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Dipartimento di Ambiente e Connessa Prevenzione Primaria

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The study design and the analytical and statistical methods used in PROBE (*PROgramma per il Biomonitoraggio dell'Esposizione della popolazione generale*: PROgramme for Biomonitoring general population Exposure) for the assessment of the internal dose of 20 metals in the Italian population are described. The PROBE results on the concentration data are presented by metal detected and, within each metal, by matrix examined (blood and serum). A summary of the toxicology and effects on the environment and humans for each metal considered is also reported. Finally, data on metals are presented for sub-groups of the population stratified for influencing variables. The present report supplies a contemporary assessment of the human exposure to metals in Italy.
Key words: Metal exposure; Biomonitoring; Italian population; Reference values

Istituto Superiore di Sanità
Programma per il biomonitoraggio dell'esposizione della popolazione italiana (PROBE): dose interna dei metalli.
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2011, ix, 83 p. Rapporti ISTISAN 11/9 (in inglese)

Sono descritti il disegno dello studio e i metodi analitici e statistici utilizzati nel progetto PROBE (PROgramma per il Biomonitoraggio dell'Esposizione della popolazione generale) per la determinazione della dose interna di 20 metalli nella popolazione italiana. I risultati di PROBE sui dati di concentrazione sono presentati separati per metallo e, all'interno di ciascun metallo, per matrice esaminata (sangue e siero). Viene anche fornita una sintesi tossicologica e degli effetti sull'ambiente e sull'uomo per ciascun metallo considerato. Infine, i dati sui metalli sono presentati per sottogruppi della popolazione stratificata per variabili che possono avere influenza sul livello del metallo stesso. Il presente rapporto fornisce una misura aggiornata del dato di esposizione della popolazione italiana ai metalli.
Parole chiave: Esposizione al metallo; Biomonitoraggio; Popolazione italiana; Valori di riferimento

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(PROgramme for Biomonitoring general population Exposure)
funded by the Italian Ministry of Health in the period 2008-2010

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ACRONYMS AND ABBREVIATIONS

Organizations and other entities

ACGIH	American Conference of Governmental Industrial Hygienists
ANMI	*Associazione Nazionale per la lotta contro le Microcitemie* (National Association against Microcytemia)
ATSDR	Agency of Toxic Substances and Disease Registry
AVIS	*Associazione Volontari Italiani Sangue* (Italian Blood Volunteer Association)
CDC	Centers for Disease Control and Prevention
DHHS	Department of Health and Human Services
EC	European Commission
EU	European Union
GerES	German Environmental Survey
HBM	Human BioMonitoring
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine
ISS	*Istituto Superiore di Sanità* (National Institute of Health in Italy)
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PROBE	*PROgramma per il Biomonitoraggio dell'Esposizione della popolazione generale* (PROgramme for Biomonitoring general population Exposure)
US EPA	US Environmental Protection Agency
US NRC	US Nuclear Regulatory Commission
WHO	World Health Organization

Technical terms

ADI	Acceptable Daily Intake
AM	Arithmetic Mean
As	Arsenic
Be	Beryllium
BEI	Biological Effect Index
Cd	Cadmium
Co	Cobalt
Cr	Chromium
CI-GM	Confidence Interval-Geometric Mean
CSF	Cerebrospinal fluid
GM	Geometric Mean
Hg	Mercury
Ir	Iridium
LoD	Limit of Detection
MAC	Maximum Allowable Concentration
MAX	Maximum value
MCL	Maximum Contaminant Level
Mn	Manganese

Mo	Molybdenum
Ni	Nickel
NADH	Nicotinamide Adenine Dinucleotide Hydrogen
NOAEL	No Observed Adverse Effect Level
Pb	Lead
Pd	Palladium
PEL	Permissible Exposure Limit
Pt	Platinum
Rh	Rhodium
RVs	Reference Values
Sb	Antimony
SF-ICP-MS	Sector Field Inductively Coupled Plasma Mass Spectrometry
Sn	Tin
STEL	Short Term Exposure Limit
Tl	Thallium
TLV	Threshold Limit Value
TWA	Time Weighted Average
U	Uranium
V	Vanadium
W	Tungsten

PREFACE

Exposure of the general population to dangerous substances continuously distributed by the human activities in the environment, food or consumer products represents one of the most important concern in public health. The only data obtained by the environmental monitoring are not able to provide a complete characterization of the human exposure and, then, of human health risk. First because, although the toxicological and/or carcinogenic properties of many pollutants are known, to date are not available a comprehensive knowledge of different exposure ways, capacities of absorption and individual susceptibilities. Further, the specific characteristics of the environmental sampling sites do not allow a right generalization and an adequate estimation of total exposure of the general population.

The risk assessment connected to the exposure to xenobiotics becomes realistic by the measure of the amount of the contaminant actually present in the organism, as it is realized by the Human BioMonitoring (HBM).

From decades in the USA a great commitment was lavished on evaluating exposure of the general population to chemical substances. In the programs of the Centers for Disease Control and prevention (CDC) many HBM campaigns were realized to characterize the quantity of exposure, to find supscetibility to specific agents, to group the population on the basis of exposure, etc. These campaigns are part of the National Health and Nutrition Examination Survey (NHANES).

Human biomonitoring has attracted great interest also in Europe and is now integrated in European Union (EU) legislation. A series of EU recommendations – as the guideline 98/24/EG issued in 1998 – summarized the different aspects of preventive protection of health from the effects of dangerous substances and the importance of health survey.

The European Environment and Health Strategy as well as the Environment and Health Action Plan 2004-2010 of the European Commission (EC) recognized the importance of the HBM and the relevance of coordination of HBM programmes in EU. Against this background, a consistent approach to HBM has been more recently developed to collect comparable HBM data in EU and to investigate what is needed to improve this harmonization across Europe (COPHES, Consortium to Perform Human Biomonitoring on a European Scale; and DEMOCOPHES, Demonstration of a study to Coordinate and Perform Human Biomonitoring on a European Scale). The final objectives of the HBM activities undertaken by all the parties involved are, therefore, to support and evaluate current and future regulations, including those defined under REACH.

In this framework, the PROBE (*PROgramma per il Biomonitoraggio dell'Esposizione della popolazione generale* – PROgramme for Biomonitoring general population Exposure) is a project representing the first attempt to estimate the internal dose of the Italian general population as a consequence of environmental exposure to metals.

The project, commissioned, funded and steered by the Italian Ministry of Health, developed and used harmonized procedures and validated protocols with the aim to establish reliable Reference Values (RVs) of twenty toxic metals for the general population or population groups, to make the results comparable with those of similar monitoring campaigns in Europe and, finally, to generate reliable information to develop exposure restriction and prevention strategies.

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INTRODUCTION

HBM – which is the direct measurement of people's exposure to the environmental contaminants by measuring them in human specimens (blood, serum, urine, hair, etc.) – emerges as an indispensable tool for combining possible health impairments and environmental influences.

The level of xenobiotics in human fluids reflects the amount of a chemical that actually gets into the body by all routes of exposure, including ingestion, inhalation and dermal absorption. Therefore, the presence of the chemical – of a metal, in the case of this report – in a person's body is indication of exposure, although it does not by itself mean that the found chemical level causes disease or an adverse effect.

The HBM data together with results from toxicological researches allow to determine which levels are safe and which are associated with disease, in practice let the identification of the hazard, and the assessment and management of the resulting risk.

Looking at the HBM pre-existing situation in Italy, the evaluation of the internal dose of metals in the general population is available only for a few geographical areas in Italy. In 1990, data have been published for 20 metals in inhabitants of the region Lumbardy (Minoia *et al*., 1990), and, after a gap of many years, in 2004, a survey on 26 metals in the region of Latium was conducted (Alimonti *et al.,* 2005a). Moreover, for some metals data are still missing for the Italian general population, and for particular population strata (by gender, age, smoking habits, etc.) information is rarely produced. The reason for the paucity of data on this topic is because the HBM data production is a time-consuming process that requires a deep estimation of several analytical and biological factors that could affects the final results.

For the assessment of reliable HBM data it is necessary to adhere to strict criteria for: i) the selection of individuals; ii) the procedures for sample collection; iii) the control of analytical variability; and iv) the statistical treatment of results (Nordberg *et al*., 1992).

Many difficulties are often encountered in performing quality control programs of metal analysis in biological fluids. For example, critical aspects are those related to the risk of contamination during fluid collection, the use of anticoagulants, the risk of losses during storage as well as the possible risk of contamination arising from metals in airborne particulates of the laboratory environment (Buratti *et al.,* 1992; Minoia *et al.,* 1992). Other crucial factors are those affecting variability of the concentrations to be determined, such as the route of absorption, the presence of sources of environmental pollution in the same residential areas, physiological variables and life-styles. These aspects are frequently disregarded or incompletely explored.

Against this background, an HBM survey on the environmental exposure of healthy adults in Italy (PROBE project) was conducted by the Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy) in the 2008-2010 period, in cooperation with the Italian Blood Volunteer Association (Associazione Volontari Italiani Sangue, AVIS). In particular, the sampling and interviews were conducted by the AVIS centres and the coordination of the project as well as the sample treatment and analyses were performed at the ISS (Bioelements and Health Unit, Department of Environment and Primary Prevention). PROBE was funded by the National Center for Diseases Control and Prevention of the Italian Ministry of Health. The Ethic Committee of the ISS has approved the project. PROBE is a population study carried out in order to determine the exposure to metals of the healthy general population in Italy. In a sample of the Italian population consisting of ca. 1400 adults aged 18-65 years and living in 5 different Regions, the internal dose of 20 metals – antimony (Sb), arsenic (As), beryllium (Be), cadmium (Cd), chromium (Cr), cobalt (Co), iridium (Ir), lead (Pb), manganese (Mn), mercury

(Hg), molybdenum (Mo), nickel (Ni), palladium (Pd), platinum (Pt), rhodium (Rh), thallium (Tl), tin (Sn), tungsten (W), uranium (U) and vanadium (V) – was examined. The description of the study design and the methods used for metal analysis and statistical evaluation, as far as the information for an easier data understanding, are reported.

The description of results is presented by metal and, for each metal, by examined matrix (blood, serum).

A brief introduction of the considered metal (toxicology, environmental and human biomonitoring literature data) is given and the statistical parameters for the distribution of these metals are reported in pertinent tables and figures.

The report also presents the metal level distributions for sub-groups; stratifications refer to sex, age, alcohol and smoking habits. The present report provides a first core of the data on HBM in Italy.

1. OBJECTIVES

Primary objective of PROBE is to supply representative data on the metals' internal dose in adults in order to highlight the environmental impact on the health of Italian population. The activities carried out were devoted to:

- develop, standardize and validate protocols and methods for samples collection and metal analysis as a basis for their reliability, transferability and comparability;
- establish RVs for the exposure of healthy adults to environmental metals;
- examine the possible influences of certain variables (demographics and habits) on the metal level of individuals;

The results provided by PROBE can be finally used as support to REACH regulation:

- to encourage further investigations (Commission Regulation No. 1907/2006, art. 45, paragraph 5);
- to identify substances of very high concern, persistent, bioaccumulating and toxic or chemicals of equivalent concern (Commission Regulation No. 1907/2006, Annex XIV);
- to assess the efficiency of risk reduction measures or of substitutional choice in authorized substances underlying the minimization requirements (Commission Regulation No. 1907/2006, art. 60, paragraph 10).

2. MATERIALS AND METHODS

2.1. Study design

To achieve the objectives, the project was divided into the following phases:

- identification of the adequate skills in the area to be potentially enrolled;
- training to enable the harmonization of procedures for collecting, storing, transporting and processing the human specimens;
- development and validation of laboratory methods for the quantification of metals;
- determination of levels of metals in study population blood and serum;
- stratification of results according to age, sex, alcohol and smoking habits.

Below, the collection and treatment protocols used in PROBE are presented in a condensed form, and a description is given of how the quantification of metals was performed.

2.1.1. Samples collection

PROBE was conducted in a target population consisted of adults aged between 18 and 65 years living in urban sites. In particular, subjects have been chosen as target population in order to obtain reliable RVs and to avoid over-exposure occupational or due to particular conditions of environmental pollution.

Furthermore, the target population was sufficiently large to be representative of the general population and to enable an evaluation of the effect of relevant confounder factors (e.g., age, sex, tobacco smoking, alcohol consumption) on the level of the chemical.

The recruitment of healthy people is supported by the fact that some pathologies are characterized by chemical elements imbalance. For example, different types of cancer such as breast cancer, malignant lymphoma, lung cancer and colorectal cancer (David *et al.,* 2001; Garg *et al.,* 1994; Sharma *et al.,* 1994; Zhao & Han, 1998); neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease and progressive demyelinating disease as multiple sclerosis (Alimonti *et al.*, 2007a; Alimonti *et al.,* 2007b; Andersen, 2004; Bocca *et al.*, 2006a; Forte *et al.*, 2005; Ristori *et al.*, 2011; Sayre *et al.*, 2001); oxidative stress and increased free radical production (Sayre *et al.*, 1999; Sayre *et al.,* 2000) are distinguished by an imbalance of chemical elements.

In the PROBE project, five urban locations (five Regions of Italy: Calabria, Latium, Umbria, Emilia Romagna, Piedmont) were selected to establish representative data for South, Central and North Italy. About 300 blood samples were collected by the AVIS centres located in each Region. Each volunteer, before blood sampling, was informed on the aims and modalities of PROBE also by means a written explanation of the survey, and expressed a written consent to participate. In the absence of such consent any information relating to potential donors was deleted from the database. Each donor was also asked to answer a short interview, in the form of questionnaire. The questionnaire used in PROBE collected information on:

- general data such as gender, age, height and weight (body mass index), place of residence and of job; anamnesis in terms of acute or chronic diseases (age at diagnosis), recent (last 60 days) drug intake, dental fillings or metal implants (type, number, how long);

- life-styles in terms of alcohol consumption (type, quantity, frequency), smoke (type, quantity, frequency), exercise (type, frequency), traffic at home and at work (type, intensity), home/work distance from potential industrial areas and type of industrial area;
- diet in terms of type (normal, vegetarian, etc.), consumption of fish (weekly amount), consumption of milk and dairy products;
- regular use of hormonal supplementation, contraceptive drugs, mineral supplementation.

Quality assurance during the sampling was conducted according to criteria harmonized between the institutions (ISS and AVIS) and laid down in checklists (operations manual). The safety measures included the use of the following set of devices and reagents: powder-free latex gloves; special blood sampling containers and needles for trace metal analysis (S-Monovette®, Sarstedt, Nümbrecht, Germany); decontaminated polystyrene disposable tubes (15 mL, Becton Dickinson Labware, Franklin Lakes, NJ, USA); and hydrogen peroxide of suprapur grade (Merck, Darmstadt, Germany).

Blood drawings were executed within 8 and 10 a.m. on subjects fasted overnight, and the venipuncture area was previously disinfected by means of hydrogen peroxide and then rinsed with deionized water. The first portion of blood was kept for blood donation and clinical parameters determination. This procedure allowed to rinse catheter and pipes and further minimize contamination by metals which can be transferred to blood. Blood and serum were collected in the S-Monovette® suitable for trace metal determination because at low level of metal impurities. The specimens were stored at -20 °C and transported to the ISS laboratory in a deep-frozen state where they were immediately storage in a refrigerator (-20 °C) until analysis.

2.1.2. Treatment

In general the entire experimental scheme was designed taking strict precautions to avoid alterations in the analytical information of the samples. On the day of analysis, one ml of blood was transferred in a polystyrene tube, previously decontaminated with a mixture of 10% v/v of nitric acid of ultrapure grade (Carlo Erba, Milan, Italy), added of 2 ml of nitric acid and microwave digested at atmospheric pressure in accordance with the following procedure: enhancement of temperature up to 80°C within 1 hr; digestion at 80°C for 5 hrs. A microwave oven (Milestone ETHOS MEGA II, FKV, Bergamo, Italy) equipped with a rotor (Milestone MultiPREP 80) designed for the digestion of 80 samples in one cycle was adopted for blood mineralization (Bocca *et al.*, 2003a; Bocca *et al.,* 2005). In order to control the digestion conditions an optical fiber temperature probe was placed in one of the tubes filled with the same reaction mixture. Serum was simple diluted with high purity deionised water (EASY Pure system, Barnstead, Dubuque, USA) on the day of analysis.

2.1.3. Analytical method

Twenty metals – Sb, As, Be, Cd, Cr, Co, Ir, Pb, Mn, Hg, Mo, Ni, Pd, Pt, Rh, Tl, Sn, W, U and V – were measured in blood and serum of the PROBE participants. The selection of metals was based on a comprise among different requirements:

- gravity of known or suspected health effects subsequent to the environmental exposure to the metal;
- the need to assess the effectiveness of public health actions to reduce exposure to a metal;
- the availability of adequate sample amounts;

– the availability of a multi-elemental analytical technique with adequate accuracy, precision, sensitivity, specificity, and throughput.

The analytical method used for measuring the metals in blood and serum was based on Sector Field Inductively Coupled Plasma Mass Spectrometry (SF-ICP-MS). Laboratory measurements underwent extensive quality control including tolerance limits for operational parameters, method validation and the calculation of uncertainty of measurements. According to the Decision 2002/657/EC and the most of the European and/or international organizations, the following validation performances were assessed: linearity; Limit of Detection (LoD) and limit of quantification; specificity; accuracy (precision and trueness); and robustness (AOAC, 1998; Commission Decision 2002/657/EC; LGC, 2003; NATA, 2009; Thompson *et al.*, 2002). As regards the uncertainty estimate, the basic concept adopted was not to identify the individual uncertainty sources that contributed to the total uncertainty budget, but to use data (namely, the precision and trueness) that were available in the laboratory in which the individual uncertainty components were already grouped. These grouped data were then used to calculate the total uncertainty. Then, other uncertainty sources were evaluated as possible factors to the total uncertainty only if they were not considered during the validation study and if they resulted to be significant respect to major sources of uncertainty. Details about this approach were given in several international guidelines and recent publications (Alimonti *et al.*, 2005b; Barwick *et al.*, 2000a; Barwick *et al.,* 2000b; Bocca *et al.*, 2006a; Ellison *et al.*, 1998; Eurolab, 2007; ISO Guide 98, 1995; ISO TS 21748, 2004; Linsinger, 2008; Maroto *et al.*, 1999; Priel, 2009). The criteria adopted and the results obtained for method's validation and uncertainty of measurements in the SF-ICP-MS analysis of 20 metals in serum are reported in other papers (Bocca *et al.*, 2010; Bocca *et al.,* 2011). In Table 1 LoD values in the matrices and the total uncertainty of the methods are reported.

