of scientific investigations on the dynamics of local populations. This is a key issue for long-term monitoring and surveys, whose importance is increasingly recognized in ecotoxicology (Kendall, 2016). Moreover, lethal, or at least invasive methods inducing a risk for either survival or reproduction of captured individuals, cannot be applied on many rare and/or endangered species for conservation issues. In addition to important physiological parameters informing about the health status of individuals, blood, as integuments like feathers or hairs that are also widely used in ecotoxicology, provides information about the level of exposure to contaminants.

Free-ranging terrestrial vertebrates are considered to be exposed to metals mainly through ingestion of food and water, and secondarily through inhalation of aerosols and, in some instances, vapors (Shore and Rattner, 2001; Smith et al., 2007). Whatever the exposure route, metals, after uptake, are transported and distributed to different organs within the body through blood, the main transporting medium in the body

(Fig. 1). Excretion or clearance of metals from an organ or from the body as a whole can occur through various routes, including or not a transport through blood (Fig. 1), and depends on a number of metal-specific processes and their role (e.g. essential or non-essential metals) in organisms (Elder et al., 2015). Epidemiological studies on human and laboratory experiments on model organisms have allowed the development of toxicokinetic studies for several metals. Toxicokinetics refer to the processes of absorption, distribution, biotransformation (i.e. formation or breakdown of metal-carbon bonds, or change of oxidation state of a metal in the biological system) and excretion, quantitatively studied as a function of time (Elder et al., 2015). According to general concepts in toxicokinetics, a constant exposure, associated to constant absorption and elimination rates, would lead, over time, to a steady-state equilibrium, where metal concentrations in blood could be used as a reliable estimate of concentrations in the organs. In the wild, however, the exposure of small mammals in a contaminated site is likely to be far from constant. Exposure of free-ranging mammals to metals, indeed, has been shown to greatly vary over time and space, with e.g. heterogeneity of soil contamination, habitat use, diet and foraging behaviour of organisms, or variations of food resources in the field (Smith et al. 2007, van den Brink et al., 2011). Bioavailability (i.e. the fraction of the total concentration of a metal in a given compartment that can actually be transferred into an organism) of metals in soils can also dramatically vary with both characteristics of the considered metal and the properties of the contaminated medium (Harmsen, 2007). This is likely to be the case for metals in plant and animal tissues small mammals feed on but that issue has been less studied for terrestrial organisms than in the aquatic environment (see e.g. Rainbow et al., 2011) or for human foodstuffs (Elder et al., 2015). The rate of clearance of metals from organs (into blood or through excretion, Fig. 1), usually measured by the biological half-time (i.e. the time it takes to the concentration to be reduced to half of its initial value), is another process that influences the metal concentration in blood, and may therefore influence the relationship of metal concentrations between blood and organs.

In the line of some previous developments of minimally invasive ecotoxicological methods on small mammals (Tête et al., 2013; 2014; 2015), the present work aims at studying the relationships between the concentrations of 18 essential and non-essential trace elements in blood and their concentrations in the

liver and the kidneys, two accumulation and target organs, in small mammals sampled along a pollution gradient in Northern France. We hypothesise that blood concentrations of elements with high internal turn-over will show a strong relationship between blood and internal tissues, allowing to develop simple modelling to be further used in ecotoxicology of free-ranging small mammals. Weak or no relationships will probably be found for elements whose blood concentration is more linked to daily exposure and/or for other toxicokinetic reasons.

2. Materials and Methods

2.1. *Study site*

We conducted fieldwork in an area surrounding the former lead (Pb) and zinc (Zn) smelter named Metaleurop Nord (Hauts-de-France Region, northern France, 5025042N, 300055E). The smelter was established by the end of the 20th century, until its closure in 2003. Major emissions leading up to the smelter's closure were cadmium (Cd), lead (Pb), zinc (Zn). Soil contamination levels on this area are well documented and reported high Cd, Pb and Zn levels of contamination, ranging from 0.1 to 2,402 mg/kg for Cd, from 16 to 41,960 mg/kg for Pb and from 44 to 38,760 mg/kg for Zn (*per* dry weight, Douay et al., 2009; Fritsch et al., 2010a). Cadmium, Pb and Zn concentrations in soils from woody habitats are highly correlated, with coefficients of determination ranging from 0.6 to 0.8. Concentrations decrease with the distance to the smelter and are related to the prevailing SW–NE winds (Fritsch et al., 2010b) but anthropogenic activities disturb this global pattern (Douay et al., 2009). A 40 km² (8×5 km) study area around the former smelter was divided into 160 squares (500×500 m). Four sampling squares across an environmental metal contamination gradient were studied (from control to highly contaminated squares) for the present study. Based on the Cd, Pb and Zn concentrations, sampling squares were classified as: control (“C”), low (“L”), medium (“M”) and high (“H”) pollution level (Table 1).

2.2. *Data collection*

From the 30th of September to the 10th of October 2014, 10 lines of 10 non-lethal INRA traps spaced 3 m apart were placed on each site for 3 consecutive trap nights. A total of 120 wood mice (*Apodemus sylvaticus*) were trapped along the gradient of pollution, according to the following distribution: 27

individuals at site ‘‘control’’, 33 at site ‘‘L’’, 34 at site ‘‘M’’ and 26 at site ‘‘H’’ (Table 1). No difference in age using crystalline lens mass (ANOVA, F=1,83; Df=3; *p*=0,146) nor in sex-ratio (F=1,56; Df=1**;** *p*=0,196) were observed between sites. Before animal sacrifice by cervical dislocation (following the American Veterinary Medical Association ethical guidelines (Sikes and the Animal Care and Use Committee of the American Society of Mammalogists, 2016), blood was collected from the orbital sinus using a Pasteur pipette, immediately transferred into heparinised microtubes. Blood samples were then stored at 4-8°C before freezing at -20°C within the following next 10 hours. Individuals were weighed, measured and sexed during dissection at the laboratory. The crystalline lenses were sampled and kept in a 3% formalin solution. All procedures involving the handling of animals were conducted by certified persons. During dissections, livers and kidneys were collected (mean liver mass: 1.010g ± 0.261**g**; mean kidney mass: 0.222g ± 0.045**g**), dried (65°C, drying oven) and stored until analysis. Sampling authorization was given by the Direction Régionale de l’Environnement, de l’Aménagement et du Logement (DREAL) of the Hauts-de-France Region.

2.3. *Metal analysis*

The concentrations of 18 metals (aluminum (Al), antimony (Sb), arsenic (As), Cd, chromium (Cr), cobalt (Co), copper (Cu), iron (Fe), Pb, manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), strontium (Sr), tin (Sn), titanium (Ti), thallium (Tl), and Zn) were determined in blood samples and organs. Blood samples were acid digested in 700 µl of nitric acid (HNO_3, 65%, analytical quality, Optima) for half a day in open tubes under fume hood, and then for 60 h in closed tubes at 60°C in an oven. After digestion, samples were diluted to 30 ml by the addition of ultra-pure water (18.2 MV.cm-²). Liver and kidney dried samples were digested with nitric acid (HNO_3 at 69%) and then diluted by adding ultra-pure water (Elga, 18.2 MV.cm-²) prior to analyses. Blood and organs metals were analysed by Inductively Coupled Plasma—Mass Spectrometry (ICP-MS, ThermoFischer Scientific XSeries 2). Over the 18 metals measured, only 11 (Cd; Cu; Fe; Mn; Mo; Pb; Se; Sn; Ti, Tl, Zn) had a satisfactory proportion of values above quantification limits (Table S1), allowing further statistical analyses. For the values under quantification limits for these elements, values were replaced by the quantification limit divided by square root of two for statistical analysis (Helsel, 2010). Repeatability (within-run precision) and reproducibility of the measurements were surveyed

(checking of RSD values and use of internal standards), and quality control (control solutions and blanks to check for the absence of drift) was conducted during measurements. Analysis accuracy was checked using certified reference materials (National Research Council Canada TORT-2 Lobster hepatopancreas, eEuropean Reference Material ERM®-CE196 Bovine blood). Blanks (acid + ultra-pure water) and certified reference materials were prepared and analysed using the same methods as the blood samples. Average recoveries of the certified reference materials are given Table S1. The concentrations of metals in the blood are expressed as µg/L and as µg/g dry mass for the liver and kidneys.

2.4. *Statistical analyses*

General Linear Models were used to investigate the relationship between blood and organs (liver and kidney) metal concentrations. A backward selection procedure starting from a full model that included all factors and their two-way interactions was performed. Quasi likelihood estimations were used to estimate the scale parameter, and the significance of terms in the model was tested using F-tests. Starting by continuous covariates, non-significant terms at $p \leq 0.05$ were sequentially removed to achieve a minimal adequate model (Crawley, 1993). Wherever an interaction term was left in a model, the two corresponding factors were also included as main effects. All tissue concentrations (from blood, liver and kidneys) were log-transformed (log 10(x+1)) and normality and homoscedasticity assumptions were checked graphically. Full models tested were: [Organ] ~ [Blood] + Sex + Crystalline mass + Sex*[Blood] + Crystalline mass*[Blood]. To reduce the effect of outliers, we removed points with a Cook's distance (Cook, 1977) of ≥0.95, and reran the linear regression. Tissue concentrations of metals were compared along the environmental contamination gradient of Cd, Pb and Zn using ANOVA test. When significant differences were detected among study squares, multiple comparisons were performed using Tukey HSD test. Each analysis was performed with the software R v. 3.15.1 (R Development Core Team).

3. Results

3.1. *Metal concentrations around the former smelter*

Among the 18 elements measured, Cu, Fe, Pb, Se, and Zn were the only elements to exhibit concentrations above the quantification limits of the analytical instruments, whatever the fluid (blood) or tissue (kidney

and liver). Cd, Mn, Mo, Ti, and Tl were not always detectable in blood, while Sn was hardly detectable in organs. Over the 18 metals measured, only 11 (Cd; Cu; Fe; Mn; Mo; Pb; Se; Sn; Ti, Tl, Zn) had a satisfactory proportion of values above quantification limits and were included in further statistical analyses. Complete trace metal concentrations measured in blood, liver and kidneys are presented in Table S1.

The concentrations of Cd, Pb and Zn in blood, in the liver and in kidneys (Fig. 2) of wood mice showed a high variability, depending on squares. Lead concentrations in kidneys were significantly higher only in mouse coming from the most contaminated site ($F=38.2$; $Df=3$; $p<0.001$, Fig. 2A). In the liver, Pb concentrations also varied along the gradient ($F=12.0$; $Df=3$; $p<0.001$; Fig. 2B), with concentrations from the lowly and the highly contaminated squares not differing among them, but being significantly higher than those in the control and the medium squares ($p<0.001$). Concentrations from the highest contaminated square were also higher than in the medium level, and concentrations from the lowest contaminated square were higher than in the intermediate level of environmental pollution. The pattern was quite similar for ($F=16.34$; $Df=3$; $p<0.001$, Fig. 2H). For Cd, contrary to blood for which no differences were observed along the pollution gradient ($F=0.29$; $Df=3$; $p=0.83$, data not shown), liver ($F=14.45$; $Df=3$; $p<0.001$, Fig. 2C) and kidneys ($F=16.89$; $Df=3$; $p<0.001$, Fig. 2D) concentrations increased along the pollution gradient, except in the highest contaminated square where concentrations were not statistically higher than in the medium level of pollution. Zinc concentrations in blood (Fig. 2G), kidneys (Fig. 2E) and the liver (Fig. 2F) did not show any significant increase along the contamination gradient, even if, for blood and the liver, concentrations at the low level of contamination square were sometimes higher than in some other squares. Comparisons of concentrations in blood and the organs for the others metals (Cu, Fe, Mn, Mo, Se, Sn, Ti and Tl) along the contaminated gradient are presented in supplementary materials (Table S1 and Fig. S1), and are not presented here and will not be discussed extensively because the concentrations in the soils for those metals are not available. Only the relationships between blood and organs will be discussed for Cu, Fe, Mn, Mo, Se, Sn, Ti and Tl.