Table 1. Limits of detection (µg/L) and expanded uncertainty of measurements (%)[a]

Metal	Blood		Serum	
	LoD	***uncertainty***	***LoD***	***uncertainty***
As	0.27	21.1	0.15	24.3
Be	0.045	23.4	0.022	19.2
Cd	0.10	26.0	0.015	19.9
Co	0.010	19.8	0.035	24.4
Cr	0.04	21.6	0.015	27.9
Hg	0.29	10.9	0.08	19.8
Ir	5.00 *	19.8	0.50 *	27.4
Mn	0.78	17.3	0.01	17.4
Mo	0.31	16.3	0.050	20.4
Ni	0.35	17.1	0.03	16.3
Pb	1.03	11.9	0.04	23.2
Pd	15.0*	24.9	2.85*	21.8
Pt	5.00*	22.2	0.74*	27.6
Rh	15.0*	21.7	2.05*	19.8
Sb	0.15	26.0	0.012	18.4
Sn	0.095	14.1	0.06	22.2
Tl	0.015	14.6	0.005	18.8
U	0.0015	17.4	-	-
V	0.024	18.7	0.015	19.8
W	0.005	17.4	0.019	16.7

[a] for a coverage factor k of 2 (ISO Guide 98, 1995) *= ng/L

2.2. Statistical method

The distributions of levels of metals in blood and serum are described by the following statistical parameters: dimension of population understudied (N), sub-groups in the population (classes), samples size in each class (N), percentiles (5^{th}: P5; 10^{th}: P10, 25^{th}: P25 50^{th}: P50; 75^{th}: P75; 90^{th}: P90; 95^{th}: P95), maximum value (MAX), arithmetic mean (AM), geometric mean (GM) and the 95% Confidence Interval for the Geometric Mean (CI-GM).

Percentiles and maximum values help to describe the distribution of the samples. The higher percentiles (P75, P90, P95) provided for each metal convey useful information about the upper distribution of levels in the population. The P95 percentiles, i.e., the upper limit of derived RVs, are helpful for determining whether levels observed in separate public health investigations or other studies are unusual.

The GM is preferred because takes into account all values measured and represents the "ideal" measure of central tendency in the event of logarithmic normal distribution. The difference between AM and GM or median can be regarded as an indicator of skewness. In calculations the values below the LoD were included as LoD/2, and the number of these cases is reported in the Tables of the Appendix A (as N<LoD).

The Kolmogorov-Smirnov test was applied to the data set for checking the normality of the distribution. All the elements were not normally distributed also because all concentration values were considered without esclusion of extreme values. The levels of metals are described not only for the total data set of 18- to 65-year-old adults but also for different sub-groups. The definition of these sub-groups is based on variables selected for stratification: gender, age (three groups), alcohol and smoking habits (three groups).

To test significant differences existing between the metal body burdens found in the groups of persons defined by the respective stratification variable, the Mann-Whitney U-test (for two groups to be compared) or the Kruskal-Wallis test (for more than two groups to be compared) were applied.

All tabulated stratification variables for CI-GM have been graphically displayed in the Figures of Appendix A. If a stratification variable is marked with asterisks, it has to be assumed that differences between the groups of persons are present at level of $p<0.001$ (*) or $p<0.01$ (**). Statistical calculations were performed with the statistics software SPSS for Windows, Version 17. The data set is updated to 31^{st} of December 2010.

3. RESULTS

In the Appendix A the results are reported for 20 metals in blood and serum of 18- to 65-year-old adults in Italy. The data are the basis to establish and update, respectively, RVs in Italian adults. The objective of the present section is to provide a quick and complete overview of the results of PROBE.

The description has been structured by type of metal measured, and Tables for each metal for blood and serum are reported. A short introductory overview is given on the importance of the individual metal, in terms of toxicological classification and environmental health relevance. Generally, the information was compiled privileging documents of national and international agencies and organizations, as the Agency for Toxic Substances and Disease Registry (ATSDR), the US Environmental Protection Agency (US EPA), and the agencies of the World Health Organization (WHO). The metal-specific Tables in Appendix A state the levels for the total population and for defined sub-groups. In the Tables, the results of tests are marked with asterisks to show the significant differences between the sub-populations (*p* levels).

3.1. Antimony (Sb)

3.1.1. General information

The International Agency for Research on Cancer (IARC) has classified Sb trioxide in Group 2B (a possible human carcinogen) and Sb trisulphide in Group 3 (not classifiable as to its carcinogenicity to humans) (IARC, 1989). More recently the EC has classified Sb trioxide in Category 3 with limited evidence for a carcinogenic effect (ESIS, 2009; EURAR, 2008). Workplace standards and recommendations for air exposure were established by Occupational Safety and Health Administration (OSHA) and by American Conference on Governmental Industrial Hygienists (ACGIH); in particular, a TLV (Threshold Limit Value) of 0.5 mg/m^3 as Time Weighted Average (TWA) was set (ACGHI, 1989; OSHA, 1989). A drinking water standard of 5 µg/L has been established by the European Directive 98/83 (Council Directive 98/83/EC, 1998).

The general population is exposed to Sb mainly from ingestion of food but also to some extent from water, air, dust, or direct dermal contact with consumer products containing Sb (EURAR, 2008). However, the low levels of Sb to which the general population is exposed are not expected to cause any adverse health effects (ATSDR, 1992).

Chronic occupational exposure to Sb *via* inhalation causes damage to the lungs, known as *Sb pneumoconiosis*, involving airway obstruction, bronchospasm, and hyperinflation, as well as respiratory irritation and interstitial inflammation (ATSDR, 1992). Urine and faeces are the major routes of Sb excretion; furthermore it was noticed that pentavalent Sb tends to be easier excreted in urine than the trivalent form (Elinder & Friberg, 1986).

3.1.2. Biomonitoring data

Antimony is commonly measured in blood and urine and this measurement is reflective of exposure to Sb and Sb-related compounds, such as Sb oxide (ATSDR, 1992). A renal elimination half-life of approximately 95 hrs has been estimated following occupational

inhalation of Sb trioxide and stibine (SbH_3) in 21 employees of a battery manufacturing plant (Kentner *et al.*, 1995). In the National Health and Nutrition Examination Survey (NHANES) the GM of Sb in urine and in urine corrected for creatinine was below the LoD (i.e., <0.07 μg/L), while the 50th percentile was 0.08 μg/L and μg/g creatinine corrected (CDC, 2009).

In a study carried out in 2001 in the region of Québec City, the means of Sb in urine were 0.04 μg/L and 0.05 μg/g of creatinine, respectively, and the 50th percentile was 0.05 μg/L and the same value when creatinine corrected. Levels of Sb in urine, blood and scalp-hair referred to a control group were determined by Gebel *et al*., values of 0.60 μg/24 h, 0.48 μg/L and 0.026 μg/g were found respectively (Gebel *et al*., 1998). In Italy, different human matrices have been investigated since 1990: in blood a mean value of 0.47 μg/L was found (Alimonti *et al*., 2005a); in serum mean values ≤0.5 μg/L were determined (Alimonti *et al*., 2005a; Minoia *et al*., 1990); in urine ≤0.79 μg/L (Alimonti *et al*., 2005b; Minoia *et al*., 1990); in cerebrospinal fluid (CSF) ≤0.44 μg/L (Alimonti *et al*., 2007a; Sabbioni *et al*., 1992).

PROBE results *(Table A1, Figure A1)*

BLOOD: no significant differences were found between two or more groups in each class.

SERUM: some differences among the groups were observed but they are difficult to interpret as serum Sb is not the most suitable biomarker of exposure.

3.2. Arsenic (As)

3.2.1. General information

IARC has assessed that inorganic As is carcinogenic to humans (Group 1) (IARC, 1987). US EPA also has classified inorganic As as a known human carcinogen. Arsenic is one of the most toxic elements that can be found and humans can be exposed to As through food, water and air. Exposure may also occur through skin contact with soil or water containing As. Levels of As in food are quite low but levels of fairly harmless organic forms of As (i.e. arsenobetaine, arsenocholine, trimethylarsine oxide and arsenosugars) in fish and seafood may be high. ACGIH provides an occupational Biological Effect Index (BEI) for urinary inorganic As plus metabolites equal to 35 μg/L (ACGIH, 2007). The Directive 98/83/CE set a value of 10 μg/L for As in drinking water (Council Directive 98/83/EC, 1998). Inorganic As is well absorbed from the gastrointestinal tract and to a lesser degree through inhalation, but is poorly absorbed by skin (WHO-IPCS, 2001). After absorption, inorganic As is widely distributed within the body.

3.2.2. Biomonitoring data

Urinary As level is a good biomarker of dose and reflects recent exposures (WHO-IPCS, 2001). Urinary As levels is considered a better predictor for risk of arsenical skin lesions than As levels in drinking water in Bangladesh (Ahsan *et al.*, 2000). Levels of total urinary As in the US population (NHANES) were 8.30 μg/L and 8.45 μg/g of creatinine as GM (CDC, 2009). In 1998, in the German Environmental Survey (GerES III), median urinary total levels of As varied with seafood intake, but As had decreased since the prior 1990-1992 survey, and these levels were about two-fold lower than those for the US population in NHANES 2003-2004 (Caldwell *et al.*, 2009; Schulz *et al.*, 2007). Some noncancerogenic effects of As (e.g., dermal keratosis, vasospasm, and peripheral neuropathy) have been associated with urinary levels as low as 50-100

µg/L in chronically exposed populations (ACGIH, 2001a; Blom *et al.*, 1985; Tseng *et al.*, 2006; Valenzuela *et al.*, 2005; WHO-IPCS, 2001). In Italy As levels in different matrices were investigated. For example in 1990 a mean of 7.9 µg/L in a study including 470 subjects was found as total As in blood (Minoia *et al.*, 1990). In the same study the average of total urinary As was 16.7 µg/L. In hair 0.08 µg/g as GM was found (Wolfsperger *et al.*, 1994). On few subjects a mean value of 0.21 µg/L was found in CSF (Sabbioni *et al.*, 1992).

PROBE results *(Table A2, Figure A2)*

No significant differences were found between two or more groups in each class.

3.3. Beryllium (Be)

3.3.1. General information

IARC has classified Be and Be-compounds in Group 1 (carcinogenic to humans) (IARC, 1993). US EPA has classified Be as a probable human carcinogen (US EPA, 1998) and EU contends that Be may cause cancer by inhalation. As Be is rarely found in drinking water at concentrations of concern, WHO not considered necessary to set a formal guideline value (WHO, 2001a). OSHA set a limit of 2 µg/m^3 as an 8-hour TWA in the workplace, but it has recently obtained information suggesting that limit for Be may not be adequate to prevent the occurrence of chronic beryllium disease, a disabling and often fatal lung disease, among exposed workers (ATSDR, 2002). The environmental exposure of the general population to trace amounts of Be is primarily by food and drinking water, with smaller contributions from air and incidental ingestion of dust. Other sources of exposure are represented by cigarette smoke and hazardous wastes (ATSDR, 2002). Effects on human health from low doses or environmental levels of Be are not known yet. Elimination is very slow and occurs primarily in urine. Unabsorbed Be is eliminated *via* faeces (WHO, 2001a).

3.3.2. Biomonitoring data

Urine is usually considered as biomarker to detect exposure to Be. Among the biomonitoring studies of the general population, urinary Be was detected in the US campaigns since 1999 (CDC, 2009) and results have been always below the LoD (0.013 µg /L). Apostoli and Schaller (Apostoli & Schaller, 2001), in fact, reported values between 0.12 and 0.15 µg/L in workers exposed at concentrations corresponding to the TLV (Apostoli & Schaller, 2001). In Italy in the last years Be were investigated in different human matrices, such as blood, serum, urine and CSF: 0.42 µg/L was the mean level found in blood (Alimonti *et al.*, 2005a); mean values ≤0.21 µg/L in serum (Alimonti *et al.,* 2005a; Minoia *et al.*, 1990); 0.4 µg/L in urine (Minoia *et al.*, 1990) and 0.70 µg/L in CSF (Alimonti *et al.*, 2007a).

PROBE results *(Table A3, Figure A3)*

BLOOD: no significant differences were found between two or more groups in each class.

SERUM: no smokers and smokers showed higher levels than ex smokers.

3.4. Cadmium (Cd)

3.4.1. General information

Cadmium has shown reproductive effects and teratogenicity in animal studies, as to be classified by IARC as carcinogenic to humans (Group 1) (IARC, 1993). In 2002, ACGIH set a TLV-TWA of 0.01 mg/m^3 as inhalable fraction and 0.002 mg/m^3 as respirable fraction for the occupational exposure (ACGIH, 2002). In EU the Directive 98/83/CE set a value of 5 μg/L for Cd in drinking water (Council Directive 98/83/EC, 1998). For the general population, with the exception of smoking, the main source of exposure to Cd is represented by food (EFSA, 2009a). The intake of Cd through drinking water is a minimum contribution to the total intake. The risk of absorption *via* dermal contact is negligible. However, levels of Cd may vary and are influenced by factors such as the intake of essential nutrients (iron, calcium, zinc, copper) and proteins. Cadmium exposure has been associated with nephrotoxicity, osteoporosis, neurotoxicity, carcinogenicity and genotoxicity, teratogenicity, endocrine and then reproductive effects. Exposures to low doses are, however, associated with increased levels of Cd in urine and blood, where Cd is bound mainly in red cells (> 90%) or to high molecular weight proteins.

3.4.2. Biomonitoring data

Cadmium levels in blood reflect both recent and chronic exposures. For exposures at low doses, such as environmental levels, Cd levels in urine were also able to account for exposure. The general population surveys conducted so far show similar values both in blood and urine (Becker *et al.*, 2003; Friedman *et al.*, 2006; Wilhelm *et al.*, 2006). In general, women show higher levels of Cd in blood and urine than men of similar age (Horiguchi *et al.*, 2004; Olsson *et al.*, 2002; Wennberg *et al.*, 2006). With regard to smoking, the levels of Cd in blood and urine are generally higher, even double than non-smokers (Becker *et al.*, 2003; Mannino *et al.*, 2004; Olsson *et al.*, 2002). The concentration of Cd in blood in the general population ranged from about 0.4 to 1.0 μg/L for no smokers and 1.4-4.0 μg/L for smokers (Elinder, 1985). NHANES found Cd in blood 0.304 μg/L as GM and 1.60 μg/L as 95th percentile (CDC, 2009). Environmental exposure can elevate blood Cd concentration to above 10 μg/L (Shiwen *et al.*, 1990), and workers occupationally exposed to Cd by inhalation may have blood levels ranging up to 50 μg/L (Roels *et al.*, 1981). In urine, NHANES found 0.211 μg/L as GM and 1.15 μg/L as 95th percentile, and very similar values if data were creatinine corrected (CDC, 2009). In Italy, for the general population, mean blood Cd concentrations ranged from 0.6 μg/L (Minoia *et al.*, 1990) to 1.09 μg/L (Alimonti *et al.*, 2009); in serum values from 0.07 μg/L (Alimonti *et al.*, 2009) to 0.2 μg/L (Minoia *et al.*, 1990) were found; in urine values <1 μg/L were reported (Alimonti *et al.*, 2009; Minoia *et al.*, 1990); in hair only one study reported a GM of 0.05 μg/g (Wolfsperger *et al*., 1994); in CSF mean values between 0.05 and 1.70 μg/L (Alimonti *et al.*, 2007a; Sabbioni *et al.*, 1992); in nails mean values ≤0.05 μg/g (Bergomi *et al.*, 2002; Bergomi *et al.,* 2005; Vinceti *et al.*, 2005) and concentrations <1.0 μg/L were found in breast milk (Coni *et al.*, 1990; Turconi *et al.*, 2004).

PROBE results *(Table A4, Figure A4)*

BLOOD: significantly higher concentrations were observed in smokers.

SERUM: no significant differences were found between two or more groups in each class.

3.5. Chromium (Cr)

3.5.1. General information

The hexavalent Cr is a toxic form that results from industrial pollution and it was classified as human carcinogen (Group 1) by IARC based on evidence in humans of an increased risk of respiratory cancers, primarily lung and naso-pharyngeal (IARC, 1980; IARC, 1990). For the occupational exposure to Cr dusts, that represents the main route of occupational exposure, ACGIH set a TLV-TWA of 0.5 mg/m^3 as Cr(III); 0.05 mg/m^3 as Cr(VI) water soluble compounds and 0.01 mg/m^3 as Cr(VI) water insoluble compounds. For the occupational exposure a urine BEI of 10 µg/g of creatinine during the 8-hr workshift as total Cr was set by ACGHI (ACGIH, 2002). Human exposure to Cr may occur by drinking water but the main source of Cr exposure for the general population is by food intake (93-98% of the total intake *vs.* 1.9-7% in water). Skin contact and tobacco smoke are other sources of exposure. In animal studies, Cr was found to accumulate mainly in liver, kidneys, spleen, and bone marrow after both oral and parenteral administration of different Cr compounds (Janus *et al.*, 1990). Animal studies show that urine is the major route of elimination of absorbed Cr (Janus *et al.*, 1990) and minor routes of excretion include breast milk, sweat, hair and nails (ATSDR, 2008). Because of the carcinogenicity of Cr(VI) by the inhalation route and its genotoxicity, in EU the current guideline value of 50 µg/L of total Cr in drinking water (Council Directive 98/83/EC, 1998) has been questioned, but the available toxicological data do not support the derivation of a new value.

3.5.2. Biomonitoring data

For the general population, an average urinary Cr excretion of 0.22 µg/L was set by the National Research Council (NAS/NRC, 1989). Literature data for the Italian general population reported mean levels of urinary Cr ≤0.61 µg/L (Alimonti *et al.*, 2009; Apostoli *et al.*, 1997; Minoia *et al.*, 1990). Blood Cr, is another accepted biomarker of exposure for the general population and in Italy mean levels ≤0.78 µg/L were found (Alimonti *et al.*, 2005a, Alimonti *et al.,* 2009; Minoia *et al.*, 1990). Other biological matrices were also investigated; in serum levels ≤0.17 µg/L were found (Alimonti *et al.*, 2005a; Alimonti *et al.,* 2009; Minoia *et al.*, 1990); in hair 0.68 µg/g (Wolfsperger *et al.*, 1994); in CSF ≤1.28 µg/L (Bergomi *et al.*, 2002); in nails ≤3.23 µg/g (Bergomi *et al.* 2002; Bergomi *et al.,* 2005; Vinceti *et al.*, 2005), in breast milk the range 0.027-3.0 µg/L as mean values (Aquilio *et al.*, 1996; Clemente *et al.*, 1982; Coni *et al.*, 1990).

PROBE results *(Table A5, Figure A5)*

No significant differences were found between two or more groups in each class.

3.6. Cobalt (Co)

3.6.1. General information

Based on the animal data, IARC has classified Co, Co compounds, Co-sulfate and other soluble Co(II) salts as possibly carcinogenic to humans (Group 2B) (IARC, 1991). The hydrous forms of Co dichloride are considered as toxic for reproduction and carcinogenic (Category 1B)

according to Annex VI of Regulation EC n. 1272/2008 (European Commission, 2008). Cobalt(II) cations are also considered genotoxic under *in vitro* and *in vivo* conditions (Commission Regulation No. 790/2009; EFSA, 2009b). The maximum OSHA permissible level (PEL) for metallic Co is 100 μg/m^3 of air as TWA; a BEI of 15 μg/L for urinary inorganic Co, except insoluble Co-oxides, has been set by ACGHI (ACGHI, 2000). People can be exposed to Co by breathing air, drinking water, eating food and by skin contact with soil, water, cobalt alloys, or other substances containing Co. Children may also be exposed to Co by eating filth. In general food is the largest source of Co intake. Industrial exposure to Co mainly from breathing Co-containing dust results in serious effects on lungs, including asthma, pneumonia and wheezing. After exposure Co is excreted from the body quickly by faeces and the rest is absorbed into blood and then into tissues, mainly liver, kidneys and bones. The absorbed Co leaves the body for the most part by urine. Skin exposure to Co can occur only if skin is damaged (ATSDR, 2004).

3.6.2. Biomonitoring data

Urinary levels of Co decline rapidly within 24 hrs after exposure (Alexandersson, 1988) and urinary measurements mainly reflect recent exposure. In non-occupationally exposed subjects, the urinary and serum Co are usually <2.0 μg/g creatinine and 0.4 μg/L respectively (ATSDR, 2004). In the last NHANES carried out in 2003-2004, the CDC found 0.316 μg/L as GM of urinary Co and 1.16 μg/L as 95th percentile; similar values if corrected by creatinine (0.314 μg/g and 1.02 μg/g, respectively) (CDC, 2009). In Italy mean values ≤0.39 μg/L in blood and in serum ≤0.21 μg/L were found (Alimonti *et al.*, 2005a; Alimonti *et al.,* 2009; Minoia *et al.*, 1990); while ≤0.57 μg/L in urine (Alimonti *et al.*, 2009; Minoia *et al.*, 1990) and 0.01 μg/g in hair were found (Wolfsperger *et al.*, 1994).

PROBE results *(Table A6, Figure A6)*

BLOOD and SERUM: significant differences were observed in the gender class with a larger content of Co in females.

3.7. Iridium (Ir)

3.7.1. General information

Iridium together with Os, Pd, Pt, Rh and Ru is included in the so-called Platinum Group Elements (PGEs). Although the PGEs are relatively inert, these metals undergo environmental transformations into more reactive species which may be bioavailable (Philippeit & Angerer, 2001; Rauch *et al.*, 2001). Data on Ir toxicity are still few, so occupational limits neither drinking water limits have been set by institutions, nor Ir has been classified by IARC (Stellman, 1998). Thus, the increasing industrial use of Ir, especially in automotive catalysts could result in a higher exposure by inhalation for workers exposed to vehicle traffic as well as for the general population (Botrè *et al.*, 2007). Iridium deposited at bronchial and bronchiole level was then eliminated by lungs, with a half time of 6 hrs, while metal particles accumulated in the pulmonary parenchyma had a slower clearance, with a half time of 22-24 days. The material removed from lungs was then found in the gastrointestinal tract and thus eliminated in faeces, for 96% of the absorbed dose. Gastrointestinal absorption is moderate (Casarett & Doull,

1969) as well as the distribution to other organs and urinary excretion. There is not much information on the health effects caused by Ir, except for some occupational case reports of contact dermatitis (Bergman *et al.*, 1995; Cristaudo *et al.*, 2005; Santucci *et al.*, 2000; Sheard, 1955).

3.7.2. Biomonitoring data

Few biomonitoring data concerning Ir are available: one study has been performed by Becker *et al*. (Becker *et al.*, 2003) during the GerES III in 1998 and mean levels of urinary Ir of 0.41 ng/g of creatinine were set. In Italy one study carried out on subjects living in Northern Italy by Minoia *et al*. reported urinary Ir levels of 18 ng/L (Minoia *et al.,* 1990). Another study performed by Iavicoli *et al*. (Iavicoli *et al.*, 2008) was carried out in order to assess the degree of exposure of municipal drivers and urban general population. In this study no differences between the two groups were noticed and mean levels of urinary Ir of 13.4 ng/L (11.2 ng/g creatinine corrected) for the control group and 13.8 ng/L (9.24 ng/g creatinine corrected) for the tram drivers were found.

PROBE results *(Table A7, Figure A7)*

BLOOD: males showed significantly higher Ir concentrations than females.

SERUM: significant higher levels were observed in the youngest group in comparison with the elders. The no alcohol consumers showed Ir levels higher than drinkers.

3.8. Lead (Pb)

3.8.1. General information

Lead is a toxic element and IARC classified inorganic Pb compounds in Group 2A, as probable human carcinogens (IARC, 2006). Workplace standards and guidelines for Pb exposure and monitoring have been established by ACGIH: a TLV-TWA of 0.05 mg/m^3 and a BEI of 300 μg/L for Pb in blood (ACGHI, 2002). The European Directive 98/83/CE for drinking water quality established for Pb a maximum level of 10 μg/L (Council Directive 98/83/EC, 1998). Lead enters the environment from a variety of natural and human source and the historical use of leaded fuels also resulted in a wide environmental distribution of Pb (WHO, 2000). Exposure to Pb occurs in many industrial activities especially due to battery and radiator manufacturing; the general population is exposed to Pb through soil, household dust, food, drinking water and air. The effects of Pb are the same whether it enters the body through breathing or swallowing. The main target for Pb toxicity is the nervous system, both in adults and children and even in foetuses and infants (ATSDR, 2007).

3.8.2. Biomonitoring data

Blood Pb is the matrix of choice to evaluate human exposure to Pb, but other matrices such as urine, bone, hair, and teeth can also been used. In a general population survey in Germany a GM of 30.7 μg/L of blood Pb was reported (Becker *et al.*, 2002), while in USA the latest NHANES survey (2003-2004) reported a GM of 14.3 μg/L (CDC, 2009). In a study carried out

in the region of Québec City the GM and the 90th percentile of blood Pb were 21.5 and 42.1 μg/L, respectively (INSPQ, 2004). In Italy Pb was investigated in several matrices: mean levels from 26.4 to 157.7 μg/L were found in blood (Alimonti *et al.*, 2005a; Alimonti *et al.,* 2009; L'Abbate *et al.*, 1991; Minoia *et al.*, 1990); levels between 0.24 and 0.54 μg/L in serum (Alimonti *et al.*, 2005a; Alimonti *et al.,* 2009; Minoia *et al.*, 1990); values ranging from 1.80 to 17.0 μg/L in urine (Alimonti *et al.*, 2007a; Minoia *et al.*, 1990), whilst Wolfsperger *et al.* reported a GM of 1.92 μg/g for Pb in hair (Wolfsperger *et al.*, 1994). In 2007 a study investigated Pb in CSF and a mean value of 0.91 μg/L was found (Alimonti *et al.*, 2007b). Furthermore, in nails mean values ≤1.22 μg/g (Bergomi *et al.*, 2002; Bergomi *et al.,* 2005; Vinceti *et al.*, 2005) and in breast milk levels ≤0.9 μg/g (Coni *et al.*, 1990; Perrone *et al.*, 1994) and ≤126.5 μg/L (Guidi *et al.*, 1992; Turconi *et al.*, 2004) were found.

PROBE results *(Table A8, Figure A8)*

BLOOD: differences were observed in all classes; a major content of Pb was noticed in males than in females; in the age class the effect of the increasing age on the concentration of Pb was evident; the smokers and the ex smokers have a higher concentration than no smokers; Pb was higher in alcohol consumers than in no consumers.

SERUM: also in this matrix, higher levels of Pb were found in the smokers and ex smokers than in no smokers.

3.9. Manganese (Mn)

3.9.1. General information

IARC has not published an evaluation of the carcinogenicity of Mn (ATSDR, 2000). For US EPA Mn is not classifiable as to human carcinogenicity (absence of human data and inadequate animal data, Group D) (US EPA, 1996). Due to the health effects resulting from occupational exposure most of the industrialized countries have established occupational exposure limits for Mn: ACGIH set a TLV (8-hr TWA) for Mn of 0.2 mg/m^3 (ACGIH, 2007). WHO has established a health-based drinking water guideline for Mn of 400 μg/L (WHO, 2004a) whilst a value of 50 μg/L is the limit set by the European Directive 98/83/CE (Council Directive 98/83/EC, 1998). Manganese is an essential nutrient for the maintenance of human health and it is involved in the formation of bone, cellular protection from free radical damage, and aminoacid, cholesterol, and carbohydrate metabolism, but the excessive exposure to Mn can cause neurological effects (such as parkinsonism) (ATSDR, 2000; IOM, 2001). Food is the main source of Mn exposure for the general population and the main routes of absorption are the respiratory and gastrointestinal tracts (ATSDR, 2000). Biliary excretion is the main excretory pathway and a large fraction of the element is excreted in faeces (Davis *et al.*, 1993; Malecki *et al.*, 1996).

3.9.2. Biomonitoring data

Concentrations in blood and urine can be used to evaluate exposure to Mn. Whole blood is preferred rather than plasma or serum as blood concentrations tend to reflect the overall body burden of Mn. Concentrations in urine are more commonly used to measure levels following

acute exposure as urine is only responsive to significant fluctuations in Mn intake (IOM, 2001). The reference range for Mn is approximately from 4 to 14 μg/L in whole blood, from 0.15 to 2.65 μg/L in serum, and from 0.97 to 1.07 μg/L in urine (ATSDR, 2000). In the 3rd NHANES, Mn detected in urine samples was 1.19 μg/L as mean (CDC, 2009). In the Québec City region, GM and 90th percentile values of Mn in blood amounted to 9.33 μg/L and 13.74 μg/L, respectively (INSPQ, 2004). In Italy, Mn has been investigated in different human fluids and tissues: in blood Mn concentrations ranged from 7.63 to 8.80 μg/L as mean values and in serum mean values ≤0.62 μg/L were found (Alimonti *et al.*, 2005a, Alimonti *et al.*2009; Minoia *et al.*, 1990); in urine mean levels ranged from 0.22 to 1.02 μg/L (Alimonti *et al.*, 2009; Minoia *et al.*, 1990); in hair 0.28 μg/g (Bocca *et al.*, 2006b), in CSF 0.95 μg/L (Alimonti *et al.*, 2007a) and in nails 0.8 μg/g were found as mean values (Bergomi *et al.*, 2002).

PROBE results *(Table A9, Figure A9)*

BLOOD: main significant differences were observed in the alcohol class (no drinkers with higher levels) and then in the smoking class (no smokers with higher levels).

SERUM: no significant differences were found between two or more groups in each class.

3.10. Mercury (Hg)

3.10.1. General information

Mercury is known to be toxic to both humans and the environment. IARC determined that methyl-Hg compounds are possible human carcinogens (Group 2B), and metallic Hg and inorganic Hg compounds were put in Group 3B, not classifiable as to their carcinogenicity (IARC, 1993). Occupational limits for elemental and inorganic Hg were placed: ACGIH set a TLV-TWA of 0.025 mg/m^3, a BEI of 35 μg/g creatinine for total Hg in urine and a BEI of 15 μg/L for total inorganic Hg in blood (ACGHI, 1996). EU set a value of 1.0 μg/L for Hg in drinking water (Council Directive 98/83/EC, 1998). Exposure of the general population is primarily to methyl-Hg and occurs *via* contaminated fish and seafood. To a much lesser extent, the general population is exposed to inorganic Hg from dental amalgams but this kind of exposure has not been definitely associated with neurologic effects (Bates *et al.*, 2004; Bellinger *et al.*, 2006; DeRouen *et al.*, 2006; Factor-Litvak *et al.*, 2003). The inorganic Hg represents 14-26% of the total Hg in blood (Kingman *et al.*, 1998). About 95% of organic Hg is absorbed from the gastrointestinal tract and distributed to all tissues, including hair, with the highest accumulation in kidneys (ATSDR, 1999a). The majority of Hg in the body is excreted *via* faeces, with a small amount excreted as inorganic Hg in urine (ATSDR, 1999a). The toxic effects of Hg depend on the form and exposure route and included respiratory, cardiovascular, renal and neurological effects.

3.10.2. Biomonitorng data

Human exposure to Hg is generally evaluated by measuring Hg levels in blood and urine, although hair can be used as a biomarker of exposure (ATSDR, 1999a). Typically, blood and urine Hg levels are reported as total Hg, which comprises inorganic and organic forms of Hg. The concentration of total Hg in blood is accepted as a reasonable measure of methyl Hg exposure. WHO estimated that the mean total blood Hg concentration for the general population

is *ca*. 8 μg/L; however, high fish consumers can have blood concentrations as high as 200 μg/L (ATSDR, 1999a). Typical total Hg concentrations in urine ranged 4-5 μg/L. In the region of Québec City, GM and the 90th percentiles of total Hg in blood were 0.74 μg/L and 2.01 μg/L, respectively (INSPQ, 2004). In Germany the GM for blood Hg was 0.58 μg/L for adults in a population survey in 1998 (Becker *et al.*, 2002). In 1216 blood donors from the Czech Republic (1996-98) a median concentration of blood Hg of 0.78 μg/L for adults and 0.46 μg/L for children was found (Benes *et al.*, 2000). In NHANES survey a GM of 0.797 μg/L for total Hg in blood and a GM of 0.447 μg/L (0.443 μg/g creatinine) in urine were found (CDC, 2009). In Italy mean Hg ranges for the general population were 3.49-6.36 μg/L in blood, 1.32-2.1 μg/L in serum (Alimonti *et al.*, 2005a; Alimonti *et al.,* 2009; Minoia *et al.*, 1990) and 1.15-3.5 μg/L in urine (Alimonti *et al.*, 2009; Apostoli *et al.*, 2002; Minoia *et al.*, 1990; Soleo *et al.*, 2003). In two studies levels of Hg in CSF ≤1.05 μg/g were found (Alimonti *et al.*, 2007; Sabbioni *et al.*, 1992).

PROBE results *(Table A10, Figure A10)*

BLOOD: males showed significant higher Hg concentrations than females.

SERUM: no significant differences were found between two or more groups in each class.

3.11. Molybdenum (Mo)

3.11.1. General information

Molybdenum has not been systematically evaluated for carcinogenicity by IARC (US EPA, 1993). It is considered to be an essential element with an estimated daily requirement of 0.1-0.3 mg for adults (WHO, 1996; WHO, 2003a). The general population is mainly exposed to Mo *via* water and locally produced food. WHO recommends a maximum level of Mo in drinking water of 0.07 mg/L (WHO, 2003a). Following gastrointestinal absorption, Mo rapidly appears in blood and in most organs with the highest concentrations in liver, kidneys and bones (WHO, 1996; WHO, 2003a). Urinary excretion of Mo is intense and rapid in the few hours (IMOA, 2007). Molybdenum is considered to be medium toxic, but chronic exposure to very high levels of Mo (the more toxic hexavalent molybdate ion) may result in higher serum uric acid levels. Other symptoms include gout, severe diarrhea, growth depression, and anaemia (US EPA, 1993). The Panel on Micronutrients of the Institute of Medicine (IOM) identified a no observed adverse effect level (NOAEL) of 0.9 mg/kg/day and established a tolerable upper intake level of 0.03 mg/kg/day in humans (IOM, 2001). A long term inhalation bioassay of Mo-trioxide in mice yielded "some evidences" of carcinogenicity (NTP, 1997), but available epidemiologic data are scant.

3.11.2. Biomonitoring data

Serum, plasma and whole blood Mo levels are associated with its intake (Turnlund & Keyes, 2004). The values of Mo in blood are slightly higher than those reported for plasma and serum, because this metal is firmly bound to the erythrocyte and plasma proteins. In Canada, GM and 90th percentiles for blood Mo were 1.14 μg/L and 1.90 μg/L, respectively (INSPQ, 2004). In Italy, reference ranges of 1.02-6.03 μg/L (mean of 3.06 μg/L) for blood Mo were assessed (Alimonti *et al.*, 2005a). Similarly, in blood donors living in Venezuela the GM for blood Mo was 2.66 μg/L (range, 1.20-4.80 μg/L) (Burguera & Brown, 2007). These range values overlapped most

information available in the literature, such as the results reported by Heitland and Köster (range, 0.06-4.00 μg/L) (Heitland & Köster, 2006) and Iyengar and Woittiez (range, 0.8-3.3 μg/L) (Iyengar *et al*., 1985; Iyengar & Woittiez, 1998). In serum, a Mo level of 0.5-0.6 μg/L was proposed for the general population (Versieck & Cornelis, 1980), and later reports would suggest slightly higher values, *ca.* 0.8 μg/L (Alimonti *et al*., 2005a). In urine, GM and 90th percentile values were 44.25 μg/L and 115.16 μg/L, respectively (INSPQ, 2004). In USA, adults showed GM and 95th percentile values for urinary Mo of 35.9 and 133 μg/L (36.9 and 118 μg/g of creatinine, respectively) (CDC, 2009). These levels were similar to those reported for smaller European population surveys. For instance, in Danish inhabitants the reference interval for Mo in urine was 10.0-124.0 μg/L (mean, 42.5 μg/L) (Iversen *et al.*, 1998); in Italy the mean urinary Mo was 36.9 μg/L (Alimonti *et al.*, 2009). In CSF, Mo values were found in the range 0.45-3.3 μg/L (Alimonti *et al.*, 2007; Sabbioni *et al.*, 1992).

PROBE results *(Table A11, Figure A11)*

BLOOD: significant differences were found in the alcohol class with no drinkers with higher levels of Mo.

SERUM: ex smokers showed higher levels than the other groups and the no drinkers showed significant higher Mo concentrations than drinkers.

3.12. Nickel (Ni)

3.12.1. General information

In 1990, IARC classified all Ni compounds, except metallic Ni, as carcinogenic to humans in Group 2B (IARC, 1990). A very important source of Ni exposure in human populations is dietary; furthermore, Ni is widely used in alloys and products that come into repetitive contact with the skin, *e.g.,* jewellery, buttons, coins, intrauterine devices, household cleanings and cosmetics (ATSDR, 2005a; Basketter *et al.*, 2003; Petrucci *et al.*, 2009). Other sources of Ni exposure for the general population include air, drinking water, soil, and household dust (WHO, 1991). ACGIH set a TLV-TWA of 1.5 mg/m^3 for metallic Ni, 0.1 mg/m^3 for soluble compounds, 0.2 mg/m^3 for insoluble compounds (ACGIH, 2007). A Canadian study assessed that metallic Ni was not a concern for human health at current levels of exposure, while the oxidic-, sulphidic- and soluble-Ni compounds are entering the environment under conditions that may constitute a danger to human life (Environment Canada and Health Canada, 1994).The most common health effect related to Ni is the allergy; in Europe and in USA, the prevalence rates of allergic contact dermatitis to Ni are of *ca.* 20% (Bocca *et al.*, 2009; ESSCA, 2004). Approximately 20-35% of inhaled Ni is absorbed in blood (ATSDR, 2005a), while only 1-10% of ingested Ni is absorbed depending largely on the composition of the diet (WHO, 1991). Nickel is excreted in urine and faeces, and has an estimated half-life from 17 to 48 hrs (Nieboer & Fletcher, 2001). Nickel can also be measured in hair and breast milk and in organs as lungs, thyroid, adrenals, kidneys, heart, liver, brain, spleen, and pancreas (Sunderman, 1993).