3.2. *Relationships between trace element concentrations in different tissues*

The relationships between blood and tissue concentrations varied considerably between elements and tissues. Copper (Cu) and Ti concentrations in tissues could not be modelled by any of our study variables (Table 2, Fig. S2 and S3). When examining Pb concentrations in liver and kidneys (Fig. 3A and 3B), increases in blood Pb predicted increases in organs (R^2=0.64, $p < 0.001$ for liver and R^2=0.56, $p < 0.001$ for kidneys, Table 2). Molybdenum (Mo) was the only other element for which blood concentration was the only variable retained in models to predict organ concentrations. Contrary to Pb, however, the coefficients of determination of the models for Mo were low (R^2= 0.26 for the liver, R^2= 0.13 for kidneys, Table 2). Selenium (Fig. 4) and Tl (Fig. S2 and S3) provided good models with coefficients of determination ranging from 0.69 to 0.89, but sex was a variable to consider in the modelling of liver concentrations for both elements. Cadmium concentrations in kidneys (Fig. 3D) were mainly predicted by age as assessed by crystalline masses (R^2=0.43; p = 0.01; Table 2) and by the age (partial R^2= 0.04; $p < 0.001$) and blood concentration with a weak explanation power (partial R^2= 0.30; p = 0.01) in liver (R^2= 0.34; $p < 0.001$). Iron (Fe) concentrations in organs were poorly modelled (R^2<0.11) by blood concentrations for kidneys and by blood concentrations and sex for the liver (Table 2, Fig. 4). The liver concentrations for Zn, as for Tl, were significantly related to blood concentrations (p = 0.01 for Zn and p = 0.0001 for Tl) and to the interaction term between blood concentration and crystalline mass or sex, respectively (blood concentration*sex: p = 0.01 for Zn and blood concentration* crystalline mass: p = 0.02 for Tl, Table 2). Models for Zn exhibited relatively low coefficients of determination (R^2= 0.28 for the liver, R^2= 0.14 for kidneys).

4. Discussion

Measuring pollutants using internal tissue samples from small mammals is the current reference method to estimate the degree of exposure to, and the subsequent accumulation of, cumulative compounds. However, in recent years, for both scientific and ethical reasons, there is a strong and ongoing tendency to use non-destructive samples in biomonitoring studies. The main objective of the present study was therefore to evaluate whether blood concentration values can be indicative of liver and kidney trace metals concentration in wood mice (*Apodemus sylvaticus*) under field conditions. Studies of metal accumulation in small mammals have included many taxa, such as wood, field and yellow-necked mice (Damek-Poprawa

and Sawicka-Kapusta, 2003; van den Brink et al., 2010; Tête et al., 2014), voles (Appleton et al., 2000), moles (Komarnicki, 2000), or shrews (Hamers et al., 2006; Sánchez-Chardi and Nadal, 2007; Moriarty et al., 2012; Drouhot et al., 2014). However, most of these studies focused on organs (mainly liver and kidney) using lethal methods. Contrary to bird species (Dauwe et al., 2005; Scheifler et al., 2006; Espín et al., 2016), scarce information on blood metal concentrations are available in literature for small mammals in their natural environment (Rogival et al., 2006; Vermeulen et al., 2009).

Here, the significant correlations observed between blood and tissue concentrations for Se, Pb, and Tl indicates that blood samples are suitable to estimate concentrations of these metals in liver and kidneys in the wood mice. For both Se and Tl, sex or its interaction with blood concentration is a variable retained in the final models but, according to the partial R^2 of the variables (Table 2), its weight is low, and sex can relatively easily determined on alive animals using anogenital distance. Furthermore, these correlations have been observed over large concentration ranges, and occurred despite the varying relative age (using the crystalline mass as a proxy) or sex. Blood sampling could therefore be an adequate non-lethal method for estimating these metal concentrations in internal tissues over a wide range of biological and environmental conditions. For some other metals, however, the low (Fe, Mo and Zn), or even absent (Cu, Ti) relationship between blood and organ concentrations indicates that blood samples could hardly or not be used to predict tissue contamination in wild wood mice, at least for the metal concentrations recorded on our study site. Cd concentrations in organs were shown to be much more dependent of the age (as estimated here by the crystalline lenses mass) than by the concentrations in the blood. Similar pattern was noted on the same study site using hair (Tête et al., 2014) and the influence of age on Cd accumulation in various tissues is a well-known issue. In the present study, investigations for this compound were however limited by the relatively low number of samples above detection limits in blood. It is worth to note that, in the present study, the essentiality of metals is not a key factor in explaining high or weak relationships between blood and organs. Rather, a better knowledge of toxicokinetics of the different metals wild animals may be exposed to would allow gaining insight in the understanding of internal exchanges between blood and organs.

Toxicokinetics of Cd, one of the main metals found in mining and smelting-impacted sites (including our study site of Metaleurop Nord), have been relatively extensively studied, mainly in birds. Cd accumulation occurs primarily in kidneys and in the liver (Scheuhammer, 1987) and the release from kidneys has been proved to be very slow (Mayack et al., 1981). Thus, under conditions of chronic dietary exposure, Cd concentrations in kidneys are thought to represent long-term accumulation (Scheuhammer, 1987). In contrast, Cd in the blood equilibrates with exposure over a much shorter period of time (Hammond and Beliles, 1980), suggesting that concentrations in blood represent short term exposure. In addition, relative Cd accumulation by kidneys and the liver is dependent on the magnitude of the exposure; with increasing exposure, a higher proportion is deposited in the liver (Hammond and Beliles, 1980; Scheuhammer, 1987). Since blood concentrations of Cd under steady-state conditions are expected to equilibrate with concentrations in both the liver and kidneys (García-Fernández et al., 1997), changes in liver-kidney ratios of Cd will likely also influence blood-kidney ratios. For example, changes in body and organ masses may alter blood-organ ratios of metals. Moreover, and contrary to the liver or kidneys, blood does not constitute a tissue of storage. In the present study, the lowest concentrations of most elements were indeed found in the blood. In wild birds, Garcia-Fernandez et al. (1997) showed that Cd levels in blood represent a very small part of only 0.5% of Cd body burden, while liver and kidneys together contain 92% of the total (of which 61% for kidneys only). Moreover, it is possible that concentrations of elements in blood did not change in the same manner as those in the liver or kidneys because metal sequestration features and speciation (differed between the tissues, see Vijver et al., (2004) for details). For instance, it has been shown in the rainbow trout (*Oncorhynchus mykiss*) that the patterns of subcellular partitioning of Cd varied according to target organs, with a different pattern of Cd accumulation in subcellular fractions in the gill and in the liver (Kamunde, 2009). Thus, changes in body and organ masses associated to blood and organs differences in their proportions of free/bound metals may stress different levels of total metals between blood and organs.

The imprecise relationship between blood and hepatic concentrations of metals may also be attributed partially to their different elimination rates in tissues. The elimination rate is initially faster from liver than

from blood (Heinz et al., 1990). Additionally, binding of metals to inorganic molecules in the liver (as well as in other organs) may result in the formation of inert complexes with a long biological half-life (Scheuhammer et al., 1998) and the proportion of the total metal pool that is bound may affect its distribution among different tissues (Cuvin-Aralar and Furness, 1991). Taken together, those data indicate that internal exchanges and rates of turn-over among tissues are key parameters in explaining blood-organ relationships, an area that would need further research.

General increase in concentrations of essential (Fe, Mg, Mn, Cu, and Cr) and non-essential elements (Pb) with age have been reported in organs in the wood mice (Lopes et al., 2002; Beernaert et al., 2007) and in other mammals (Scheirs et al., 2006; Outridge and Scheuhammer, 1993; Sánchez-Chardi and Nadal, 2007). In our study, except for Cd, we did not detect age-related effects in the relationship between blood and organs concentrations. Age-related increases in organs have been reported for Cd (Sheffield et al., 2001) and translate a Cd accumulation in storage organs along small mammals life.

The present study provides original results on the relationships between blood and organs concentrations for several metals. Our study provides simple and relatively accurate models (with R^2 ranging from 0.56 to 0.91) for Se, Pb and Tl, suggesting that blood sampling may be a useful tool in order to study these metals in wild, free-ranging small mammals. Conversely, for other metals such as Cd, Cu, Fe, Mo, Ti, and Zn**,** and in our levels of metals concentrations, blood concentrations were not a good indicator of internal concentrations, suggesting that blood sampling as a non-lethal methodology to predict organ concentrations may not be relevant for those metals. Further studies are clearly needed on other sites, on several years or at different seasons, and on different (small) mammal species to test (and modify if needed) the models developed here. The method would particularly be applicable where destructive sampling cannot be allowed, in protected areas and/or on endangered species.

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420

421

422 **Tables**

423 Table 1. Summary of study squares characteristics. Median [minimum - maximum] Cd, Pb and ZN concentrations (µg/g, dry weight) in soils collected in the

424 vicinity of the former Metaleurop Nord smelter. Results are presented for each sampling unit (square) corresponding to each pollution level.

Sampling squares		Control	Low	Medium	High
Dominant habitat		Forest	Forest	Forest	Forest
Distance from Metaleurop (median, km)		11.2	3.0	1.4	0.6
Soil contamination levels (from Fritsch et al. 2010)	*Pb*	110 [73 - 182]	261.5 [149 - 333]	526 [245 - 1260]	1357 [755 - 6809]
	Cd	1.6 [1.3 - 2.0]	4.0 [1.5 - 6.0]	9.7 [3.6 - 19.5]	59.3 [15.3 - 236.5]
	Zn	183 [150 - 267]	322.5 [114 - 407]	586 [303 - 1044]	1802 [1069 - 6035]
Number of wood mouse (♂ ; ♀)		27 (11 ; 16)	33 (18 ; 15)	34 (23 ; 11)	26 (14 ; 12)

425

426

427 Table 2. Results from general linear models linking metal blood concentrations to liver and kidneys concentrations in wood mice. A backward selection
428 procedure was used, with least significant variables being removed sequentially, until a minimum adequate model (presented). Bold indicates significant *p*
429 values.