3.12.2. Biomonitoring data

A RV of 3.0 μg/L for urinary Ni was proposed based on studies with adults performed in Denmark, Finland, Germany, Italy, Norway, Russia and USA (German Human Biomonitoring

Commission, 2001). In a large HBM survey performed in the Québec City region, GM and 90th percentiles of urinary Ni were 1.78 μg/L and 4.46 μg/L, respectively (INSPQ, 2004). Smaller studies reported a median value for urinary Ni of 1.7 μg/L in UK citizens (White & Sabbioni, 1998) and a mean content of 0.87 μg/L in Italian people (Alimonti *et al.*, 2009). The RVs for blood Ni were <0.59 μg/L and 0.85 μg/L as GM and 90th percentile in Canada (INSPQ, 2004); 0.08 μg/L as GM in Germany (Heitland & Köster, 2006); 0.89 μg/L as mean in Italy (Alimonti *et al.*, 2005a). In serum, a tentative RV for Ni of 0.47 μg/L, with a related interval between 0.23-1.03 μg/L, was reported (Bocca *et al.*, 2006a). These levels were quite similar across the different countries, *i.e.,* USA (Sunderman, 1984), Canada (Hopfer *et al.*, 1987), Denmark (Andersen *et al.,* 1986; Bro *et al.*, 1988; Christensen *et al.*, 1999) and Macedonia (Todorovska *et al.*, 2002). Increased serum levels were found in traffic police officers (Tomei *et al.*, 2004) and electroplating workers (Todorovska *et al.*, 2002). A smaller but significant increase in serum Ni content occurred in individuals after metal-on-metal alloarthroplasty of the hip, with a peak concentration of 2.16 μg/L (Dahlstrand *et al.*, 2009).

PROBE results *(Table A12, Figure A12)*

BLOOD: no significant differences were found between two or more groups in each class.

SERUM: no drinkers showed significant higher Ni concentrations than drinkers.

3.13. Palladium (Pd)

3.13.1. General information

Palladium has not been classified as carcinogenic either by IARC or OSHA or US EPA. The output and use of Pd has more than doubled in the past ten years, as it is a suitable substitute in the industry of alloys, in telecommunication equipments, as a catalyst in white gold and in most cast dental restorations and amalgams (dental alloys and white gold may contain up to 10% and 20% of Pd, respectively) as well as in cars catalytic converters (WHO-ICPS, 2002). As a consequence, many studies found an enrichment of Pd in air, soil, dust and plants in urban areas where Pd-catalysts are used (Bocca *et al.*, 2003b; Petrucci *et al.*, 2000). There is no information on the effects of Pd emitted from automobile catalytic converters on the general population, while effects have been reported due to iatrogenic and other exposures. Since 1990, multiple reports have documented patients showing allergic reactions to soluble Pd compounds (especially Pd chloride) also reflecting a cross-sensitization to other metals as Co, Cr and Ni (Cristaudo *et al.*, 2005). Oral symptoms (mucositis, stomatitis, and oral lichen planus) are associated with exposure to Pd-containing dental restorations (Fernández-Redondo *et al.*, 1998). Skin symptoms like granuloma may occur by contact with jewellery and ear piercing (Thijs *et al.*, 2008).

3.13.2. Biomonitoring data

The mean Pd level in urine of the general Italian adult population was equal to 7.7 ng/L (Bocca *et al.*, 2004), while in Germany the level ranged 13.1-48.3 ng/L (Begerow & Dunemann, 2000). Other data for urinary Pd in healthy subjects were equal to 9.5 ng/L and 9.1 ng/L (Benkhedda *et al.*, 2003; Krachler *et al.*, 1998). As regards blood, two German surveys reported mean Pd concentrations of 50.2 ng/L (range 32-78 ng/L) and <20 ng/ (range between <20-90 ng/L) (Begerow *et al.*, 1997; Heitland & Köster, 2006); similar Pd concentrations in blood were

found in Sweden, in unexposed individuals (median 35 ng/L, range 9-125 ng/L) (Rodushkin *et al.*, 1999). In serum, Pd mean concentrations of 23.1 ng/L and 50 ng/L were found in the literature (Benkhedda *et al.*, 2003; Rauch *et al.*, 2000). In occupationally exposed subjects like dental technicians, traffic controllers and catalyst production plant workers, the Pd levels in urine were higher than those found in the general population (Begerow *et al.*, 1999b; Begerow & Dunemann, 2000; Violante *et al.*, 2005).

PROBE results *(Table A13, Figure A13)*

BLOOD: no significant differences were found between two or more groups in each class.

SERUM: differences were observed in males with a major content of Pd; among the age groups the increasing age affects the concentration of Pd.

3.14. Platinum (Pt)

3.14.1. General information

Some Pt complexes, utilised as tumour treatment agents, are mutagenic and suspected human carcinogens (e.g., cisplatin in Group 2A) (IARC 1981). Platinum is used in electrodes, jewellery, dental alloys, thick-film circuits, as oxidation catalysts in chemical manufacturing, and as drugs in the treatment of cancer (e.g., cisplatin, carboplatin) (WHO, 1991). Platinum-Rh and Pt-Pd crystals are used as catalysts in vehicular catalytic converters to control exhaust emissions and increased Pt concentrations in environmental samples have been reported since the introduction of vehicles catalysts (Bocca *et al.*, 2003b; Petrucci *et al.*, 2000). Besides the exposure to Pt *via* air, there is a no negligible dietary uptake of Pt (Vaughan & Florence, 1992). Toxicity of Pt is determined by the type of compound; metallic Pt is biologically inert, whereas soluble Pt compounds, the most effective of which are chlorides, can cause hypersensitivity with symptoms that include bronchitis and asthma after inhalational exposure and contact dermatitis after skin exposure (WHO, 1991). Once ingested or inhaled, Pt metal and insoluble Pt salts are poorly absorbed (<1% of a dose) and cleared from the body within a week after a single dose. The principal deposition sites of Pt are kidneys and liver, and excretion mainly occurs in faeces and urine. In addition, new findings obtained in *in vitro* experiments suggested the potential interactions of Pt with enzymatic systems as well as with antioxidant substances, namely with NADH (Nicotinamide Adenine Dinucleotide Hydrogen) and ascorbic acid (Botrè *et al.*, 2007). Workplace air standards for external exposure are established at 1 mg/m^3 (expressed as TWA) for metal Pt and 0.002 mg/m^3 for soluble salts of Pt by OSHA, ACGIH and National Institute for Occupational Safety and Health (NIOSH) (Czerczak & Gromiec, 2000).

3.14.2. Biomonitoring data

The German RV for urinary Pt was set to 10 ng/L for groups without dental precious metals. Several studies have shown that background concentrations were usually equal or less than 10 ng/L (Wilhelm *et al.*, 2004; Herr *et al.*, 2003; Iavicoli *et al.*, 2004; Schierl *et al.*, 1998). Levels of Pt in urine for the USA population were below the LoD (40 ng/L) (CDC, 2009). In Italy, a tentative RV of 5.3 ng/L for urinary Pt was proposed for the general population (Spezia *et al.*, 2005). Blood levels of Pt given as baseline in the German population ranged 0.3-1.3 ng/L (Begerow *et al.*, 1997) and were in accordance with values reported by Messerschmidt *et al.* (<0.8-6.9 ng/L) (Messerschmidt *et al.*, 1992). Gold-platinum dental restorations increased urinary

Pt concentrations by 5 to 20-fold (Begerow *et al.*, 1999a; Herr *et al.*, 2003; Schierl, 2001). Another study found differences in the urinary Pt depending on the number of hip-endoprostheses (Zeinera *et al.*, 2009). Platinum-industry and precious-metal workers had urinary Pt concentrations about 100-times higher than general populations (Schierl *et al.*, 1998), while elevations in urinary Pt concentrations were modestly (10 times or less) associated with the handling of cisplatin and carboplatin by pharmacy and other hospital personnel (Ensslin *et al.*, 1997; Pethran *et al.*, 2003).

PROBE results *(Table A14, Figure A14)*

BLOOD: males showed significant higher Pt concentrations than females and drinkers than no drinkers.

SERUM: no drinkers showed higher Pt levels than drinkers.

3.15. Rhodium (Rh)

3.15.1. General information

Rhodium is not listed by IARC, OSHA or ACGIH as a carcinogenic metal. The increasing use of Rh in automotive catalysts and in Rh-plating jewellery has caused its increased concentration in the environment; a 27-fold enhancement in the Rh levels in air was observed over a 10-year period (Zereini *et al.*, 2001). Studies on Rh chloride metabolism in rats revealed that Rh is poorly absorbed. Initial rapid elimination of Rh occurred in urine and later via the gastrointestinal tract. Rhodium was mainly accumulated in kidneys and liver, but minor fractions are also found in soft tissues (Wiseman & Zereini, 2009). The few studies on Rh toxicity indicated that Rh salts are slightly toxic by oral ingestion and mild skin irritants (Santucci *et al.*, 2000). Rhodium was also reported as sensitizer in subjects with dental prostheses (Vilaplana *et al.*, 1994). Some cytotoxic and mutagenic properties of Rh salts, potassium pentachlororhodate(III) and ammonium hexachlororhodate(III), have been ascertained, although by far lower than that of some Pt complexes (Bünger *et al.*, 1996).

3.15.2. Biomonitoring data

Concentrations of Rh in urine samples of healthy subjects of 4.52 ng/L were found (Benkhedda *et al.*, 2003). In Italy, background levels of urinary Rh had a strong dependence on the area of residence, with mean values of 5.32 ng/L in subjects living in a rural area and 15.3 ng/L in individuals living in a urban one (Bocca *et al.*, 2004). Rhodium urinary levels differed significantly between the control group (12.2 ng/L) and tram drivers (21.7 ng/L) (Iavicoli *et al.*, 2007), although these data were lower than those found in catalyst production plant workers (range 50-270 ng/L) (Cristaudo *et al.*, 2007). Levels of Rh in blood of 130 healthy subjects from Germany were: 6 ng/L as GM with a range of 6-9 ng/L (Heitland & Köster, 2006). In Sweden, the concentration of Rh in blood of unexposed individuals was below 9 ng/L (Rodushkin *et al.*, 1999).

PROBE results *(Table A15, Figure A15)*

BLOOD: females showed significant higher Rh concentrations than males and no drinkers than drinkers.

SERUM: females showed significant higher Rh concentrations than males.

3.16. Thallium (Tl)

3.16.1. General information

US EPA considers the evidence for the carcinogenicity of Tl and Tl compounds as inadequate (US EPA, 2009). Thallium exposure occurs primarily from industrial processes such as coal-burning and smelting. Because of its toxicity, Tl was included in the list of 129 so called "priority pollutants" by the USA (US EPA, 1992). Relatively high-dose ingestion can result in gastrointestinal symptoms followed by multi-organ failure, neurologic injury and death. Chronic high-level exposures have been associated with weight loss, arthralgias and polyneuropathy (ATSDR, 2005b). Workplace air standards for Tl external exposure are established by OSHA (0.1 mg/m^3 as permissible exposure limit, PEL) and ACGIH (0.1 mg/m^3 as TLV). NIOSH has recommended that 15 mg/m^3 of Tl can be considered immediately dangerous to health. A drinking water Maximum Contaminant Level (MCL) at 2 μg/L has been established by EPA (US EPA, 1992). Following exposure, Tl is rapidly distributed to blood and to kidneys, liver, and muscle. Over the next 4-48 hrs, Tl is distributed into the central nervous system. Thallium readily crosses the placenta and also distributes into breast milk. Thallium is primarily eliminated through faeces and urine, but the elimination is slow with an elimination half-life of 3-30 days (Blanchardon, 2005); due to this prolonged elimination phase, Tl may act as a cumulative poison.

3.16.2. Biomonitoring data

The GM and 95th percentile of Tl in urine for the USA population were 0.14 μg/L (0.15 μg/g of creatinine) and 0.42 μg/L (0.33 μg/g of creatinine) in 20 years and older subjects (CDC, 2009). Other two recent studies reported values of Tl in urine ranging 0.049-0.43 μg/L (Heitland & Köster, 2006; Rodushkin *et al.*, 2004). These urine levels are generally comparable to levels observed in earlier studies (Apostoli *et al.*, 1988; Minoia *et al.*, 1990; White & Sabbioni, 1998). In blood, Minoia *et al.* (1990) found Tl in the range 0.1-1.1 μg/L (mean, 0.39 μg/L), Kemper and Bertram (1991) reported an interval of 0.2-2.0 μg/L, while White and Sabbioni (1998) proposed lower values (0.01-0.05 μg/L).

A study performed in Italy on blood donors reported a mean of 0.04 μg/L for Tl in serum (5th-95th percentiles, 0.02-0.09 μg/L) and 0.07 μg/L in blood (5th-95th percentiles, 0.03-0.15 μg/L) (Alimonti *et al.*, 2005a). On healthy volunteers the following Tl reference ranges were proposed in different matrices: 0.011-0.035 μg/L in blood, 0.01-0.24 μg/ in plasma, and 0.07-0.84 μg/L in urine (Goullé *et al.*, 2005). In asymptomatic workers urinary Tl concentrations were 500-times higher than background levels and these values are thought to correspond to workplace exposures at the TLV of 0.1 mg/m^3 (Marcus, 1985). In people living near a Tl-emitting cement plant in Germany, the urine contained Tl > 1 μg/L (Brockhaus *et al.*, 1981).

PROBE results *(Table A16, Figure A16)*

BLOOD: strong significant differences were found between drinkers and no drinkers (higher levels).

SERUM: both in the smoking and the alcohol classes the differences were due to the higher levels of Tl in no smokers and no drinkers.

3.17. Tin (Sn)

3.17.1. General information

The USA Department of Health and Human Services (DHHS), IARC and EPA have not classified metallic Sn or inorganic Sn compounds for carcinogenicity. Tin is released into the environment by both natural processes and human activities, such as mining, coal and oil combustion, but food, particularly canned food, represents the major route of human exposure to Sn (JECFA, 1989). Estimates of the mean daily intake of Sn vary from 0.1 to 100 mg (JECFA, 2000; WHO-ICPS, 1980). Exposure to some organotins (*i.e.,* dibutyltin, tributyltin, triphenyltin) can occur by eating seafood from coastal waters or from contact with household products that contain organotin compounds (i.e., some plastics) and with biocides (ATSDR, 2005c). The toxicity of metallic Sn and inorganic Sn compounds (except tin hydrides) to animal species is low; nevertheless, high doses of inorganic Sn can affect the central nervous system (WHO-ICPS, 1980). Vomiting, diarrhoea, fatigue and headache were often observed following the consumption of canned products (JECFA, 1982). Organotin compounds are more toxic than inorganic Sn; they have been shown to affect the immune system and the reproductive system in animals (ATSDR, 2005c). Both elemental Sn and inorganic Sn compounds are poorly absorbed from the gastrointestinal tract (less than 5%); while short-chain alkyl-tins and organo-inorganic salt forms (*e.g.* triethyltin chloride) are well absorbed (WHO-ICPS, 1980). Highest tissue concentrations of inorganic and organic Sn were found in bone, kidneys and liver. Absorbed inorganic tins are at least 85% excreted *via* urine, and organic forms are split between urine and bile depending on the organic component. The biological half-time of inorganic Sn in the body is about 100 days, while organic Sn varies in its tissue residence times (WHO-ICPS, 1980).

3.17.2. Biomonitoring data

Studies on Sn in human fluids are scarce. In 1980, Sn in blood was found to be below 2 µg/L (Byrne & Kosta, 1979) and, in 1990, a mean Sn in human serum of 0.50 µg/L with a range of 0.40-0.64 µg/L was obtained (Versieck & Vanballenberge, 1991). More recently, in healthy donors, reference ranges (5^{th}-95^{th} percentiles) for Sn were 0.11-1.75 µg/L (median, 1.1 µg/L) in blood, 0.05-2.28 µg/L (median, 0.32 µg/L) in serum and 0.007-0.34 µg/L (median, 0.05 µg/L) in urine (Goullé *et al.*, 2005). The same percentiles were observed in an Italian biomonitoring campaign on healthy adults: 0.27-1.69 µg/L (median, 0.53 µg/L) in serum and 0.63-2.61 µg/L (median, 1.48 µg/L) in blood (Alimonti *et al.*, 2005a). In human urine a mean Sn concentration of 0.90 µg/L was reported in 2008 for healthy subjects (Alimonti *et al.*, 2009).

PROBE results *(Table A17, Figure A17)*

BLOOD: no significant differences were found between two or more groups in each class.

SERUM: considering the gender a major content of Sn was noticed in males. Moreover, ex smokers showed a larger Sn concentration than the other groups.

3.18. Tungsten (W)

3.18.1. General information

Tungsten has not been classified with respect to its carcinogenicity by either IARC or NTP. Tungsten is released into the environment in particular via the transformation and transport mechanisms of tungsten-containing minerals (ATSDR, 2005d; Koutsospyros *et al.*, 2009). Ingestion of drinking water (containing the soluble tungstate salts) is the main route of W exposure for the population at large. It usually accumulates in liver, spleen, skeleton and kidneys (Leggett, 1997); main concentrations are in liver because W inhibits or replaces Mo in different liver enzymes. The toxicological profile of W remains rather sketchy. Occupational exposure provides indications of a possible role for metal W and tungsten-carbides in *hard metal disease*, a condition that may often be followed by pulmonary fibrosis (Catalani *et al.*, 2004). The regulation on W and W compounds provides a PEL in air of 1 mg/m^3 (TWA) for soluble W compounds and 5 mg/m^3 for insoluble W compounds (TWA) and a Short Term Exposure Limit (STEL) of 3 and 10 mg/m^3 (NIOSH, 1977). ACGIH has established TLVs for insoluble W compounds at 5 mg/m^3 (TWA) and at 10 mg/m^3 (STEL) (ACGIH, 2001b). Respective values for soluble W compounds stand at 1 mg/m^3 (TWA) and 3 mg/m^3 (STEL) (ACGIH, 2001b). In the former Soviet Union, regulations included a maximum allowable concentration (MAC) as a quantitative criterion of environmental pollution by W. The MAC values for W in drinking water and fishing water reservoirs are 0.05 and 0.0008 mg/L, respectively (Strigul *et al.*, 2009).