430

Elements	Organ	Variable	Estimates	Partial r^2	Df/DfDen*	*F* values	*P*	r^2
Cd	Liver	blood concentration	0.47	0.04	1, 116	6.89	**0.01**	0.34
		crystalline mass	57.56	0.30	1, 116	53.46	**< 0.001**	
	Kidney	crystalline mass	82.38		1, 117	88.15	**< 0.001**	0.43
Cu	Liver	blood concentration	0.05		1, 118	1.64	0.20	0.014
	Kidney	crystalline mass	-2.65		1, 117	1.36	0.24	0.01
Fe	Liver	blood concentration	0.52	0.05	1, 117	6.91	**0.01**	0.11
		sex	*female* : - 0.07	0.06	1, 117	7.75	**0.01**	
	Kidney	blood concentration	0.27		1, 117	4.44	**0.04**	0.04
Mo	Liver	blood concentration	0.21		1, 118	41.10	**< 0.001**	0.26
	Kidney	blood concentration	0.11		1, 118	18.00	**< 0.001**	0.13
Pb	Liver	blood concentration	0.37		1, 117	210.96	**< 0.001**	0.64
	Kidney	blood concentration	0.98		1, 117	148.96	**< 0.001**	0.56
Se	Liver	blood concentration	0.75	0.89	1, 117	996.40	**< 0.001**	0.89
		sex	*female* : 0.03	0.004	1, 117	5.27	**0.02**	
	Kidney	blood concentration	0.04		1, 118	272.67	**< 0.001**	0.69
Ti	Liver	blood concentration	0.01		1, 118	0.03	0.86	< 0.001
	Kidney	blood concentration	-0.0003		1, 118	0.001	0.99	< 0.001
Tl	Liver	blood concentration	0.12	0.89	1, 116	439.34	**< 0.001**	0.91
		sex	0.004		1, 116	0.0128	0.91	
		blood concentration X sex	-0.04	0.02	1, 116	16.04	**0.0001**	
	Kidney	blood concentration	0.81		1, 116	886.36	**< 0.001**	0.88
Zn	Liver	blood concentration	0.65	0.24	1, 116	38.97	**< 0.001**	0.28
		sex	1.31		1, 116	0.41	0.52	
		blood concentration X sex	-0.36	0.04	1, 116	6.13	**0.01**	
	Kidney	blood concentration	0.23		1, 116	19.97	**< 0.001**	0.14

431

* Df = variable Df ; DfDen = error Df

Figures

Fig. 1. Flow scheme describing the movement of metals among various compartments in a terrestrial vertebrate (modified from Elder et al. 2015) and its environment. Dermal contact and other minor pathways (perspiration, exfoliation of skin, loss of hair and nails, lactation…) are not presented.

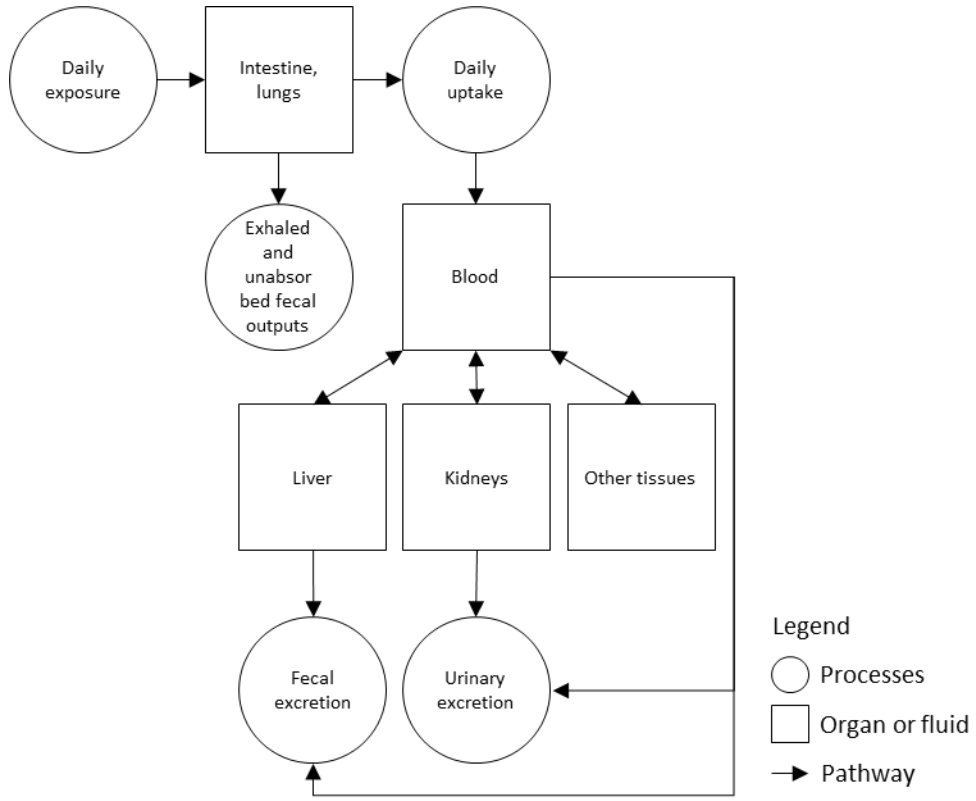


Fig. 2. Lead concentrations in kidneys (A), liver (B) and blood (H), Cd concentrations in kidney (C) and liver (D), and Zn concentrations in kidney (E), liver (F) and blood (G) along the soil metal contamination gradient (see Fritsch et al., 2010, for further details about soil contamination). Different letters correspond to significantly different means (Tukey's HSD, $p < 0.05$).

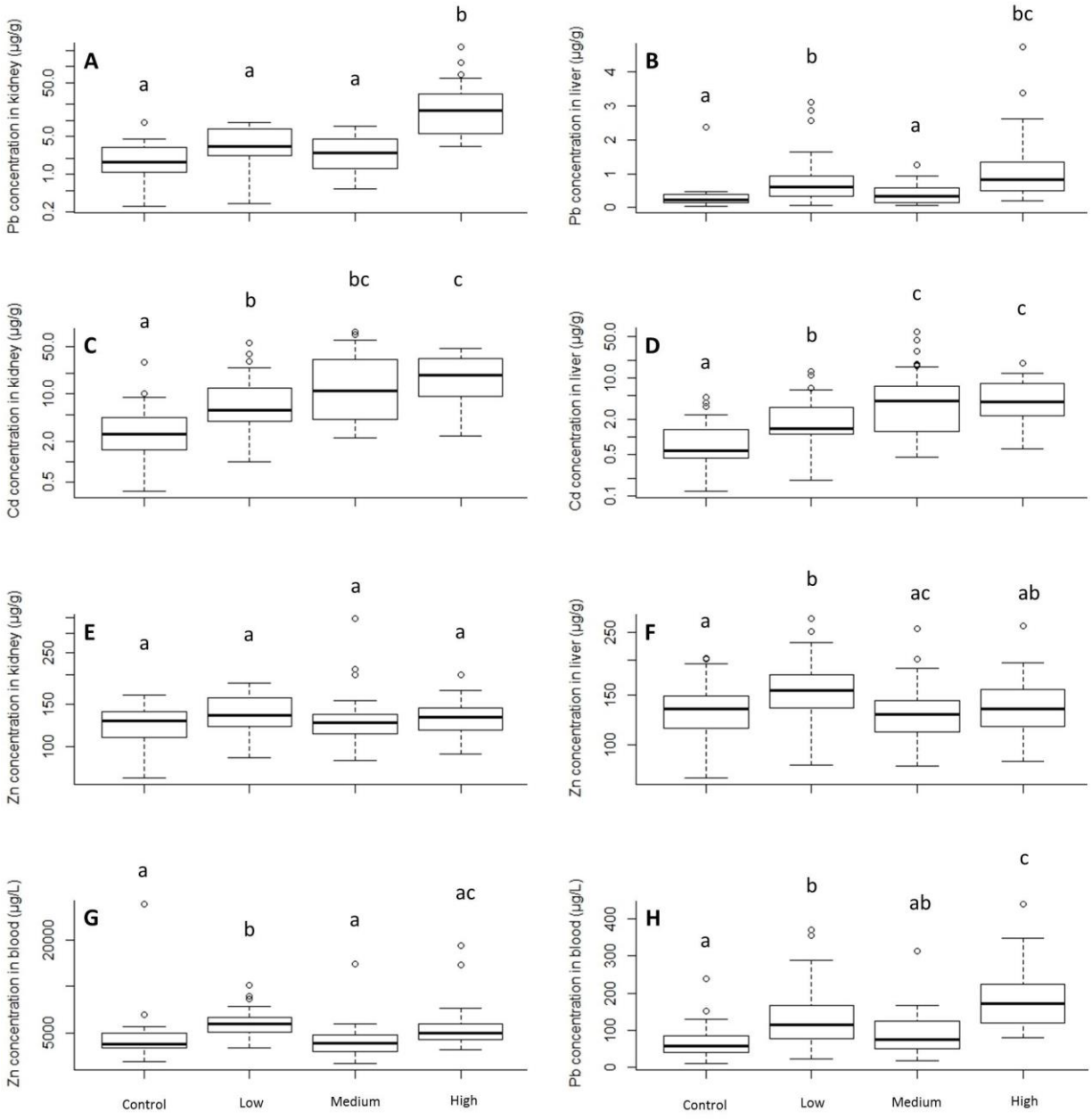
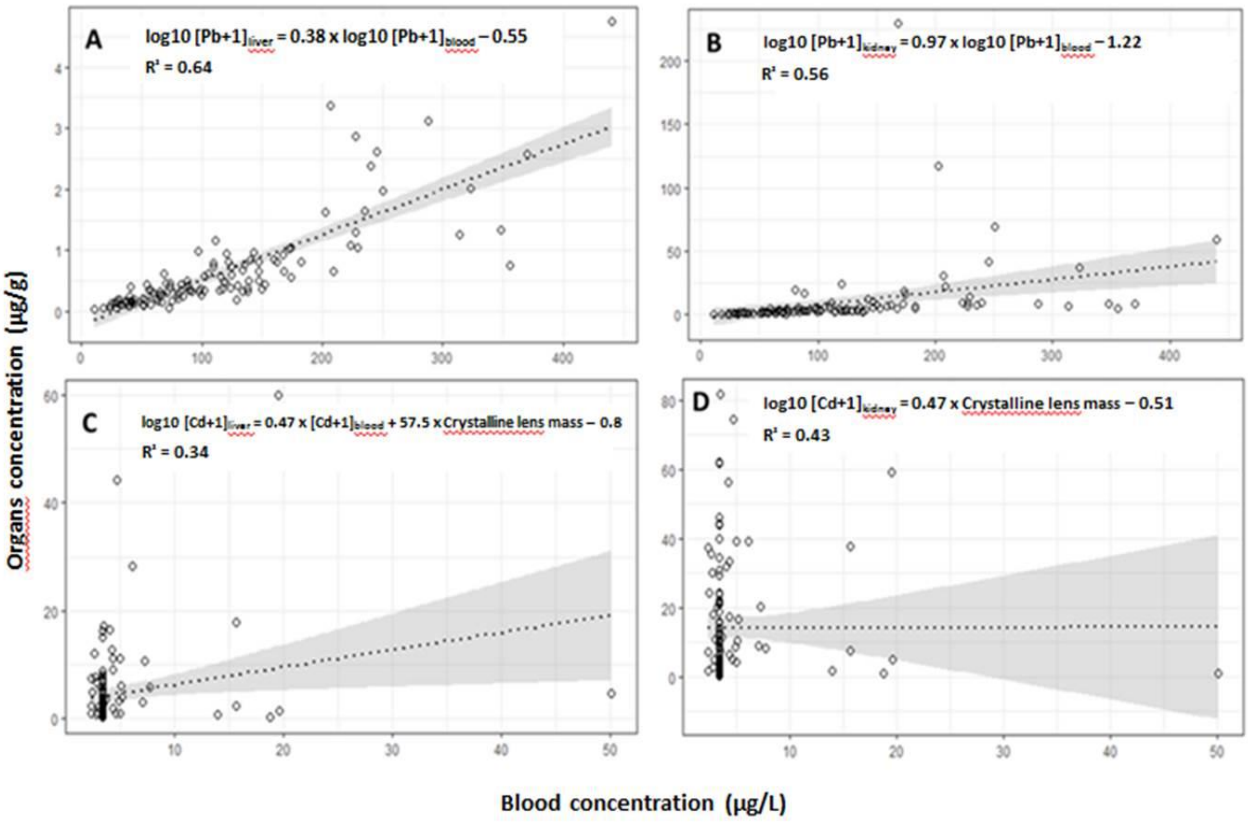
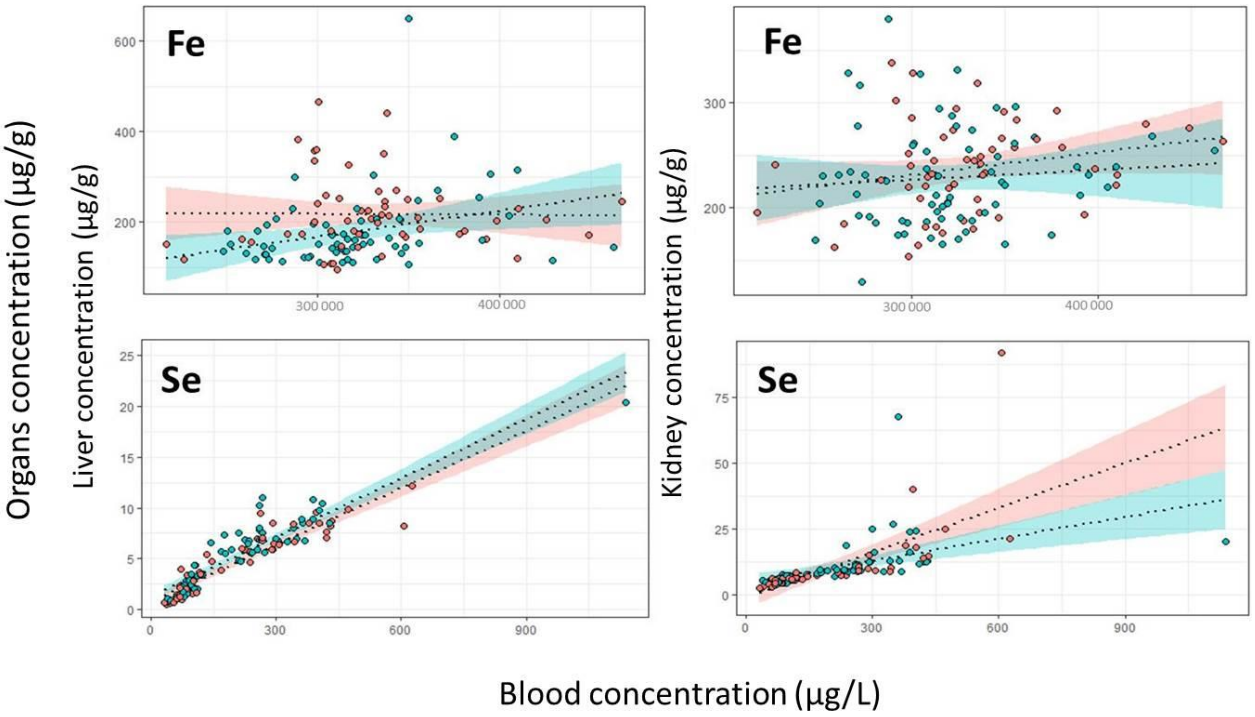


Fig. 3. Relationship between blood and organs concentrations in the wood mouse *Apodemus sylvaticus.* (A) Blood/liver Pb concentrations, (B) Blood/kidney Pb concentrations, (C) Blood/liver Cd concentrations, (D) Blood/kidney Cd concentrations. General Linear Models were used and all tissue concentrations were log (log 10(x+1)) transformed (grey represents IC 95%).



452 Fig. 4. Relationship between blood and organs concentrations (liver and kidney) in male (blue) and female
453 (red) wood mice *Apodemus sylvaticus* for iron (Fe) and selenium (Se). General Linear Models were used and
454 all tissue concentrations were log (log 10(x+1)) transformed (blue and red represent IC 95% for each sex).



455

Supplementary Data

Table S1. Certified values and average recoveries of the Certified Reference Materials used in this study (the number of reference samples analyzed for each certified reference materials is 9).

Element		Al	As	Cd	Co	Cr	Cu	Fe	Mn	Mo	Ni	Pb	Sb	Se	Sn	Sr	Ti	Tl	Zn
TORT-2	Certified values (µg/g)	NS[a]	21.6	26.7	0.51	0.77	106	105	13.6	0.95	2.5	0.35	NS	5.63	0.04[c]	45.2	NS	NS	180
	Recovery (%)	ND[b]	99	98	89	72	80	75	77	100	78	120	ND	109	171	101	ND	ND	107
ERM®-CE196	Certified values (µg/L)	NS	NS	12.33	NS	NS	NS	NS	NS	NS	NS	772	NS	NS	NS	NS	NS	NS	NS
	Recovery (%)	ND	ND	77	ND	ND	ND	ND	ND	ND	ND	79	ND	ND	ND	ND	ND	ND	ND

[a]Not specified

[b]Not determined

[c]Indicative (not certified) value

463 Table S2. Trace metal (TM) concentrations (median, mean, minimum and maximum) in blood (expressed
464 in µg/L) and organs (liver and kidney expressed in µg/g) for the 18 tested TM. Total number of samples
465 and the percentage of data under the quantification limit are given.

Element	Sex	Soil contamination level	Blood concentration (µg/L)				Liver concentration (µg/g)				Kidney concentration (µg/g)				*N*	% < LQ in blood	% < LQ in liver	% < LQ in kidney
			Median	Mean	Min	Max	Median	Mean	Min	Max	Median	Mean	Min	Max				
Al	F	Control	1036	1036	1036	1036	2,75	8,48	0,263	36,6	0,316	2,89	0,316	18,0	16	100	31	69
		Low	1036	1166	1036	2980	3,27	3,43	0,263	8,88	0,316	3,75	0,316	12,9	15	93	20	53
		Medium	1036	1036	1036	1036	3,88	4,23	0,263	9,38	2,03	4,55	0,316	17,2	11	100	9	45
		High	1036	1036	1036	1036	1,08	4,61	0,263	22,4	3,67	4,06	0,316	13,6	12	100	50	33
	M	Control	1036	1137	1036	2143	4,47	6,17	0,263	23,0	0,316	4,08	0,316	14,3	11	91	9	64
		Low	1036	1036	1036	1036	0,263	1,60	0,263	10,1	3,43	6,79	0,316	35,6	18	100	78	39
		Medium	1036	1036	1036	1036	3,51	4,56	0,263	10,1	0,316	4,95	0,316	37,2	23	100	4	52
		High	1036	1036	1036	1036	4,04	5,61	0,263	25,7	0,316	5,03	0,316	25,4	14	100	7	57
As	F	Control	8,90	8,90	8,90	8,90	0,008	0,017	0,008	0,089	0,010	0,010	0,010	0,010	16	100	88	100
		Low	8,90	8,90	8,90	8,90	0,008	0,013	0,008	0,084	0,010	0,010	0,010	0,010	15	100	7	100
		Medium	8,90	8,90	8,90	8,90	0,008	0,008	0,008	0,008	0,010	0,010	0,010	0,010	11	100	100	100
		High	8,90	8,90	8,90	8,90	0,008	0,008	0,008	0,008	0,010	0,010	0,010	0,010	12	100	100	100
	M	Control	8,90	8,90	8,90	8,90	0,008	0,013	0,008	0,063	0,010	0,010	0,010	0,010	11	100	91	100
		Low	8,90	8,90	8,90	8,90	0,008	0,008	0,008	0,008	0,010	0,010	0,010	0,010	18	94	100	100
		Medium	8,90	8,90	8,90	8,90	0,008	0,014	0,008	0,144	0,010	0,017	0,010	0,173	23	100	4	96
		High	8,90	9,30	8,90	14,6	0,008	0,027	0,008	0,104	0,010	0,010	0,010	0,010	14	7	79	100
Cd	F	Control	3,46	3,46	3,46	3,46	0,731	1,13	0,261	3,79	3,40	5,27	0,741	29,2	16	100	0	0
		Low	3,46	5,56	2,40	19,6	2,27	3,97	0,186	12,8	6,87	15,9	1,02	56,4	15	40	0	0
		Medium	3,46	5,45	3,46	19,6	5,99	14,9	0,460	59,9	13,4	27,4	2,77	74,4	11	64	0	0
		High	3,46	4,46	2,72	15,6	3,38	5,62	0,635	17,9	19,4	21,1	2,40	46,1	12	58	0	0
	M	Control	3,46	9,24	3,46	50,0	0,523	0,945	0,121	4,70	1,74	2,70	0,376	7,56	11	82	0	0
		Low	3,46	3,49	2,40	4,68	1,36	1,72	0,740	3,59	5,23	6,31	2,23	12,2	18	67	0	0
		Medium	3,46	3,82	3,40	7,80	3,51	5,37	0,713	17,1	9,61	17,7	2,26	81,5	23	70	0	0
		High	3,46	3,99	2,40	7,28	3,96	5,14	1,13	11,0	18,5	19,8	4,48	37,3	14	50	0	0
Co	F	Control	6,01	6,14	5,64	7,64	0,085	0,076	0,002	0,189	0,149	0,182	0,055	0,870	16	81	25	0
		Low	6,01	6,01	6,01	6,01	0,055	0,063	0,002	0,195	0,099	0,117	0,050	0,362	15	100	33	0
		Medium	6,01	6,01	6,01	6,01	0,076	0,070	0,002	0,096	0,106	0,105	0,060	0,152	11	100	91	0
		High	6,01	6,01	6,01	6,01	0,073	0,077	0,002	0,151	0,098	0,110	0,002	0,196	12	100	17	8
	M	Control	6,01	6,10	6,01	7,04	0,12	0,13	0,002	0,260	0,111	0,125	0,002	0,224	11	91	9	91
		Low	6,01	6,36	6,01	11,96	0,067	0,067	0,002	0,173	0,096	0,145	0,002	1,02	18	94	28	11
		Medium	6,01	6,01	6,01	6,01	0,087	0,074	0,002	0,130	0,097	0,103	0,045	0,196	23	100	13	0
		High	6,01	6,01	6,01	6,01	0,086	0,084	0,002	0,171	0,105	0,119	0,065	0,218	14	100	7	0
Cr	F	Control	10,7	10,7	10,7	10,7	0,005	0,015	0,005	0,110	0,006	0,043	0,006	0,236	16	100	81	81
		Low	10,7	10,7	10,7	10,7	0,005	0,015	0,005	0,134	0,006	0,071	0,006	0,712	15	100	87	80
		Medium	10,7	10,7	10,7	10,7	0,005	0,009	0,005	0,049	0,006	0,047	0,006	0,189	11	100	91	27
		High	10,7	10,7	10,7	10,7	0,005	0,005	0,005	0,005	0,036	0,074	0,006	0,377	12	100	100	50
	M	Control	10,7	19,1	10,7	112	0,005	0,018	0,005	0,088	0,006	0,006	0,006	0,006	11	100	82	100
		Low	10,7	10,7	10,7	10,7	0,005	0,007	0,005	0,039	0,006	0,078	0,006	0,305	18	94	94	61
		Medium	10,7	10,7	10,7	10,7	0,005	0,008	0,005	0,036	0,006	0,037	0,006	0,263	23	100	91	78
		High	10,7	13,0	10,7	43,4	0,005	0,009	0,005	0,039	0,006	0,091	0,006	0,738	14	93	86	57
Cu	F	Control	496	503	377	674	10,4	10,6	7,72	13,9	18,8	18,1	10,2	21,7	16	0	0	0
		Low	883	941	624	1380	10,2	10,6	7,60	15,6	17,3	17,4	11,5	24,4	15	0	0	0
		Medium	736	847	502	1499	11,4	11,2	8,58	15,1	18,3	18,4	13,6	24,9	11	0	0	0
		High	820	962	725	2532	9,61	9,85	7,76	12,0	15,8	16,9	13,2	22,2	12	0	0	0
	M	Control	525	578	365	1232	11,2	10,9	8,25	14,0	18,3	18,4	12,4	23,9	11	0	0	0
		Low	975	995	761	1472	10,1	10,4	8,01	12,8	17,2	17,2	11,3	21,7	18	0	0	0
		Medium	749	809	563	1856	10,9	11,1	7,50	14,8	17,6	18,3	11,9	27,7	23	0	0	0
		High	876	917	726	1480	10,6	10,5	7,60	13,0	18,0	18,0	11,8	27,7	14	0	0	0
Fe	F	Control	322820	351815	283240	467200	187	196	95	384	232	238	154	338	16	0	0	0
		Low	339400	343781	298440	425600	210	239	167	441	251	252	190	294	15	0	0	0
		Medium	307600	299731	216720	342920	259	253	118	467	241	233	181	328	11	0	0	0
		High	322280	315720	258280	380640	178	186	124	245	215	224	163	302	12	0	0	0
	M	Control	348120	348317	266760	429200	161	222	114	649	220	218	174	268	11	0	0	0
		Low	316200	311915	248240	355880	151	157	112	248	224	226	129	331	18	0	0	0
		Medium	307640	311092	251880	462400	152	187	117	390	212	229	170	379	23	0	0	0
		High	326320	322020	250200	366000	154	162	107	270	247	238	165	327	14	0	0	0
Mn	F	Control	25,3	25,3	25,3	25,3	5,57	5,90	3,93	8,16	6,71	6,37	3,61	8,82	16	100	0	0
		Low	26,4	34,4	20,2	91,1	4,74	4,78	3,56	6,28	6,08	6,01	3,95	7,63	15	73	0	0
		Medium	25,3	29,1	21,5	62,2	6,54	6,29	4,29	8,42	6,16	6,12	4,77	8,08	11	64	0	0
		High	25,3	31,1	18,2	86,2	5,08	4,98	3,64	7,13	5,03	5,12	3,89	6,30	12	25	0	0
	M	Control	25,3	25,3	25,3	25,3	7,23	7,08	3,69	12,76	6,42	6,45	3,34	9,09	11	100	0	0
		Low	25,3	26,9	16,6	48,5	4,54	4,87	3,26	7,61	5,62	5,35	3,03	8,79	18	44	0	0
		Medium	25,3	27,3	20,9	59,4	5,10	5,18	3,16	7,81	5,51	5,77	2,94	9,97	23	78	0	0
		High	24,6	24,8	16,0	36,7	4,42	4,50	2,18	5,98	5,13	5,24	3,49	8,00	14	7	0	0
Mo	F	Control	6,80	7,45	3,80	19,5	2,76	2,96	1,77	4,67	1,73	1,77	0,994	2,40	16	0	0	0
		Low	6,52	6,57	2,77	16,4	2,59	2,54	1,01	4,71	1,64	1,60	0,834	2,20	15	33	0	0
		Medium	8,48	8,09	2,77	13,3	3,46	3,38	2,41	4,42	2,24	2,19	1,48	2,80	11	9	0	0
		High	3,69	6,47	2,77	16,5	2,89	2,92	2,05	4,70	2,01	1,87	1,12	2,33	12	60	0	0
	M	Control	5,94	6,95	3,52	15,4	3,07	3,15	1,90	5,05	1,58	1,73	1,35	2,41	11	0	0	0
		Low	6,32	7,09	2,77	13,6	2,84	2,90	2,03	4,15	1,77	1,77	0,927	2,32	18	22	0	0
		Medium	6,44	7,80	2,77	35,0	3,24	3,23	2,22	4,14	1,80	2,01	1,30	3,08	23	78	0	0
		High	6,10	7,56	2,77	22,3	3,24	3,02	1,48	4,21	1,84	1,76	1,08	2,40	14	43	0	0