3.18.2. Biomonitoring data

For the USA adult population, a GM concentration for urinary W of 0.063 µg/g of creatinine (or 0.062 µg/L) was reported (CDC, 2009). A study of unexposed adults yielded values similar to those found in the USA individuals (Schramel *et al.*, 1997). For the Italian population, reference ranges for W (5th-95th percentiles) were: 0.015-0.149 µg/L in urine; 0.01-0.06 µg/L in serum and 0.03-0.14 µg/L in blood (Alimonti *et al.*, 2005a; Alimonti *et al.,* 2005b). In France, the following 5th-95th percentiles for W in healthy volunteers were proposed: 0.004-0.082 µg/L in blood; 0.09-0.75 µg/L in plasma; and 0.01-0.09 µg/L in urine (Goullé *et al.*, 2005). In a Nevada community where W was found at increased levels in drinking water, the median urinary levels in residents were 15-fold higher than median levels in the USA population (CDC, 2003). The association of W content in urine and the exposure of workers employed in cemented carbide industry (mean values of 4.12 µg/L in workers *vs.* 0.06 µg/L in controls) was reported (De Palma *et al.*, 2010). Also patients with medically-inserted W embolization coils showed elevated W levels in blood, urine and hair (Bachthaler *et al.*, 2004).

PROBE results *(Table A18, Figure A18)*

BLOOD: males showed higher levels than females; significant higher levels were found in the youngest subjects (18-35 years).

SERUM: males showed higher levels than females and higher levels were found in no drinkers.

3.19. Uranium (U)

3.19.1. General information

There are no ratings for U human carcinogenicity (ATSDR, 1999b). The general population is exposed to U primarily via food (especially root vegetables) and drinking water (WHO, 2003b). The amount of U in air is usually very small (Roth, 2001). People who live near facilities that made or tested nuclear weapons, or facilities that mine or process U ore or enrich U for reactor fuel, may have increased exposure. About 99% of the U ingested is excreted in faeces, the remainder enters into blood. Most of this absorbed U is excreted *via* kidneys within 24 hrs (ATSDR, 1999b). A small amount of blood U deposits in bones, where it remains for years (Li *et al.*, 2005). Inhaled U-containing particles are retained in lungs, where limited absorption occurs (< 5%); inhaled U seems to increase the risk of lung cancer (ATSDR, 1999b). Moreover, nephrotoxicity of U in humans has recently been documented (Kurttio *et al.*, 2002). Regarding regulatory limits, the minimal risk level proposed by ATSDR is an oral uptake of 2 μg/kg/bw per day (ATSDR, 1999b). WHO established a TDI for U of 0.6 μg/kg body weight per day (WHO, 1998; WHO, 2003b). The MCL for naturally occurring U in drinking water is 30 μg/L for US EPA, and 15 μg/L for WHO (US EPA 2000; WHO, 2004b). The OSHA established a PEL for airborne insoluble U in the workplace at 0.25 mg/m^3 and for airborne soluble U at 0.05 mg/m^3. ACGIH for soluble and insoluble U reported TLVs of 0.2 mg/m^3 (TWA) and 0.6 mg/m^3 (STEL).

3.19.2. Biomonitoring data

WHO suggested that urinary U levels in the general population ranged 0.004-0.057 μg/L (WHO, 2001b). The NHANES survey reported a GM for the total population of 0.008 μg/L (95th percentile: 0.031 μg/L or 0.029 μg/g of creatinine) in urine (CDC, 2009). Other population groups have shown urinary U similar to those in the US population. In unexposed Japanese urinary U ranged 0.008-0.035 μg/L (median, 0.004 μg/L) (Tolmachev *et al.*, 2006); in the Finnish population the mean value was 0.016 μg/L (Muikku *et al.*, 2009), and 0.001-0.011 μg/L in UK (Jones *et al.*, 2007). In people exposed to natural U via well water, urinary mean U was as high as 9.55 μg/L (Orloff *et al.*, 2004); as for similarly exposed Finnish population whose median urinary U raised up to 5.65 μg/L (Kurttio *et al.*, 2002; Kurttio *et al.,* 2006). The USA Nuclear Regulatory Commission has set an action level of 15 μg/L urinary U to protect people who are occupationally exposed (US NRC, 1978). The veterans of the Gulf War with retained depleted U shrapnel in their bodies had levels about 500 times higher than those for the non-exposed veterans (McDiarmid *et al.*, 2005). In blood, typical blood U levels in unexposed individuals were <0.005 μg/L (Byrne & Benedik, 1991) or 0.004 μg/L as median blood value (5th-95th percentiles, 0.002-0.006 μg/L), and 0.007 μg/L (5th-95th percentiles, 0.004-0.011 μg/L) in serum (Goullé *et al.*, 2005).

PROBE results *(Table A19, Figure A19)*

BLOOD: significant higher levels were found in the youngest subjects (18-35 years).

SERUM: in consequence of too higher concentration values due to contamination problems not yet solved, data for blood were not here reported.

3.20. Vanadium (V)

3.20.1. General information

DHHS, IARC and EPA have not classified V as to its human carcinogenicity. Vanadium is a common component of hard steel alloys used for automobile parts, springs, and ball bearings. Small amounts of V are used in making rubber, plastics, ceramics, and other chemicals (ATSDR, 2009). Although most foods contain low concentrations of V (<1 ng/g), food is the major source of exposure to V for the general population (WHO, 1988). Higher levels are found in seafoods. Lungs absorb soluble V compounds well, but the absorption of V salts from the gastrointestinal tract is poor. The excretion of V by kidneys is rapid with a biological half-life of 20-40 hrs in urine (Barceloux, 1999). Vanadium is probably an essential trace element, but a V-deficiency disease has not been identified in humans. In general, the toxicity of V compounds is low. Pentavalent compounds are the most toxic and the toxicity of V compounds usually increases as the valence increases (WHO, 1988). Most of the toxic effects of V result from local irritation of the eyes and upper respiratory tract rather than systemic toxicity (WHO, 1988). The effects on cholesterol levels, haematopoieses, carcinogenic and mutagenic effects after V exposure need further investigation; the scanty evidence of spermato- and gonado-toxic effects also needs corroboration (Cohen *et al.*, 1992; Sabbioni *et al.*, 1991; WHO, 1988).

3.20.2. Biomonitoring data

In a critical review for concentration of V in human fluids, values around 0.51 μg/L or slightly lower for urine and around 0.051 μg/L for blood and serum may be considered tentative RVs (Sabbioni *et al.*, 1996). In two individual studies performed in Italy, mean urinary V of healthy people was 0.8 μg/L and 0.14 μg/L in 1990 and 2009, respectively (Alimonti *et al.*, 2009; Minoia *et al.*, 1990). Mean V concentrations in blood and serum of healthy Italian subjects were 0.09 μg/L and 0.06 μg/L, respectively (Alimonti *et al.*, 2005a). Another study reported a blood V median level for adults of 0.056 μg/L (range 0.032-0.095 μg/L) (Kučeraa *et al.*, 1992). Inhalation of V contaminated workplace air occurring for instance at boiler cleaning, V-pentoxide production and in metallurgical industries significantly increases levels in blood, serum and urine (US EPA 1977; Kučeraa *et al.,* 1992; WHO, 1988). Significantly higher serum V was observed for patients with neurotic depression and manic-depressive illness compared to healthy controls (Simmonoff *et al.*, 1987). Elevated serum V was also found in patients with chronic renal failure on chronic hemodialysis therapy (Tsukamoto *et al.*, 1990).

PROBE results *(Table A20, Figure A20)*

BLOOD: the youngest groups showed higher concentrations than the elders; no drinkers and no smokers showed higher levels than consumers;

SERUM: for the gender class significant differences were found with higher V levels in males.

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APPENDIX A
Metal concentrations in blood and serum in Italian adults (18-65 years)

ANTIMONY (Sb)

Table A1. Antimony: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.15, N<LoD: 74)											
Total (1423)	<LoD	0.17	0.22	0.32	0.44	0.61	0.72	10.9	0.37	0.31	0.30-0.32
Gender (1423)											
Male (953)	0.15	0.17	0.22	0.32	0.43	0.60	0.70	3.38	0.36	0.31	0.30-0.32
Female (470)	<LoD	0.17	0.22	0.31	0.45	0.64	0.73	10.9	0.38	0.31	0.29-0.33
Age, years (1423)											
18-35 (516)	<LoD	0.17	0.23	0.32	0.44	0.63	0.73	10.9	0.39	0.32	0.30-0.33
36-50 (582)	0.15	0.17	0.22	0.32	0.43	0.60	0.70	3.38	0.36	0.31	0.30-0.33
51-65 (325)	<LoD	0.16	0.21	0.30	0.43	0.60	0.71	1.41	0.35	0.30	0.28-0.31
Smoking (1389)											
No (831)	0.15	0.17	0.22	0.32	0.43	0.60	0.71	10.9	0.37	0.31	0.30-0.32
Yes (315)	<LoD	0.17	0.22	0.31	0.43	0.61	0.72	1.95	0.36	0.31	0.29-0.33
Ex (243)	<LoD	0.15	0.24	0.35	0.46	0.67	0.76	1.22	0.37	0.32	0.29-0.34
Alcohol (1384)											
No (617)	<LoD	0.16	0.22	0.31	0.42	0.56	0.64	10.9	0.36	0.30	0.29-0.31
Yes (767)	<LoD	0.17	0.23	0.33	0.45	0.65	0.78	3.38	0.38	0.32	0.31-0.33
SERUM (LoD 0.012, N<LoD: 8)											
Total (1334)	0.026	0.033	0.051	0.082	0.126	0.190	0.265	1.11	0.106	0.081	0.077-0.084
Gender (1334)											
Male (890)	0.027	0.035	0.053	0.085	0.130	0.193	0.263	1.11	0.107	0.083	0.080-0.087
Female (454)	0.024	0.029	0.046	0.075	0.120	0.183	0.282	0.76	0.102	0.075	0.070-0.080
Age, years (1344)											
18-35 (479)	0.028	0.035	0.056	0.087	0.130	0.195	0.340	1.11	0.116	0.087	0.081-0.093
36-50 (558)	0.026	0.034	0.051	0.083	0.127	0.190	0.255	0.69	0.103	0.080	0.076-0.085
51-65 (307)	0.022	0.029	0.047	0.073	0.111	0.178	0.241	0.62	0.094	0.072	0.066-0.078
Smoking (1319)											
No (783)	0.026	0.034	0.052	0.085	0.128	0.191	0.264	1.11	0.107	0.082	0.078-0.086
Yes (300)	0.029	0.034	0.055	0.081	0.137	0.200	0.351	0.79	0.116	0.087	0.080-0.094
Ex (236)	0.024	0.029	0.049	0.074	0.114	0.165	0.205	0.63	0.092	0.072	0.066-0.079
Alcohol (1315)											
No (572)	0.028	0.035	0.055	0.085	0.132	0.205	0.294	1.11	0.114	0.087	0.082-0.092
Yes (743)	0.025	0.031	0.049	0.079	0.125	0.178	0.250	0.79	0.100	0.077	0.073-0.081

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

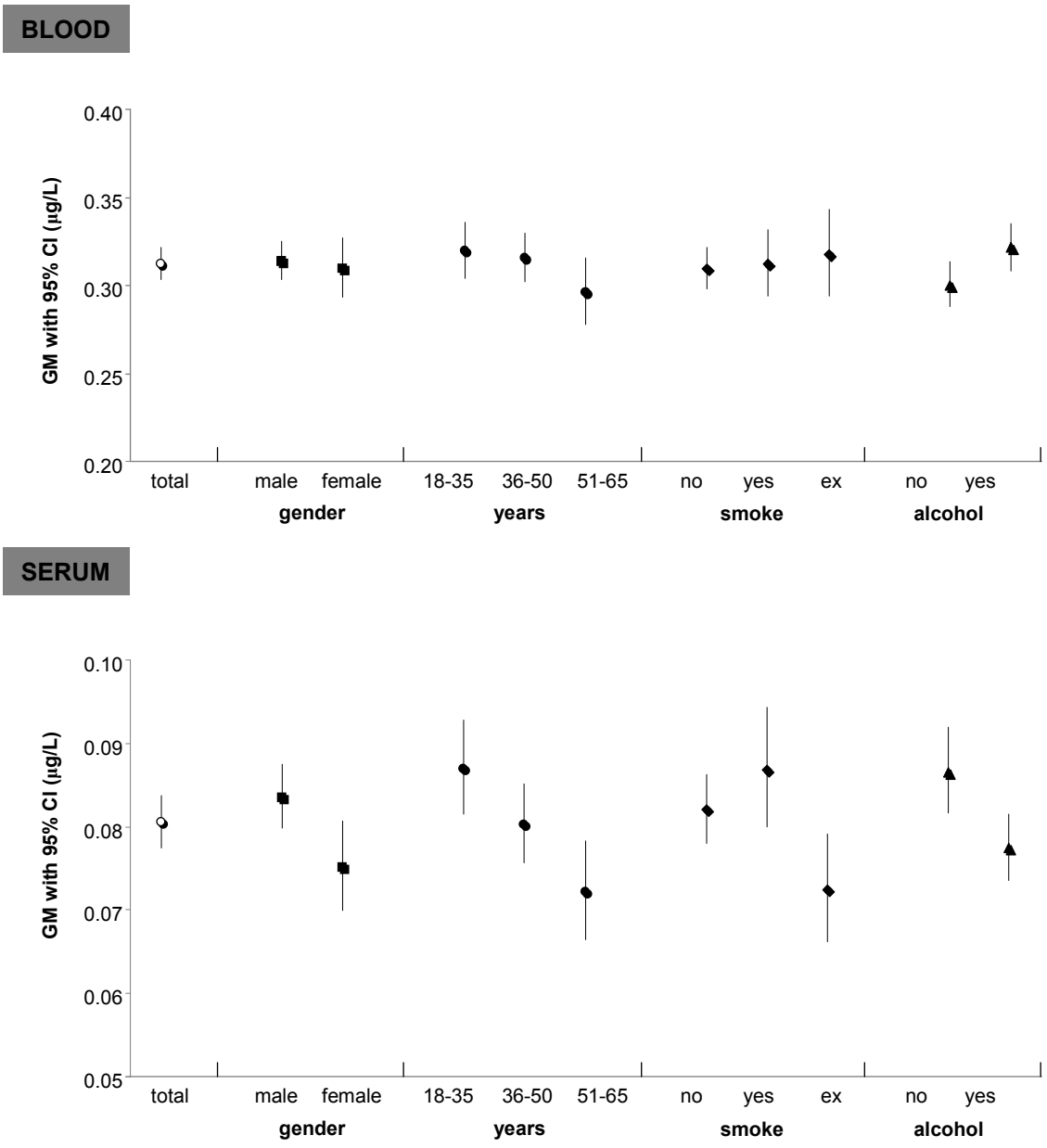


Figure A1. Antimony: GM concentrations in different classes

ARSENIC (As)

Table A2. Arsenic: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.27, N<LoD: 63)											
Total (1423)	0.28	0.38	0.64	1.16	2.01	3.70	5.32	15.5	1.70	1.14	1.09-1.20
Gender (1423)											
Male (953)	0.29	0.38	0.67	1.16	2.08	3.63	5.33	13.5	1.71	1.16	1.09-1.23
Female (470)	<LoD	0.36	0.62	1.12	1.92	3.82	5.32	15.5	1.66	1.10	1.01-1.20
Age, years (1423)											
18-35 (516)	<LoD	0.39	0.63	1.19	1.96	3.78	5.32	11.6	1.67	1.13	1.04-1.22
36-50 (582)	0.30	0.39	0.64	1.14	2.03	3.55	4.99	11.4	1.64	1.14	1.06-1.23
51-65 (325)	<LoD	0.34	0.66	1.14	2.13	4.23	5.78	15.5	1.84	1.16	1.04-1.29
Smoking (1389)											
No (831)	0.27	0.36	0.63	1.14	2.00	3.61	5.39	15.5	1.69	1.12	1.06-1.20
Yes (315)	<LoD	0.33	0.59	1.08	1.90	3.65	5.23	8.33	1.59	1.06	0.96-1.18
Ex (243)	0.35	0.44	0.72	1.25	2.20	4.09	5.88	9.82	1.80	1.26	1.13-1.41
Alcohol (1384)											
No (617)	<LoD	0.35	0.63	1.13	2.03	3.36	4.97	15.5	1.65	1.11	1.03-1.19
Yes (767)	0.29	0.39	0.64	1.17	1.98	3.86	5.41	12.0	1.71	1.15	1.08-1.23
SERUM (LoD 0.15, N<LoD: 88)[a]											
Total (892)	<LoD	0.15	0.28	0.51	1.08	2.00	3.12	27.11	0.96	0.53	0.49-0.57
Gender (892)											
Male (575)	<LoD	0.16	0.28	0.52	1.12	1.97	2.98	11.8	0.92	0.54	0.49-0.58
Female (317)	<LoD	<LoD	0.26	0.48	1.02	2.14	3.21	27.1	1.02	0.51	0.46-0.58
Age, years (892)											
18-35 (297)	<LoD	<LoD	0.25	0.50	1.01	1.85	2.80	11.8	0.88	0.48	0.42-0.54
36-50 (379)	<LoD	0.17	0.29	0.51	1.11	1.97	2.85	7.92	0.91	0.55	0.49-0.60
51-65 (216)	<LoD	0.16	0.28	0.52	1.11	2.16	3.72	27.1	1.15	0.57	0.49-0.66
Smoking (869)											
No (499)	<LoD	<LoD	0.28	0.51	1.05	2.00	3.33	14.6	0.93	0.53	0.48-0.58
Yes (202)	<LoD	<LoD	0.24	0.47	1.05	2.00	2.74	9.11	0.87	0.50	0.43-0.58
Ex (168)	<LoD	0.16	0.29	0.53	1.11	2.25	3.92	27.1	1.13	0.56	0.47-0.66
Alcohol (869)											
No (314)	<LoD	<LoD	0.25	0.48	0.97	1.92	2.46	14.6	0.82	0.49	0.44-0.55
Yes (555)	<LoD	<LoD	0.28	0.51	1.11	2.16	3.75	27.1	1.03	0.55	0.50-0.60

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.
[a] The analysis for this element was not fully carried out