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Element	Sex	Soil contamination level	Blood concentration (µg/L)				Liver concentration (µg/g)				Kidney concentration (µg/g)				*N*	% < LQ in blood	% < LQ in liver	% < LQ in kidney
			Median	Mean	Min	Max	Median	Mean	Min	Max	Median	Mean	Min	Max				
Ni	F	Control	101	191	56	1089	0,009	0,040	0,009	0,308	0,011	0,082	0,011	0,427	16	0	87	75
		Low	44	90	22	396	0,009	0,032	0,009	0,274	0,011	0,055	0,011	0,281	15	47	9	80
		Medium	117	157	22	365	0,009	0,294	0,009	3,15	0,011	0,134	0,011	1,21	11	82	83	18
		High	99	579	22	3116	0,009	0,024	0,009	0,117	0,011	0,079	0,011	0,390	12	50	64	67
	M	Control	71,0	771	21,9	8164	0,009	0,070	0,009	0,259	0,102	0,248	0,011	0,936	11	9	89	45
		Low	62,3	132	21,9	440	0,009	0,104	0,009	1,36	0,116	0,303	0,011	1,46	18	39	96	50
		Medium	72,4	163	21,9	890	0,009	0,012	0,009	0,072	0,011	0,095	0,011	0,480	23	83	86	70
		High	88,3	641	21,9	2124	0,009	0,061	0,009	0,633	0,011	0,027	0,011	0,161	14	36	0	86
Pb	F	Control	53,1	62,5	24,0	129	0,237	0,270	0,072	0,481	1,65	2,09	0,427	4,42	16	0	0	0
		Low	141	285	72,6	1901	0,816	0,922	0,055	2,88	3,97	4,59	0,286	9,17	15	0	0	0
		Medium	75,0	98,0	33,7	314	0,272	0,433	0,126	1,27	2,34	3,02	1,00	7,15	11	0	0	0
		High	145	156	80,3	250	0,698	0,774	0,207	1,97	12,8	34,9	4,64	229	12	0	0	0
	M	Control	64,7	75,8	10,8	240	0,257	0,433	0,047	2,38	1,96	2,66	0,259	9,10	11	0	0	0
		Low	91,4	107	23,0	288	0,346	0,643	0,082	3,11	3,16	3,89	0,451	9,14	18	0	0	0
		Medium	73,2	85,7	17,9	168	0,345	0,378	0,055	0,926	2,95	3,06	0,54	7,74	23	0	0	0
		High	178	207	87,6	440	1,00	1,48	0,196	4,74	17,5	27,1	3,26	117	14	0	0	0
Sb	F	Control	3,95	3,95	3,95	3,95	0,002	0,002	0,002	0,002	0,003	0,003	0,003	0,003	16	100	100	100
		Low	3,95	3,95	3,95	3,95	0,002	0,002	0,002	0,002	0,003	0,003	0,003	0,003	15	100	100	100
		Medium	3,95	3,95	3,95	3,95	0,002	0,002	0,002	0,002	0,003	0,003	0,003	0,003	11	100	92	100
		High	3,95	3,95	3,95	3,95	0,002	0,003	0,002	0,010	0,003	0,006	0,003	0,040	12	100	92	83
	M	Control	3,95	3,95	3,95	3,95	0,002	0,002	0,002	0,002	0,003	0,003	0,003	0,003	11	100	89	100
		Low	3,95	3,95	3,95	3,95	0,002	0,003	0,002	0,016	0,003	0,003	0,003	0,003	18	100	96	100
		Medium	3,95	3,95	3,95	3,95	0,002	0,003	0,002	0,008	0,003	0,003	0,003	0,003	23	100	93	100
		High	3,95	3,95	3,95	3,95	0,002	0,004	0,002	0,022	0,003	0,005	0,003	0,032	14	100	0	93
Se	F	Control	92,5	95,4	62,5	146	2,34	2,64	1,01	5,44	5,52	5,38	2,85	8,46	16	0	0	0
		Low	70,5	81,5	32,2	239	1,43	1,78	0,462	4,68	5,69	5,17	2,65	7,45	15	0	0	0
		Medium	267	277	218	345	6,63	6,98	5,76	9,45	9,21	9,89	7,16	15,1	11	0	0	0
		High	421	428	256	626	8,36	8,48	6,49	12,1	16,3	24,2	9,46	91,7	12	0	0	0
	M	Control	91,2	90,1	73,3	112	2,04	2,19	1,27	3,51	5,20	5,43	4,02	7,39	11	0	0	0
		Low	91,0	84,8	39,7	124	2,51	2,42	0,85	4,39	6,00	5,79	4,14	7,68	18	0	0	0
		Medium	242	239	145	369	6,73	6,85	4,75	11,0	9,18	9,43	7,09	12,5	23	0	0	0
		High	363	406	238	1137	8,50	9,01	5,61	20,3	17,3	21,2	9,19	67,5	14	0	0	0
Sn	F	Control	21,4	21,7	12,9	30,1	0,004	0,024	0,004	0,283	0,005	0,007	0,005	0,037	16	0	87	94
		Low	18,6	20,0	13,0	29,4	0,004	0,006	0,004	0,023	0,005	0,009	0,005	0,062	15	0	9	93
		Medium	13,2	31,2	8,36	208	0,004	0,008	0,004	0,050	0,005	0,005	0,005	0,005	11	0	92	100
		High	15,0	15,9	11,6	27,4	0,004	0,005	0,004	0,021	0,005	0,009	0,005	0,033	12	0	91	83
	M	Control	23,1	227	17,8	2341	0,004	0,006	0,004	0,028	0,005	0,005	0,005	0,005	11	0	89	100
		Low	14,1	15,7	9,04	32,0	0,004	0,011	0,004	0,084	0,005	0,005	0,005	0,005	18	0	89	100
		Medium	17,2	30,3	9,52	283	0,004	0,004	0,004	0,004	0,005	0,010	0,005	0,051	23	0	93	87
		High	16,8	31,8	11,2	202	0,004	0,005	0,004	0,019	0,005	0,008	0,005	0,051	14	0	69	93
Sr	F	Control	63,5	63,5	63,5	63,5	0,030	0,115	0,030	0,700	0,036	0,196	0,036	0,701	16	100	80	69
		Low	63,5	63,5	63,5	63,5	0,200	0,246	0,030	0,531	0,036	0,340	0,036	0,921	15	100	36	53
		Medium	63,5	63,5	63,5	63,5	0,209	0,182	0,030	0,346	0,036	0,371	0,036	0,988	11	100	50	55
		High	63,5	63,5	63,5	63,5	0,085	0,152	0,030	0,403	0,036	0,122	0,036	0,581	12	100	45	83
	M	Control	63,5	63,5	63,5	63,5	0,152	0,179	0,030	0,404	0,036	0,277	0,036	0,918	11	100	11	73
		Low	63,5	63,5	63,5	63,5	0,258	0,268	0,030	0,582	0,036	0,356	0,036	1,22	18	100	52	56
		Medium	63,5	63,5	63,5	63,5	0,030	0,135	0,030	0,561	0,036	0,224	0,036	1,13	23	100	86	65
		High	63,5	63,5	63,5	63,5	0,030	0,051	0,030	0,186	0,036	0,248	0,036	1,23	14	100	0	64
Ti	F	Control	59,1	63,2	59,1	124	1,86	1,99	1,57	2,83	2,30	2,27	1,10	3,68	16	94	0	0
		Low	111	114	59,1	219	1,88	1,95	1,54	2,69	1,91	2,21	1,49	3,41	15	87	0	0
		Medium	85,7	84,2	59,1	145	1,83	2,10	1,68	2,95	2,14	2,11	1,48	2,99	11	45	0	0
		High	59,1	78,6	59,1	151	1,76	2,02	1,42	3,45	2,46	2,43	1,29	3,43	12	58	0	0
	M	Control	59,1	59,1	59,1	59,1	2,26	2,33	1,56	3,27	2,08	2,26	0,024	4,36	11	100	0	91
		Low	98,0	95,5	59,1	172	1,77	1,83	1,45	2,43	2,58	2,62	1,59	4,13	18	17	0	0
		Medium	59,1	72,0	59,1	109	1,91	2,01	1,49	2,78	2,02	2,11	1,39	3,99	23	61	0	0
		High	60,6	76,2	59,1	128	1,93	1,90	1,31	2,28	1,77	1,96	1,17	2,84	14	50	0	0
Tl	F	Control	0,198	0,201	0,198	0,240	0,002	0,002	0,001	0,005	0,024	0,026	0,000	0,060	16	94	0	6
		Low	0,198	0,198	0,198	0,198	0,003	0,005	0,001	0,014	0,047	0,048	0,006	0,136	15	100	0	0
		Medium	0,198	0,205	0,198	0,280	0,004	0,005	0,001	0,015	0,026	0,040	0,013	0,132	11	91	0	0
		High	0,520	0,666	0,198	2,08	0,031	0,040	0,007	0,135	0,260	0,459	0,125	1,65	12	25	0	0
	M	Control	0,198	0,198	0,198	0,198	0,003	0,003	0,001	0,009	0,036	0,037	0,010	0,078	11	100	0	0
		Low	0,198	0,210	0,198	0,400	0,004	0,004	0,002	0,006	0,034	0,035	0,007	0,077	18	89	0	0
		Medium	0,198	0,198	0,198	0,198	0,004	0,007	0,002	0,023	0,039	0,074	0,009	0,286	23	100	0	0
		High	0,660	1,98	0,198	13,2	0,043	0,135	0,012	0,867	0,499	1,21	0,149	7,06	14	7	0	0
Zn	F	Control	4224	4411	3377	5300	124	134	76,4	203	134	129	73,7	165	16	0	0	0
		Low	6100	6290	4040	10192	147	162	84,9	280	136	138	89,4	178	15	0	0	0
		Medium	4356	4420	3208	5760	138	142	110	187	134	132	114	156	11	0	0	0
		High	4926	4994	3921	6144	137	139	97,5	196	134	136	111	172	12	0	0	0
	M	Control	4300	6848	3264	33888	135	140	105	201	124	126	105	163	11	0	0	0
		Low	5404	5673	4012	8700	159	162	125	253	134	143	103	184	18	0	0	0
		Medium	4308	4640	3327	14060	119	129	83,9	258	123	135	86,9	347	23	0	0	0
		High	5028	6738	4236	18472	133	142	87,5	264	132	133	92,5	200	14	0	0	0

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469 Table S3. Tukey's HSD tests summary. Comparisons between squares of increasing level of soil Cd, Pb and Zn
470 contamination are presented for blood, liver and kidneys.

Blood

F=4.99, **p=0.003**, Df=3

Fe	Control	Low	Medium	High
Control				
Low	0.27			
Medium	**0.001**	0.17		
High	0.09	0.91	0.60	

F=0.30, p=0.82, Df=3

Cd	Control	Low	Medium	High
Control				
Low	0.84			
Medium	0.94	0.99		
High	0.84	0.99	0.99	

F=33.51, **p<0.001**, Df=3

Cu	Control	Low	Medium	High
Control				
Low	**p<0.001**			
Medium	**p<0.001**	**0.02**		
High	**p<0.001**	0.85	0.19	

F=0.47, p=0.70, Df=3

Mn	Control	Low	Medium	High
Control				
Low	0.98			
Medium	0.99	0.91		
High	0.85	0.65	0.94	

F=0.66, p=0.57, Df=3

Mo	Control	Low	Medium	High
Control				
Low	0.92			
Medium	0.10	0.82		
High	0.73	0.97	0.59	

F=16.34, **p<0.001**, Df=3

Pb	Control	Low	Medium	High
Control				
Low	**p<0.001**			
Medium	0.28	0.07		
High	**p<0.001**	**0.04**	**p<0.001**	

F=185.7, **p<0.001**, Df=3

Se	Control	Low	Medium	High
Control				
Low	0.11			
Medium	**p<0.001**	**p<0.001**		
High	**p<0.001**	**p<0.001**	**p<0.001**	

F=2.88, **p=0.04**, Df=3

Sn	Control	Low	Medium	High
Control				
Low	**0.04**			
Medium	0.13	0.94		
High	0.11	0.99	0.99	

F=15.43, **p<0.001**, Df=3

Ti	Control	Low	Medium	High
Control				
Low	**p<0.001**			
Medium	0.07	**p<0.001**		
High	0.09	**p<0.001**	0.99	

F=19.08, **p<0.001**, Df=3

Tl	Control	Low	Medium	High
Control				
Low	0.99			
Medium	0.99	0.99		
High	**p<0.001**	**p<0.001**	**p<0.001**	

F=5.61, **p=0.001**, Df=3

Zn	Control	Low	Medium	High
Control				
Low	**0.04**			
Medium	0.85	**0.002**		
High	0.24	0.90	**0.03**	

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Kidney

F=0.21
p=0.89
Df=3

Fe	Control	Low	Medium	High
Control				
Low	0.92			
Medium	0.99	0.90		
High	0.99	0.95	0.99	

F=17.02
p<0.001
Df=3

Cd	Control	Low	Medium	High
Control				
Low	**0.004**			
Medium	**p<0.001**	0.08		
High	**p<0.001**	**0.006**	0.69	

F=0.56
p=0.64
Df=3

Cu	Control	Low	Medium	High
Control				
Low	0.76			
Medium	0.99	0.74		
High	0.86	0.99	0.84	

F=3.621
p=0.02
Df=3

Mn	Control	Low	Medium	High
Control				
Low	0.19			
Medium	0.44	0.95		
High	**0.008**	0.50	0.22	

F=4.9
p=0.003
Df=3

Mo	Control	Low	Medium	High
Control				
Low	0.91			
Medium	**0.03**	**0.002**		
High	0.96	0.67	0.11	

F=38.2
p<0.001
Df=3

Pb	Control	Low	Medium	High
Control				
Low	0.07			
Medium	0.67	0.47		
High	**p<0.001**	**p<0.001**	**p<0.001**	

F=92.1
p<0.001
Df=3

Se	Control	Low	Medium	High
Control				
Low	0.99			
Medium	**p<0.001**	**p<0.001**		
High	**p<0.001**	**p<0.001**	**p<0.001**	

F=0.452
p=0.71
Df=3

Sn	Control	Low	Medium	High
Control				
Low	0.99			
Medium	0.83	0.92		
High	0.76	0.86	0.99	

F=1.09
p=0.36
Df=3

Ti	Control	Low	Medium	High
Control				
Low	0.69			
Medium	0.95	0.32		
High	0.99	0.54	0.99	

F=19.08
p<0.001
Df=3

Tl	Control	Low	Medium	High
Control				
Low	0.99			
Medium	0.99	0.99		
High	**p<0.001**	**p<0.001**	**p<0.001**	

F=1.127
p=0.34
Df=3

Zn	Control	Low	Medium	High
Control				
Low	0.30			
Medium	0.95	0.57		
High	0.81	0.86	0.97	

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Liver

	Fe	Control	Low	Medium	High
F=0.76	Control				
p=0.52	Low	0.99			
Df=3	Medium	0.91	0.98		
	High	0.87	0.69	0.46	

	Cd	Control	Low	Medium	High
F=14.62	Control				
p<0.001	Low	**0.04**			
Df=3	Medium	**p<0.001**	**0.006**		
	High	**p<0.001**	**0.033**	0.98	

	Cu	Control	Low	Medium	High
F=1.49	Control				
p=0.22	Low	0.79			
Df=3	Medium	0.93	0.39		
	High	0.61	0.98	0.25	

	Mn	Control	Low	Medium	High
F=8.48	Control				
p<0.001	Low	**p<0.001**			
Df=3	Medium	0.18	0.11		
	High	**p<0.001**	0.97	0.06	

	Mo	Control	Low	Medium	High
F=3.97	Control				
p=0.01	Low	0.20			
Df=3	Medium	0.57	**0.005**		
	High	0.96	0.50	0.29	

	Pb	Control	Low	Medium	High
F=12	Control				
p<0.001	Low	**0.004**			
Df=3	Medium	0.87	0.03		
	High	**p<0.001**	0.20	**p<0.001**	

	Se	Control	Low	Medium	High
F=123.9	Control				
p<0.001	Low	0.28			
Df=3	Medium	**p<0.001**	**p<0.001**		
	High	**p<0.001**	**p<0.001**	**0.05**	

	Sn	Control	Low	Medium	High
F=1.01	Control				
p=0.39	Low	0.79			
Df=3	Medium	0.41	0.92		
	High	0.46	0.93	0.99	

	Ti	Control	Low	Medium	High
F=1.6	Control				
p=0.19	Low	0.19			
Df=3	Medium	0.90	0.5		
	High	0.46	0.97	0.82	

	Tl	Control	Low	Medium	High
F=10.28	Control				
p<0.001	Low	0.99			
Df=3	Medium	0.99	0.99		
	High	**p<0.001**	**p<0.001**	**p<0.001**	

	Zn	Control	Low	Medium	High
F=4.49	Control				
p=0.01	Low	**0.03**			
Df=3	Medium	0.96	**0.004**		
	High	0.99	0.08	0.85	

473

Fig. S2. Relationship between blood (in µg/L) and kidneys (in µg/g) concentrations for 9 trace metals (Se, Cd, Fe, Tl, Mo, Pb, Zn, Ti and Cu).