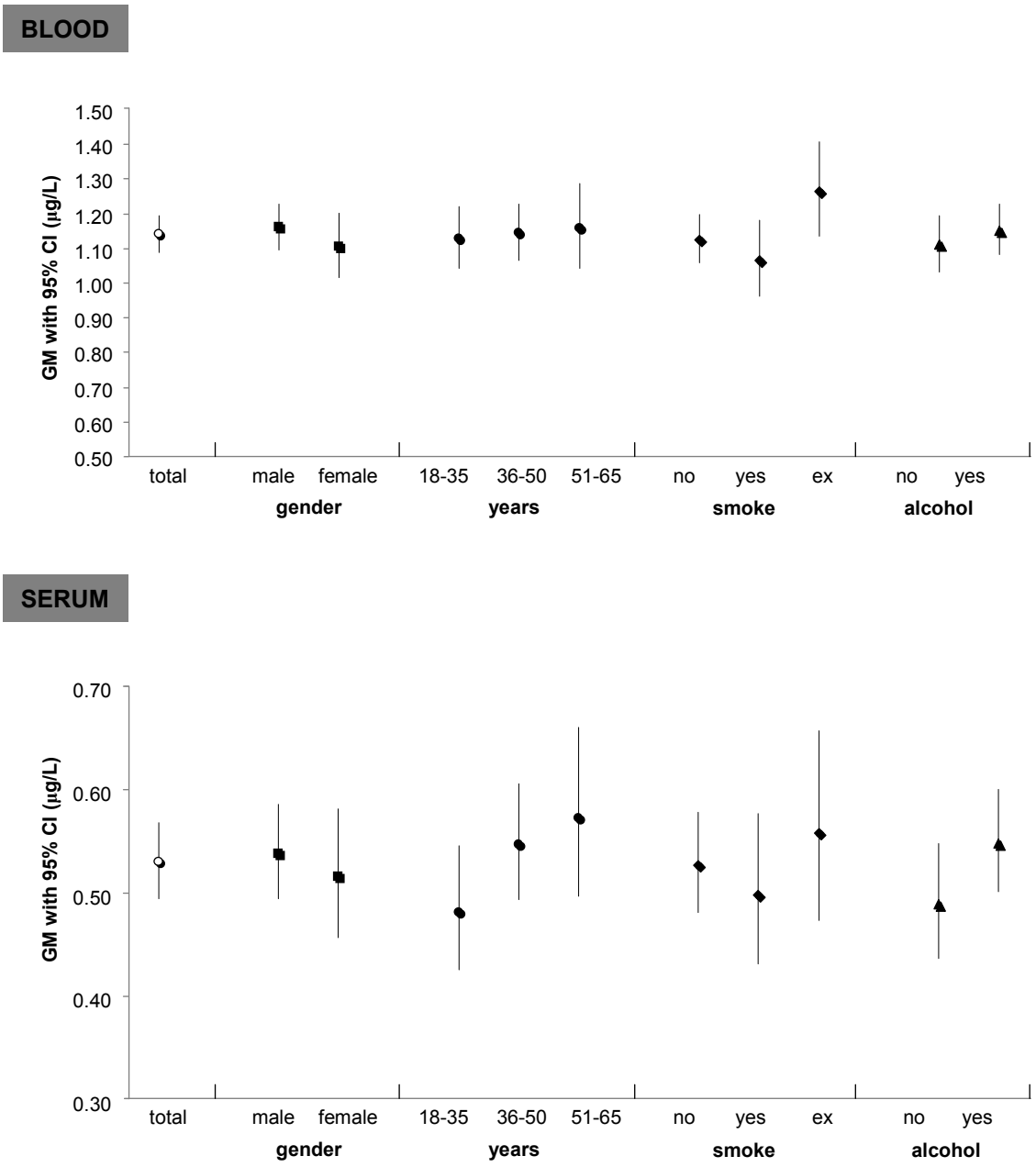


Figure A2. Arsenic: GM concentrations in different classes

BERYLLIUM (Be)

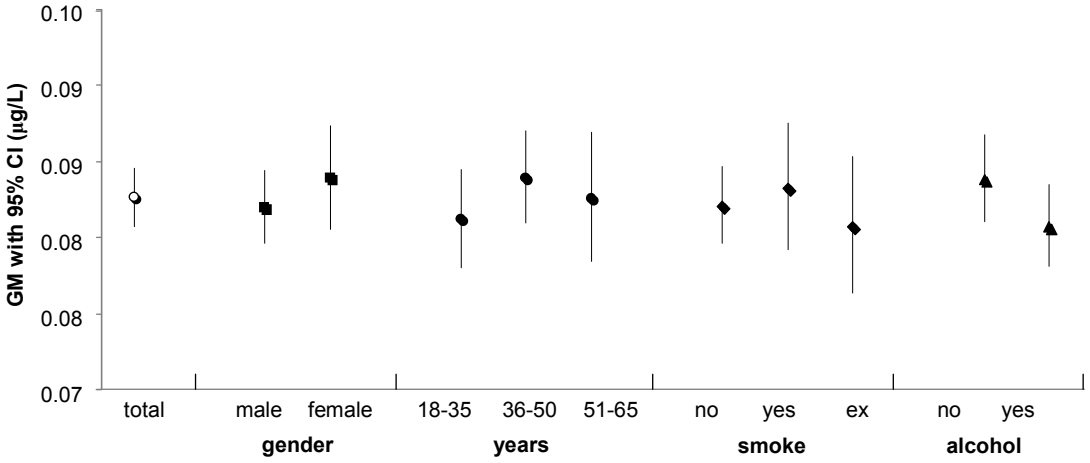
Table A3. Beryllium: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.045, N<LoD: 89)											
Total (1423)	<LoD	0.048	0.063	0.090	0.120	0.156	0.184	0.39	0.097	0.085	0.083-0.087
Gender (1423)											
Male (953)	<LoD	0.048	0.062	0.089	0.119	0.156	0.185	0.39	0.096	0.084	0.081-0.087
Female (470)	<LoD	0.048	0.066	0.090	0.120	0.159	0.182	0.39	0.098	0.087	0.083-0.091
Age, years (1423)											
18-35 (516)	<LoD	0.045	0.062	0.088	0.118	0.150	0.176	0.38	0.095	0.083	0.080-0.087
36-50 (582)	<LoD	0.049	0.064	0.090	0.120	0.158	0.186	0.39	0.098	0.087	0.083-0.090
51-65 (325)	<LoD	0.047	0.062	0.090	0.120	0.173	0.189	0.39	0.098	0.085	0.080-0.090
Smoking (1389)											
No (831)	<LoD	0.048	0.063	0.090	0.119	0.153	0.180	0.38	0.096	0.084	0.081-0.087
Yes (315)	<LoD	0.046	0.060	0.088	0.121	0.164	0.193	0.39	0.098	0.086	0.081-0.091
Ex (243)	<LoD	0.046	0.062	0.090	0.112	0.153	0.182	0.39	0.094	0.083	0.077-0.088
Alcohol (1384)											
No (617)	<LoD	0.050	0.066	0.091	0.121	0.156	0.180	0.37	0.097	0.087	0.083-0.090
Yes (767)	<LoD	0.046	0.061	0.087	0.117	0.154	0.184	0.39	0.095	0.083	0.080-0.086
SERUM (LoD 0.022, N<LoD: 84)[a]											
Total (1067)	<LoD	0.023	0.030	0.046	0.068	0.082	0.089	0.20	0.049	0.043	0.041-0.044
Gender (1067)											
Male (869)	<LoD	0.022	0.028	0.040	0.063	0.079	0.086	0.20	0.046	0.040	0.038-0.041
Female (378)	<LoD	0.024	0.036	0.055	0.073	0.085	0.091	0.20	0.056	0.049	0.046-0.052
Age, years (1067)											
18-35 (364)	<LoD	0.024	0.032	0.050	0.068	0.081	0.086	0.14	0.051	0.045	0.042-0.047
36-50 (446)	<LoD	<LoD	0.029	0.046	0.070	0.083	0.090	0.20	0.049	0.042	0.039-0.044
51-65 (257)	<LoD	0.024	0.029	0.042	0.062	0.079	0.087	0.20	0.047	0.041	0.039-0.044
Smoking (1042)**											
No (609)	<LoD	0.023	0.031	0.047	0.069	0.084	0.091	0.20	0.051	0.043	0.041-0.045
Yes (240)	<LoD	0.025	0.030	0.047	0.064	0.078	0.083	0.09	0.048	0.043	0.041-0.046
Ex (193)	<LoD	<LoD	0.027	0.037	0.061	0.074	0.084	0.20	0.044	0.038	0.035-0.041
Alcohol (1040)											
No (419)	<LoD	0.022	0.030	0.050	0.069	0.082	0.089	0.20	0.051	0.044	0.041-0.046
Yes (621)	<LoD	0.024	0.029	0.042	0.065	0.081	0.088	0.20	0.048	0.042	0.040-0.043

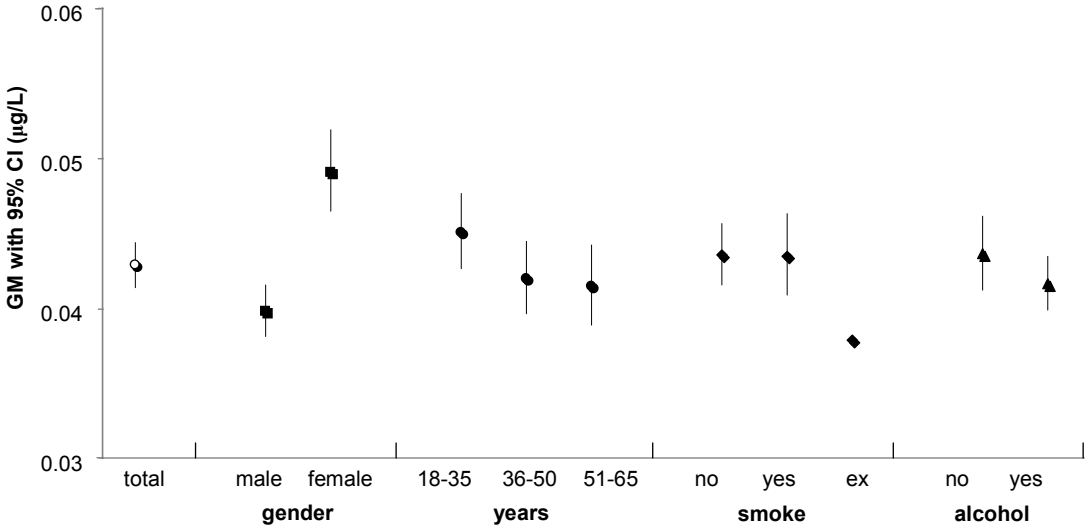
N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.
[a] The analysis for this element was not fully carried out

** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

BLOOD



SERUM



FigureA. Beryllium: GM concentrations in different classes

CADMIUM (Cd)

Table A4. Cadmium: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.10, N<LoD: 16)											
Total (1423)	0.23	0.28	0.37	0.52	0.76	1.11	1.42	3.87	0.63	0.53	0.51-0.55
Gender (1423)											
Male (953)	0.22	0.28	0.37	0.52	0.78	1.13	1.40	3.87	0.63	0.53	0.51-0.55
Female (470)	0.24	0.28	0.37	0.52	0.74	1.04	1.47	2.21	0.62	0.53	0.50-0.56
Age, years (1423)											
18-35 (516)	0.22	0.28	0.36	0.52	0.78	1.23	1.53	2.37	0.64	0.54	0.51-0.57
36-50 (582)	0.22	0.28	0.37	0.50	0.73	1.02	1.24	3.87	0.60	0.51	0.49-0.53
51-65 (325)	0.24	0.30	0.39	0.56	0.82	1.13	1.47	2.36	0.65	0.56	0.53-0.59
Smoking (1389)*											
No (831)	0.21	0.27	0.34	0.47	0.65	0.88	1.08	2.58	0.54	0.47	0.45-0.49
Yes (315)	0.28	0.34	0.51	0.76	1.12	1.52	1.94	2.60	0.86	0.74	0.70-0.79
Ex (243)	0.23	0.29	0.38	0.53	0.75	1.07	1.34	3.87	0.62	0.53	0.49-0.57
Alcohol (1384)											
No (617)	0.21	0.28	0.36	0.52	0.74	1.04	1.41	3.87	0.61	0.52	0.49-0.54
Yes (767)	0.23	0.28	0.37	0.52	0.79	1.17	1.46	2.60	0.64	0.54	0.52-0.56
SERUM (LoD 0.015, N<LoD: 11)											
Total (1344)	0.036	0.048	0.070	0.103	0.150	0.215	0.269	1.830	0.124	0.101	0.098-0.105
Gender (1344)											
Male (890)	0.033	0.047	0.068	0.099	0.150	0.214	0.266	1.250	0.122	0.099	0.095-0.103
Female (454)	0.038	0.051	0.073	0.108	0.151	0.216	0.275	1.830	0.128	0.105	0.099-0.111
Age, years (1344)											
18-35 (479)	0.032	0.043	0.068	0.099	0.155	0.218	0.272	0.610	0.119	0.098	0.092-0.104
36-50 (558)	0.038	0.052	0.071	0.105	0.151	0.214	0.265	1.250	0.127	0.105	0.099-0.110
51-65 (307)	0.032	0.047	0.068	0.106	0.141	0.213	0.278	1.830	0.126	0.099	0.092-0.107
Smoking (1319)											
No (783)	0.037	0.048	0.068	0.099	0.147	0.218	0.275	0.760	0.122	0.100	0.095-0.104
Yes (300)	0.033	0.048	0.075	0.110	0.155	0.210	0.270	1.250	0.127	0.105	0.098-0.113
Ex (236)	0.037	0.048	0.068	0.104	0.152	0.215	0.247	1.830	0.130	0.102	0.094-0.111
Alcohol (1315)											
No (572)	0.038	0.050	0.070	0.106	0.152	0.218	0.289	1.830	0.130	0.105	0.099-0.110
Yes (743)	0.033	0.046	0.069	0.103	0.150	0.213	0.258	0.760	0.121	0.099	0.095-0.104

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

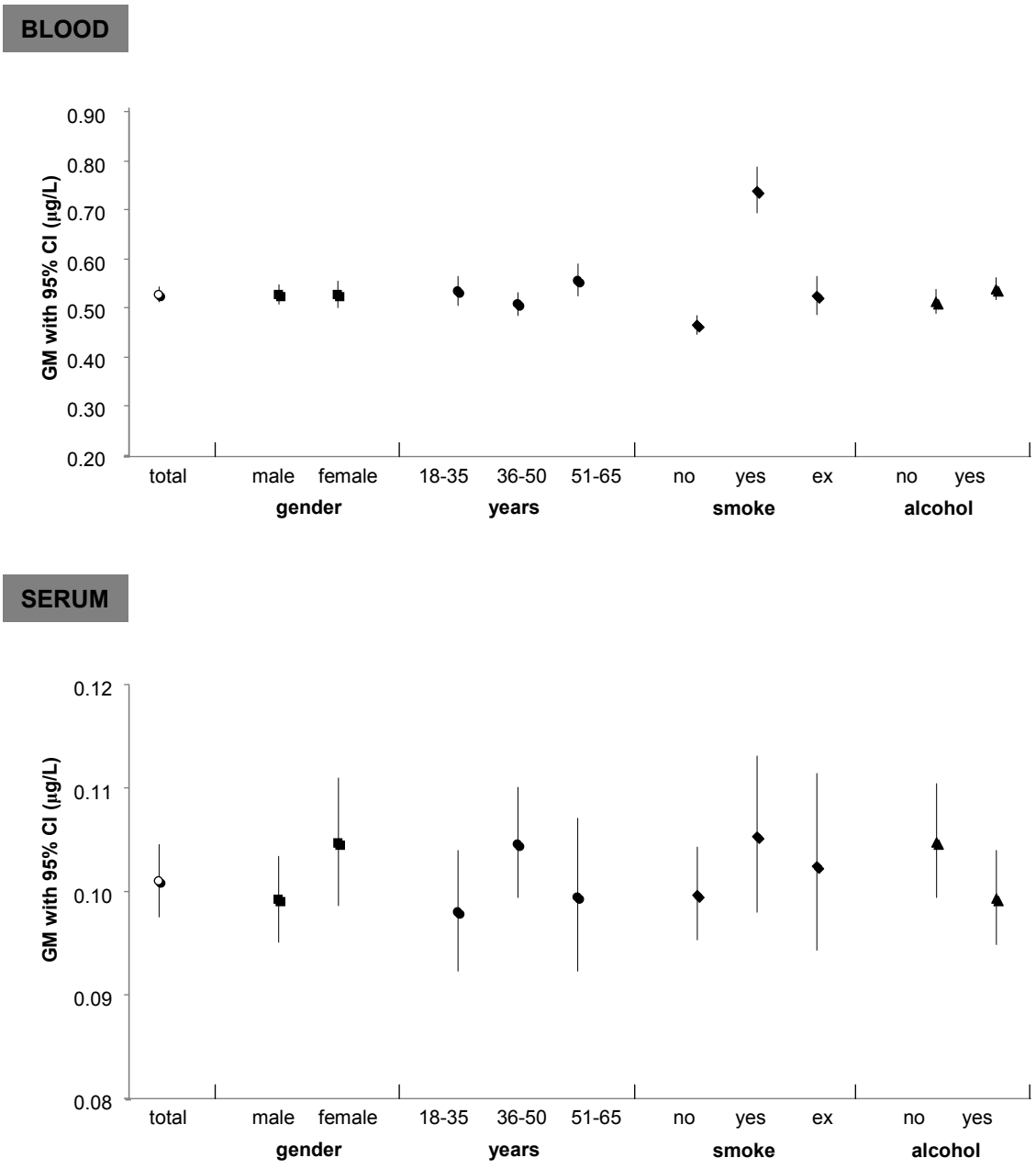


Figure A4. Cadmium: GM concentrations in different classes

CHROMIUM (Cr)