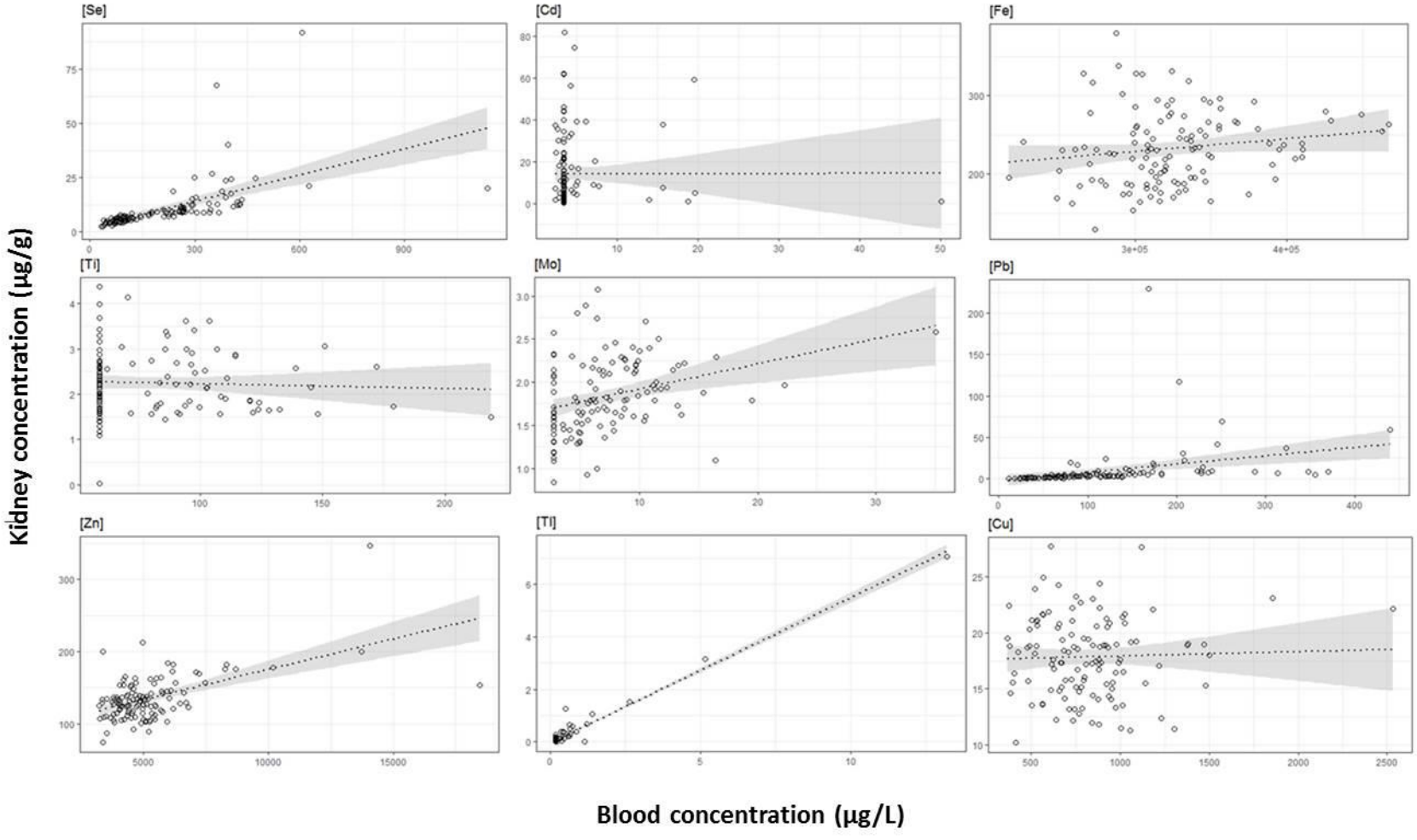


Fig. S3. Relationship between blood (µg/L) and liver (µg/g) concentrations for 9 trace metals (Se, Cd, Fe ,Tl, Mo, Pb, Zn, Ti and Cu).

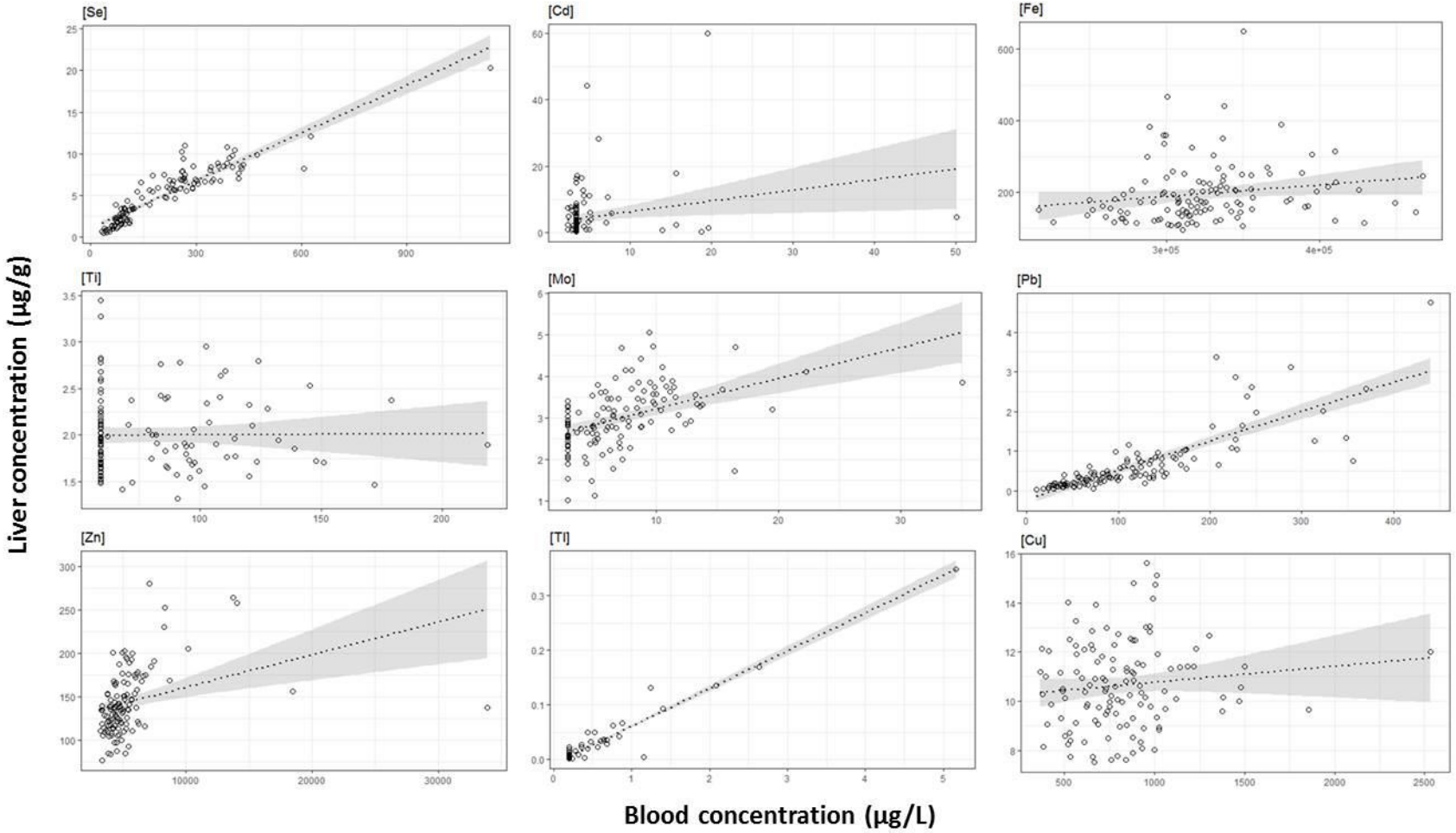
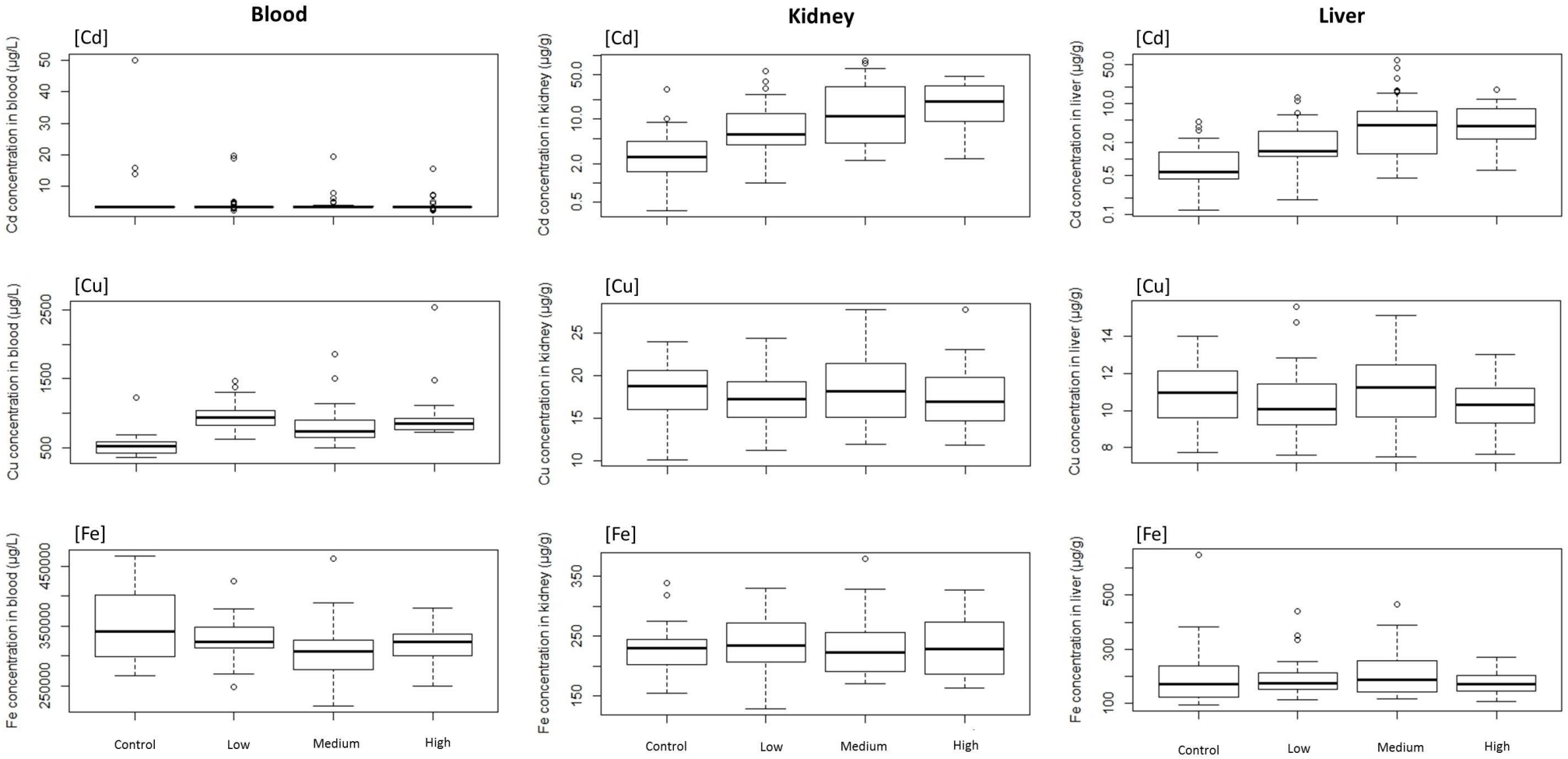
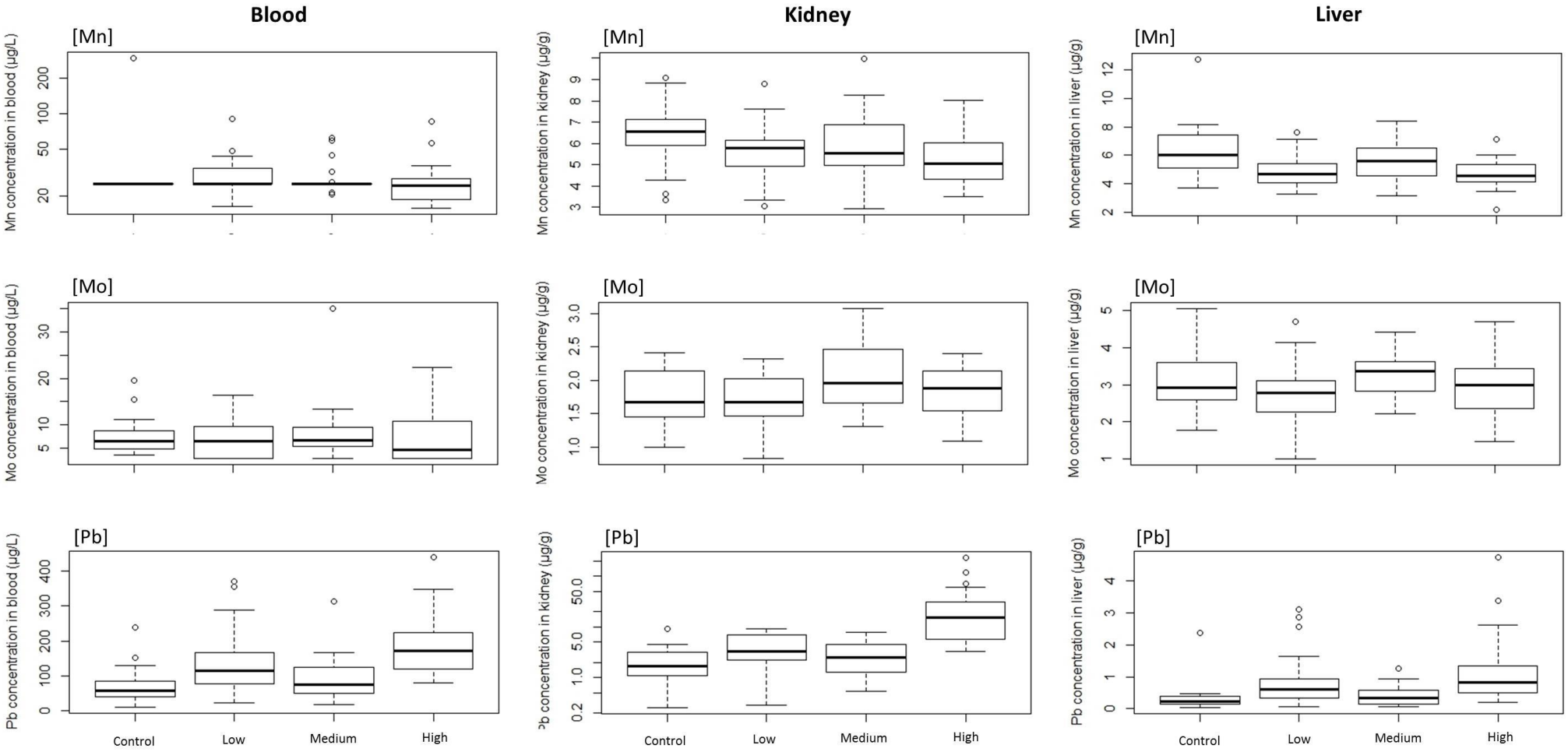


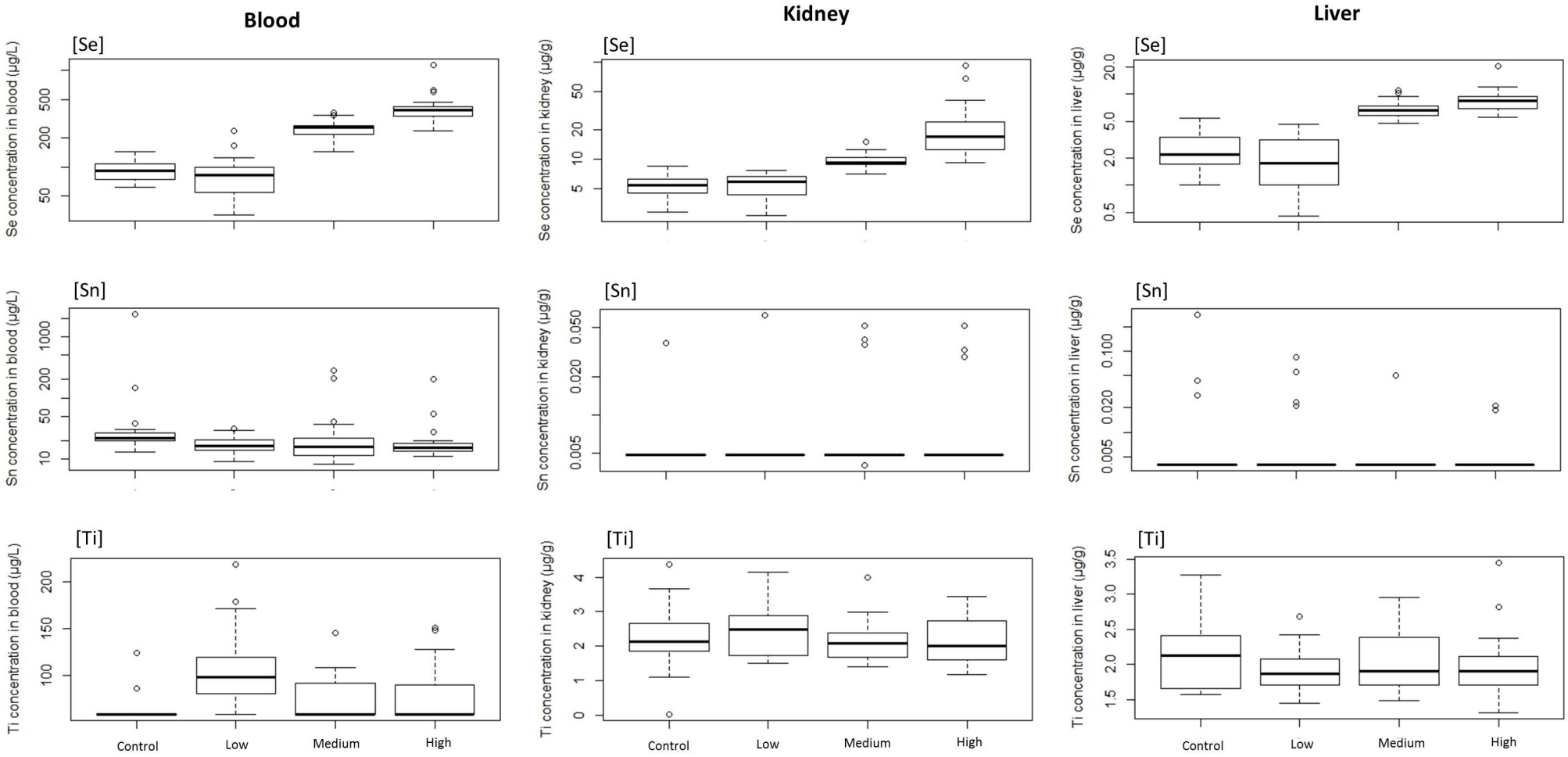
Fig. S4. Concentrations in blood, kidneys and liver along the pollution gradient based on soil concentrations for Cd, Pb and Zn, for 11 trace metals (Cd, Cu, Fe, Mn, Mo, Pb, Se, Sn, Ti, Tl and Zn).



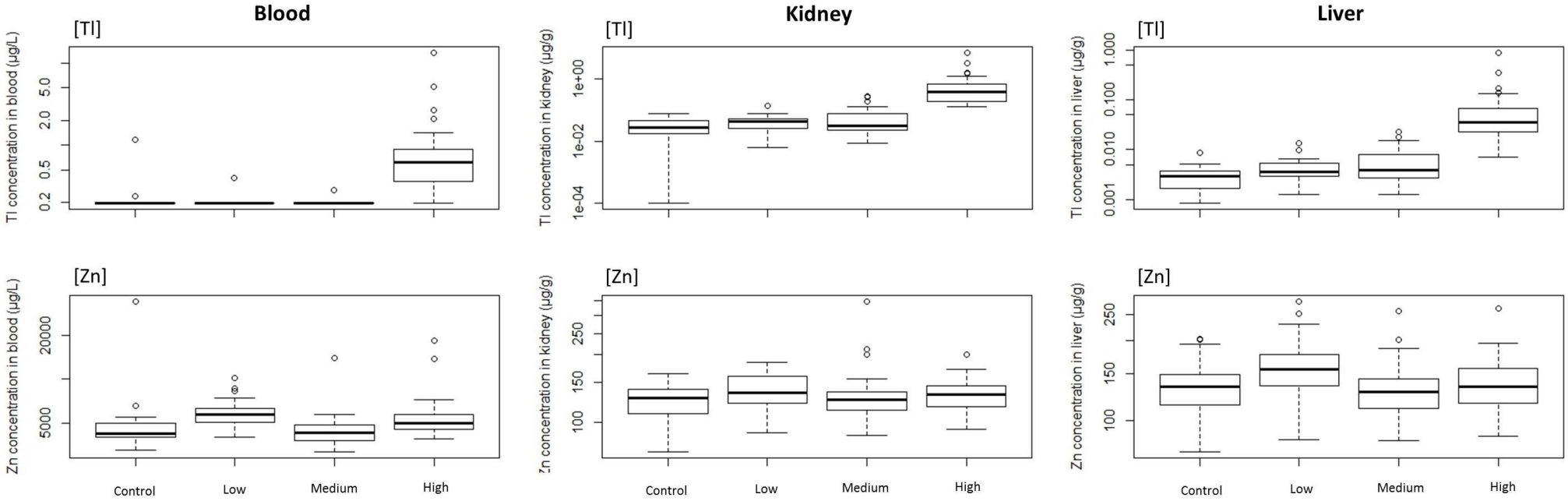

Blood
Kidney
Liver
[Mn]
[Mo]
[Pb]
Mn concentration in blood (µg/L)
Mo concentration in blood (µg/L)
Pb concentration in blood (µg/L)
Mn concentration in kidney (µg/g)
Mo concentration in kidney (µg/g)
Pb concentration in kidney (µg/g)
Mn concentration in liver (µg/g)
Mo concentration in liver (µg/g)
Pb concentration in liver (µg/g)
Control
Low
Medium
High

519

520


Blood
Kidney
Liver
[Se]
[Sn]
[Ti]
Se concentration in blood (µg/L)
Sn concentration in blood (µg/L)
Ti concentration in blood (µg/L)
Se concentration in kidney (µg/g)
Sn concentration in kidney (µg/g)
Ti concentration in kidney (µg/g)
Se concentration in liver (µg/g)
Sn concentration in liver (µg/g)
Ti concentration in liver (µg/g)
Control
Low
Medium
High

521


Blood
Kidney
Liver
[Tl]
[Zn]
Tl concentration in blood (µg/L)
Tl concentration in kidney (µg/g)
Tl concentration in liver (µg/g)
Zn concentration in blood (µg/L)
Zn concentration in kidney (µg/g)
Zn concentration in liver (µg/g)
0.2
0.5
2.0
5.0
1e-04
1e-02
1e+00
0.001
0.010
0.100
1.000
5000
20000
100
150
250
Control
Low
Medium
High

522