Table A5. Chromium: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.04, N<LoD: 18)											
Total (1423)	0.06	0.09	0.14	0.23	0.41	0.75	1.09	11.8	0.38	0.24	0.23-0.25
Gender (1423)											
Male (953)	0.06	0.09	0.14	0.22	0.41	0.75	1.11	11.8	0.37	0.24	0.23-0.25
Female (470)	0.07	0.09	0.14	0.24	0.40	0.73	1.09	5.37	0.38	0.25	0.23-0.27
Age, years (1423)											
18-35 (516)	0.07	0.09	0.15	0.24	0.41	0.80	1.07	3.69	0.36	0.25	0.23-0.27
36-50 (582)	0.06	0.09	0.14	0.21	0.41	0.77	1.14	11.8	0.39	0.24	0.22-0.26
51-65 (325)	0.06	0.09	0.14	0.22	0.39	0.67	1.13	5.37	0.38	0.24	0.21-0.26
Smoking (1389)											
No (831)	0.06	0.09	0.14	0.22	0.40	0.79	1.14	5.37	0.37	0.24	0.23-0.26
Yes (315)	0.06	0.09	0.14	0.23	0.39	0.69	0.90	4.77	0.34	0.23	0.21-0.25
Ex (243)	0.07	0.10	0.15	0.25	0.45	0.80	1.30	11.8	0.45	0.27	0.24-0.30
Alcohol (1384)											
No (617)	0.07	0.09	0.14	0.23	0.38	0.66	0.87	11.8	0.34	0.23	0.22-0.25
Yes (767)	0.06	0.09	0.15	0.23	0.44	0.85	1.28	5.84	0.41	0.25	0.24-0.27
SERUM (LoD 0.015, N<LoD: 1)											
Total (1343)	0.051	0.060	0.083	0.113	0.163	0.230	0.294	2.410	0.141	0.117	0.113-0.120
Gender (1343)											
Male (889)	0.050	0.060	0.080	0.110	0.161	0.227	0.296	2.410	0.140	0.115	0.111-0.120
Female (454)	0.051	0.063	0.086	0.115	0.166	0.237	0.286	1.590	0.142	0.119	0.113-0.126
Age, years (1343)											
18-35 (479)	0.054	0.060	0.080	0.113	0.162	0.231	0.292	1.380	0.139	0.116	0.111-0.122
36-50 (558)	0.049	0.063	0.084	0.112	0.163	0.227	0.302	2.410	0.141	0.117	0.111-0.123
51-65 (306)	0.047	0.056	0.082	0.111	0.165	0.233	0.280	1.590	0.143	0.116	0.109-0.124
Smoking (1318)											
No (782)	0.054	0.061	0.081	0.110	0.158	0.233	0.294	2.410	0.139	0.116	0.111-0.120
Yes (300)	0.053	0.062	0.088	0.121	0.171	0.232	0.311	0.950	0.147	0.124	0.116-0.131
Ex (236)	0.045	0.055	0.081	0.110	0.164	0.217	0.263	1.590	0.139	0.114	0.106-0.123
Alcohol (1314)											
No (572)	0.053	0.065	0.085	0.115	0.169	0.249	0.337	2.410	0.150	0.122	0.1116-0.128
Yes (742)	0.050	0.059	0.080	0.110	0.160	0.218	0.268	0.950	0.134	0.114	0.109-0.118

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

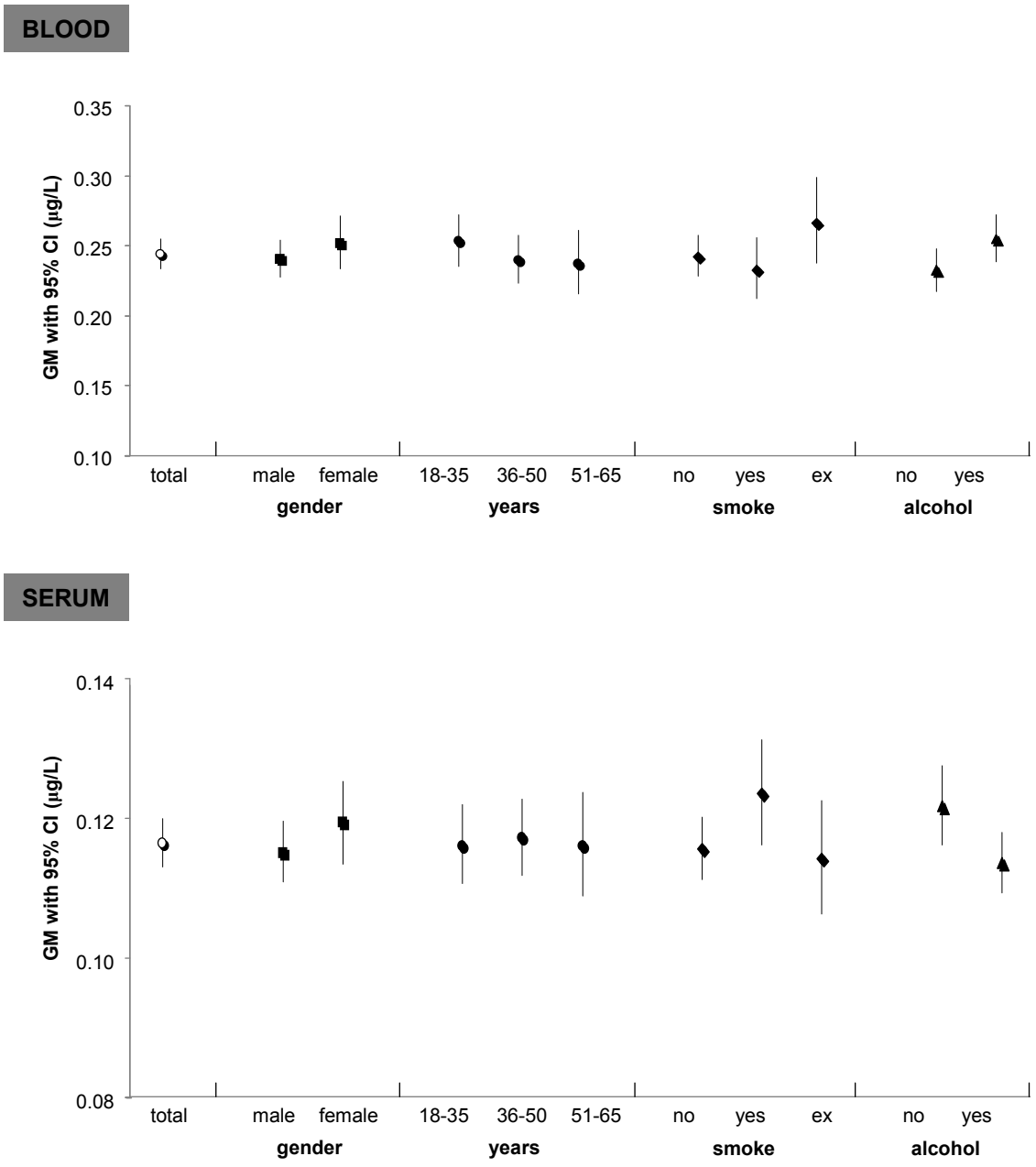


Figure A5. Chromium: GM concentrations in different classes

COBALT (Co)

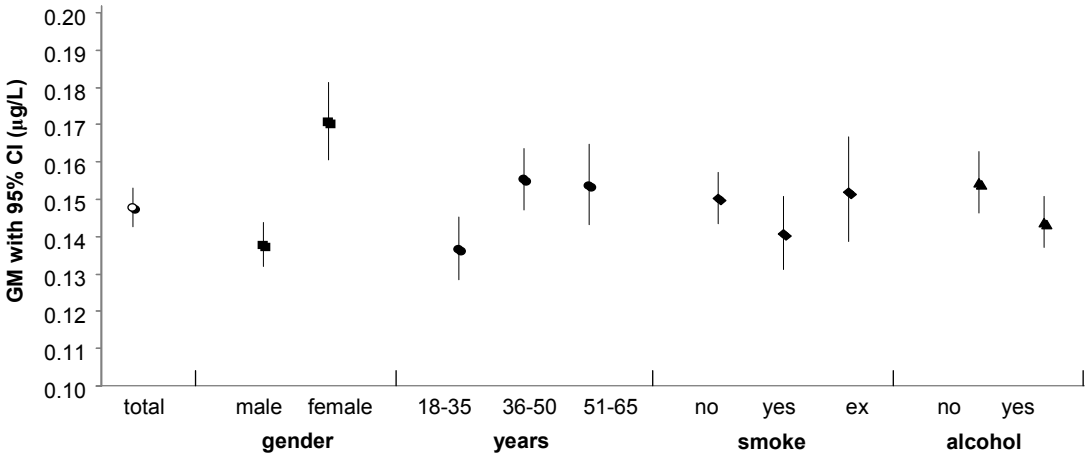
Table A6. Cobalt: concentations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.010, N<LoD: 2)											
Total (1423)	0.055	0.066	0.096	0.138	0.225	0.338	0.443	7.47	0.192	0.147	0.142-0.152
Gender (1423)*											
Male (953)	0.053	0.063	0.090	0.129	0.198	0.317	0.420	7.47	0.179	0.137	0.131-0.143
Female (470)	0.060	0.077	0.110	0.168	0.263	0.389	0.505	4.61	0.216	0.169	0.159-0.180
Age, years (1423)											
18-35 (516)	0.051	0.063	0.091	0.132	0.198	0.300	0.388	7.47	0.193	0.136	0.128-0.144
36-50 (582)	0.058	0.068	0.103	0.147	0.237	0.357	0.467	1.33	0.191	0.154	0.146-0.162
51-65 (325)	0.060	0.069	0.095	0.141	0.235	0.357	0.466	1.25	0.191	0.152	0.142-0.164
Smoking (1389)											
No (831)	0.056	0.068	0.100	0.139	0.228	0.338	0.450	7.47	0.197	0.149	0.143-0.156
Yes (315)	0.056	0.064	0.090	0.138	0.218	0.317	0.394	1.00	0.171	0.140	0.130-0.150
Ex (243)	0.052	0.065	0.097	0.143	0.225	0.380	0.504	4.61	0.207	0.151	0.138-0.165
Alcohol (1384)											
No (617)	0.058	0.069	0.101	0.146	0.240	0.360	0.474	1.33	0.192	0.153	0.145-0.161
Yes (767)	0.054	0.065	0.093	0.135	0.212	0.317	0.435	7.47	0.193	0.143	0.136-0.150
SERUM (LoD 0.035, N<LoD: 5)											
Total (1343)	0.083	0.104	0.15	0.229	0.333	0.458	0.607	15.10	0.277	0.223	0.216-0.230
Gender (1343)*											
Male (889)	0.078	0.101	0.145	0.217	0.320	0.448	0.572	15.10	0.275	0.215	0.207-0.224
Female (454)	0.085	0.107	0.160	0.243	0.352	0.481	0.629	1.190	0.280	0.238	0.226-0.251
Age, years (1343)											
18-35 (479)	0.074	0.096	0.146	0.217	0.304	0.406	0.485	15.10	0.278	0.210	0.199-0.222
36-50 (558)	0.085	0.110	0.153	0.238	0.350	0.489	0.628	1.300	0.276	0.231	0.219-0.243
51-65 (306)	0.088	0.101	0.151	0.236	0.337	0.490	0.643	1.190	0.276	0.229	0.214-0.245
Smoking (1318)											
No (782)	0.080	0.104	0.150	0.226	0.334	0.456	0.587	2.790	0.266	0.222	0.213-0.232
Yes (300)	0.081	0.100	0.146	0.238	0.325	0.435	0.563	15.10	0.307	0.219	0.203-0.237
Ex (236)	0.093	0.116	0.159	0.241	0.349	0.516	0.684	1.300	0.284	0.238	0.221-0.257
Alcohol (1314)											
No (572)	0.088	0.111	0.157	0.230	0.330	0.484	0.619	1.080	0.271	0.231	0.220-0.242
Yes (742)	0.078	0.099	0.146	0.229	0.336	0.454	0.601	15.10	0.285	0.220	0.210-0.230

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

BLOOD



SERUM

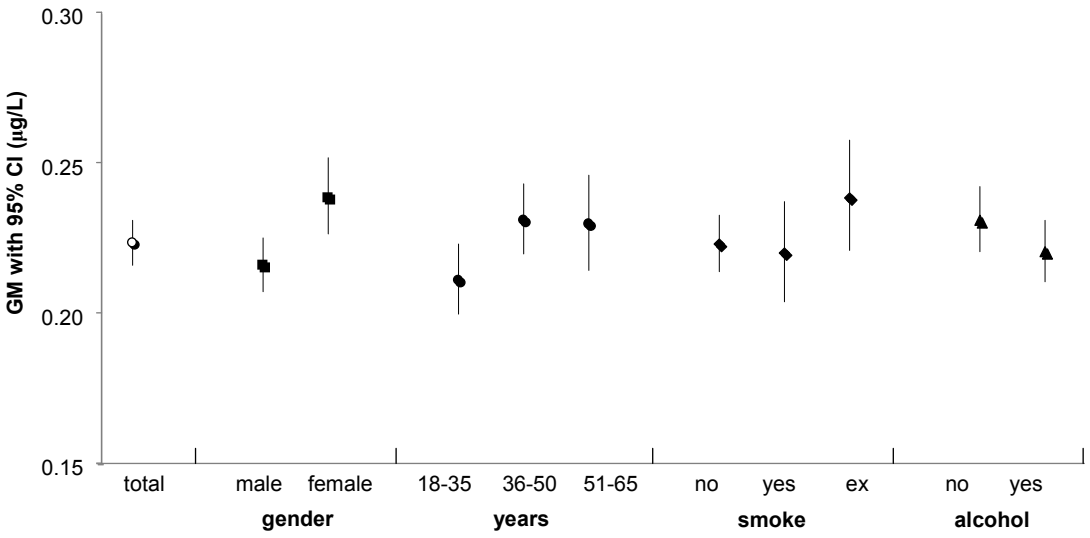


Figure A6. Cobalt: GM concentrations in different classes

IRIDIUM (Ir)

Table A7. Iridium: concentrations (ng/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 5.00, N<LoD: 91)											
Total (1423)	<LoD	5.48	6.80	9.09	12.5	17.0	20.4	36.9	10.2	9.02	8.78-9.26
Gender (1423)*											
Male (953)	<LoD	5.62	6.95	9.38	13.3	18.1	22.2	36.9	10.7	9.45	9.15-9.76
Female (470)	<LoD	5.27	6.46	8.52	10.9	15.5	18.0	26.6	9.18	8.20	7.84-8.58
Age, years (1423)											
18-35 (516)	<LoD	5.68	7.13	9.32	13.2	18.2	22.2	36.9	10.8	9.56	9.16-9.98
36-50 (582)	<LoD	5.38	6.58	8.80	12.1	16.5	19.3	31.9	9.88	8.74	8.39-9.12
51-65 (325)	<LoD	5.21	6.50	8.93	12.3	16.5	20.1	32.9	9.93	8.68	8.19-9.21
Smoking (1389)											
No (831)	<LoD	5.48	6.79	9.25	12.5	16.9	19.8	36.9	10.2	9.03	8.72-9.34
Yes (315)	<LoD	5.50	6.71	8.70	12.4	17.0	21.8	32.9	10.1	8.90	8.41-9.42
Ex (243)	<LoD	5.46	6.92	9.13	13.3	18.2	22.0	31.9	10.6	9.30	8.69-9.95
Alcohol (1384)											
No (617)	<LoD	5.57	6.80	9.14	12.1	15.8	18.2	33.9	9.86	8.86	8.52-9.20
Yes (767)	<LoD	5.40	6.81	9.04	12.8	18.7	22.3	36.9	10.5	9.20	8.86-9.56
SERUM (LoD 0.50, N<LoD: 20)											
Total (1344)	0.70	0.97	1.59	2.63	4.04	5.83	7.05	14.0	3.08	2.46	2.37-2.56
Gender (1344)											
Male (890)	0.70	0.98	1.68	2.65	4.04	5.83	6.97	14.0	3.10	2.48	2.37-2.61
Female (454)	0.68	0.95	1.49	2.57	4.02	5.78	7.29	11.8	3.03	2.41	2.26-2.58
Age, years (1344) **											
18-35 (479)	0.73	0.92	1.58	2.76	4.18	5.75	7.18	14.0	3.15	2.53	2.38-2.70
36-50 (558)	0.80	1.03	1.74	2.65	4.15	6.00	7.06	12.1	3.17	2.55	2.40-2.71
51-65 (307)	0.60	0.90	1.49	2.43	3.52	5.33	7.23	11.8	2.80	2.20	2.01-2.40
Smoking (1319)											
No (783)	0.74	1.01	1.67	2.75	4.23	5.99	7.39	12.1	3.21	2.59	2.46-2.71
Yes (300)	0.60	0.90	1.56	2.69	3.89	5.82	7.06	14.0	3.00	2.39	2.19-2.60
Ex (236)	0.61	0.94	1.39	2.42	3.73	5.51	6.67	11.8	2.84	2.21	2.00-2.45
Alcohol (1315)*											
No (572)	0.81	1.12	1.84	2.84	4.35	6.30	7.51	11.9	3.35	2.71	2.55-2.87
Yes (743)	0.63	0.90	1.44	2.47	3.85	5.45	6.80	14.0	2.90	2.30	2.18-2.42

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

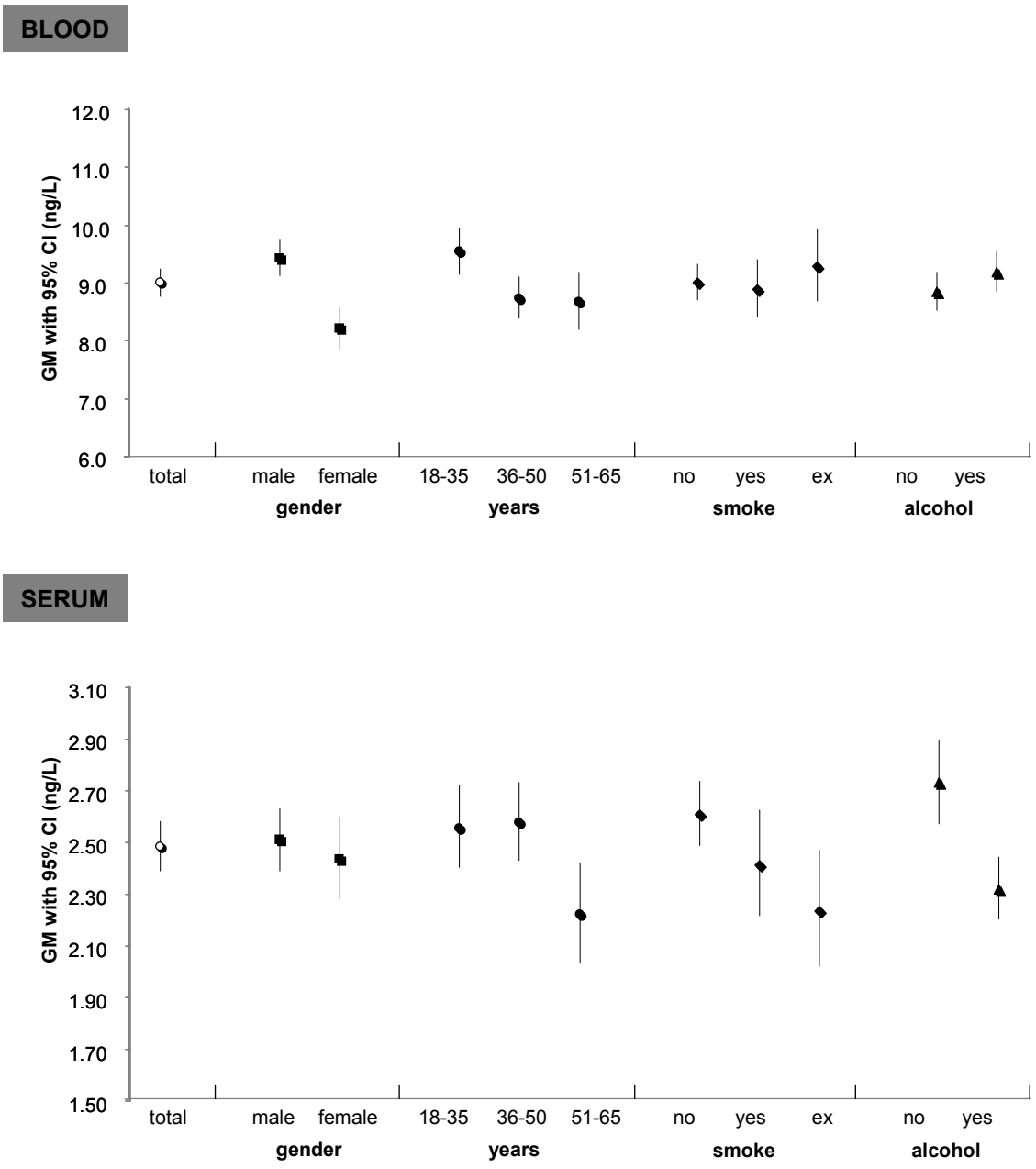


Figure A7. Iridium: GM concentrations in different classes

LEAD (Pb)

Table A8. Lead: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 1.03, N<LoD: 1)											
Total (1423)	7.38	9.04	13.0	20.2	30.9	43.4	51.7	215	24.0	19.9	19.2-20.5
Gender (1423)*											
Male (953)	8.73	10.4	15.1	22.8	33.0	45.6	53.9	209	26.2	22.2	21.4-23.0
Female (470)	6.21	7.49	10.3	15.1	24.1	38.1	44.9	215	19.6	15.9	15.0-16.9
Age, years (1423)*											
18-35 (516)	6.37	7.67	10.4	15.1	22.9	32.9	41.7	215	18.9	15.6	14.8-16.5
36-50 (582)	8.11	10.2	14.2	20.5	30.3	43.1	50.2	209	24.3	20.6	19.7-21.6
51-65 (325)	9.05	12.7	20.5	28.7	39.4	52.3	62.2	192	31.7	27.2	25.5-28.9
Smoking (1389)*											
No (831)	6.88	8.49	12.1	18.7	28.6	41.7	49.7	215	22.5	18.5	17.8-19.3
Yes (315)	7.90	9.41	13.3	21.0	32.0	44.1	50.1	192	24.8	20.8	19.5-22.2
Ex (243)	8.95	11.6	15.5	24.3	34.7	50.3	61.3	209	28.8	23.9	22.2-25.8
Alcohol (1384)*											
No (617)	6.67	8.30	11.9	17.9	28.6	40.7	50.3	215	22.2	18.1	17.2-19.0
Yes (767)	8.16	9.79	14.2	22.1	31.9	45.6	53.9	192	25.6	21.5	20.6-22.4
SERUM (LoD 0.04, N<LoD: 19)											
Total (1344)	0.05	0.07	0.11	0.17	0.27	0.44	0.60	29.3	0.26	0.17	0.17-0.18
Gender (1344)											
Male (890)	0.05	0.07	0.11	0.17	0.26	0.43	0.59	29.3	0.26	0.17	0.16-0.18
Female (454)	0.06	0.08	0.12	0.17	0.28	0.45	0.63	12.6	0.28	0.18	0.17-0.19
Age, years (1344)											
18-35 (479)	0.05	0.07	0.11	0.16	0.26	0.46	0.68	3.35	0.23	0.17	0.15-0.18
36-50 (558)	0.05	0.07	0.12	0.17	0.27	0.41	0.50	6.09	0.23	0.17	0.16-0.18
51-65 (307)	0.05	0.07	0.11	0.17	0.28	0.45	0.69	29.3	0.38	0.18	0.16-0.20
Smoking (1319)**											
No (783)	0.05	0.07	0.11	0.16	0.25	0.39	0.50	1.46	0.21	0.16	0.15-0.17
Yes (300)	0.05	0.07	0.11	0.17	0.26	0.46	0.68	6.09	0.25	0.18	0.16-0.19
Ex (236)	0.05	0.08	0.12	0.19	0.31	0.62	0.96	29.3	0.47	0.20	0.18-0.23
Alcohol (1315)											
No (572)	0.05	0.08	0.11	0.17	0.27	0.42	0.52	6.09	0.23	0.17	0.16-0.18
Yes (743)	0.05	0.07	0.11	0.17	0.27	0.46	0.65	29.3	0.29	0.17	0.16-0.18

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

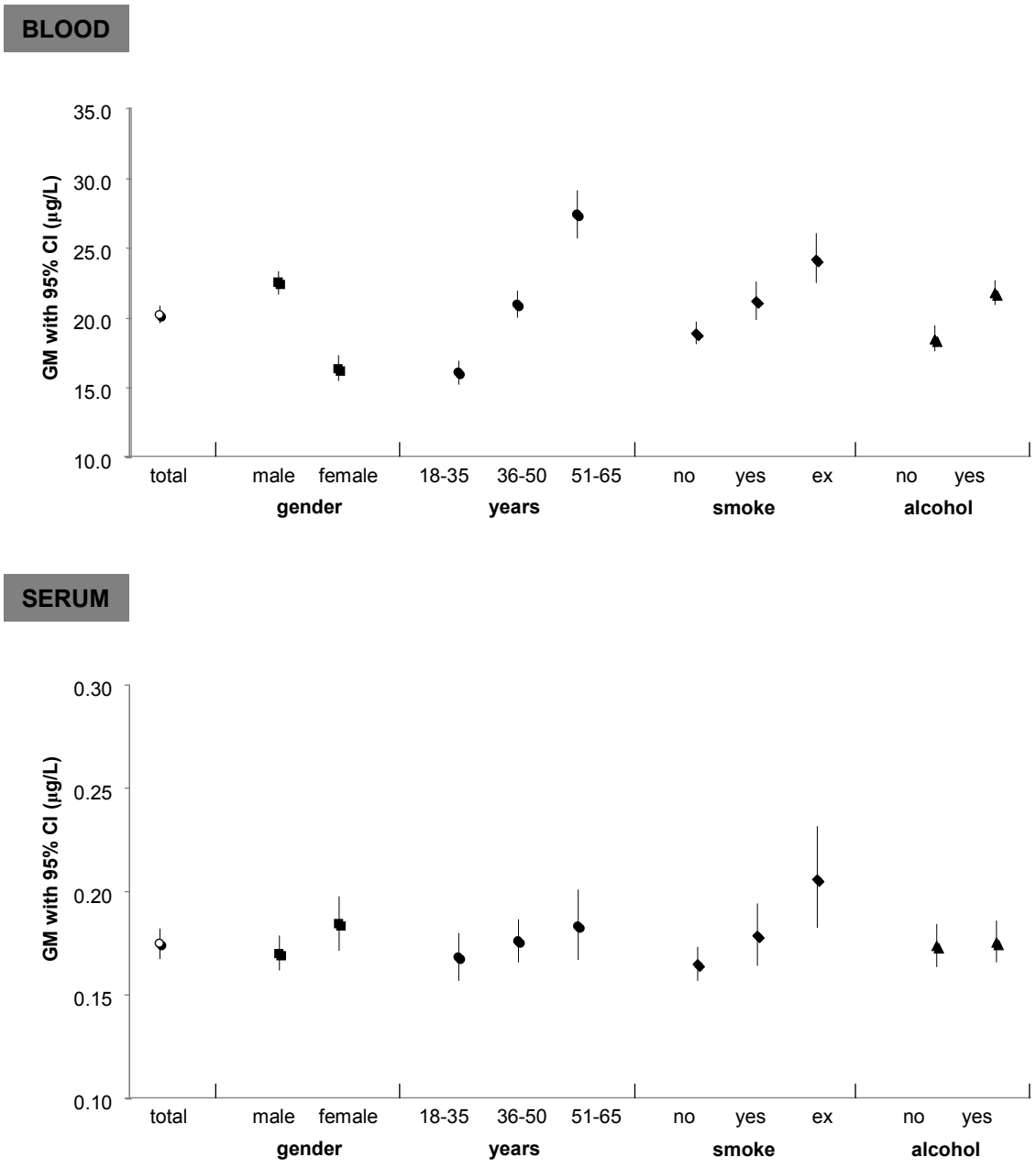


Figure A8. Lead: GM concentrations in different classes

MANGANESE (Mn)

Table A9. Manganese: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.78, N<LoD: 0)											
Total (1423)	4.41	5.19	6.56	8.30	10.4	12.8	14.5	53.4	8.74	8.19	8.04-8.35
Gender (1423)											
Male (953)	4.34	5.18	6.50	8.23	10.2	12.6	14.1	19.1	8.56	8.06	7.88-8.24
Female (470)	4.46	5.20	6.68	8.60	11.0	13.4	14.8	53.4	9.09	8.46	8.17-8.76
Age, years (1423)											
18-35 (516)	4.33	5.23	6.57	8.34	10.4	12.9	14.7	18.7	8.72	8.19	7.94-8.45
36-50 (582)	4.44	5.28	6.68	8.35	10.8	12.9	14.5	53.4	8.92	8.32	8.08-8.58
51-65 (325)	4.17	4.98	6.36	8.08	10.2	12.7	13.8	17.8	8.45	7.95	7.65-8.27
Smoking (1389)**											
No (831)	4.52	5.29	6.72	8.51	10.7	13.3	14.8	53.4	9.00	8.43	8.22-8.64
Yes (315)	4.42	5.19	6.36	7.92	9.84	12.1	13.1	19.1	8.27	7.82	7.53-8.12
Ex (243)	4.11	4.86	6.41	8.08	10.6	13.0	14.9	18.6	8.67	8.09	7.70-8.49
Alcohol (1384)*											
No (617)	4.58	5.46	6.81	8.59	10.9	13.0	14.7	19.5	9.02	8.50	8.27-8.74
Yes (767)	4.32	5.01	6.38	8.06	10.2	12.6	14.6	53.4	8.57	8.00	7.80-8.22
SERUM (LoD 0.01, N<LoD: 0)											
Total (1343)	0.48	0.57	0.71	0.89	1.05	1.25	1.41	2.33	0.90	0.85	0.84-0.87
Gender (1343)											
Male (889)	0.51	0.58	0.71	0.89	1.07	1.27	1.44	2.26	0.91	0.87	0.85-0.88
Female (454)	0.44	0.52	0.70	0.88	1.02	1.23	1.37	2.33	0.88	0.83	0.81-0.86
Age, years (1343)											
18-35 (479)	0.47	0.55	0.69	0.88	1.03	1.24	1.38	2.20	0.88	0.84	0.82-0.87
36-50 (558)	0.51	0.59	0.72	0.88	1.05	1.23	1.38	2.33	0.90	0.86	0.84-0.88
51-65 (306)	0.46	0.52	0.71	0.91	1.12	1.31	1.47	2.26	0.92	0.86	0.83-0.90
Smoking (1318)											
No (782)	0.48	0.57	0.70	0.87	1.03	1.22	1.39	2.24	0.89	0.85	0.83-0.86
Yes (300)	0.51	0.59	0.75	0.92	1.08	1.28	1.45	2.33	0.93	0.88	0.85-0.92
Ex (236)	0.47	0.56	0.71	0.89	1.10	1.30	1.42	2.26	0.91	0.87	0.83-0.90
Alcohol (1314)											
No (572)	0.51	0.58	0.71	0.87	1.03	1.27	1.46	2.33	0.90	0.85	0.83-0.88
Yes (742)	0.47	0.56	0.71	0.90	1.06	1.25	1.39	2.26	0.91	0.86	0.84-0.88

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

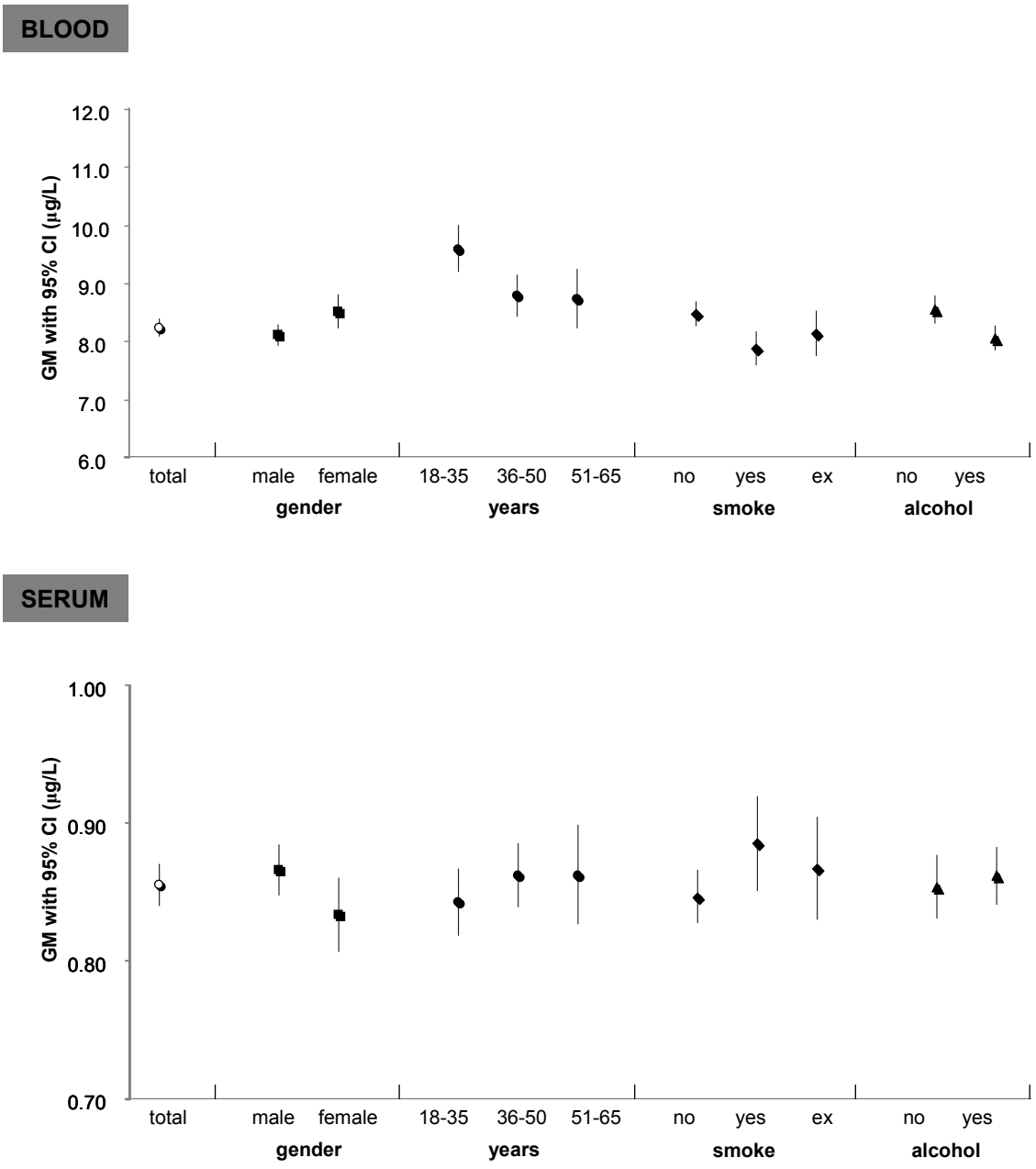


Figure A9. Manganese: GM concentrations in different classes

MERCURY (Hg)

Table A10. Mercury: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.29, N<LoD: 37)											
Total (1423)	0.35	0.47	0.72	1.15	1.95	3.40	5.16	15.0	1.68	1.19	1.15-1.25
Gender (1423)*											
Male (953)	0.36	0.48	0.76	1.25	2.15	3.71	5.50	15.0	1.81	1.27	1.21-1.34
Female (470)	0.34	0.45	0.65	1.00	1.67	2.60	3.71	11.3	1.41	1.05	0.98-1.12
Age, years (1423)											
18-35 (516)	0.35	0.49	0.71	1.15	1.75	3.13	4.52	13.8	1.58	1.15	1.08-1.23
36-50 (582)	0.36	0.45	0.71	1.13	2.11	3.53	5.22	15.0	1.72	1.20	1.12-1.28
51-65 (325)	0.34	0.47	0.76	1.24	2.14	3.60	5.19	11.3	1.76	1.25	1.14-1.37
Smoking (1389)											
No (831)	0.35	0.48	0.73	1.18	1.97	3.49	5.28	13.6	1.69	1.20	1.14-1.27
Yes (315)	0.34	0.45	0.71	1.09	1.76	2.85	3.95	13.8	1.52	1.10	1.00-1.20
Ex (243)	0.36	0.45	0.71	1.24	2.18	4.09	5.94	15.0	1.88	1.28	1.15-1.43
Alcohol (1384)											
No (617)	0.36	0.46	0.71	1.13	1.81	2.93	4.28	10.5	1.52	1.14	1.07-1.21
Yes (767)	0.34	0.47	0.73	1.18	2.03	3.76	5.73	15.0	1.81	1.23	1.16-1.31
SERUM (LoD 0.08, N<LoD: 33)											
Total (1344)	0.13	0.20	0.35	0.60	0.95	1.51	1.89	7.38	0.76	0.56	0.53-0.58
Gender (1344)											
Male (890)	0.12	0.19	0.35	0.61	1.02	1.58	2.07	7.38	0.79	0.56	0.53-0.60
Female (454)	0.15	0.22	0.36	0.58	0.90	1.31	1.63	5.22	0.70	0.55	0.51-0.58
Age, years (1344)											
18-35 (479)	0.14	0.21	0.39	0.60	0.93	1.50	1.88	5.22	0.76	0.57	0.53-0.61
36-50 (558)	0.14	0.19	0.36	0.61	0.98	1.53	1.95	7.38	0.79	0.57	0.53-0.61
51-65 (307)	0.11	0.18	0.31	0.57	0.95	1.44	1.72	3.15	0.71	0.53	0.48-0.58
Smoking (1319)											
No (783)	0.15	0.22	0.37	0.60	0.94	1.48	1.82	5.13	0.75	0.57	0.54-0.60
Yes (300)	0.08	0.16	0.30	0.56	0.90	1.46	1.65	3.67	0.69	0.49	0.44-0.55
Ex (236)	0.16	0.23	0.37	0.63	1.04	1.69	2.33	7.38	0.85	0.61	0.55-0.68
Alcohol (1315)											
No (572)	0.15	0.20	0.35	0.58	0.91	1.44	1.76	7.38	0.73	0.55	0.51-0.59
Yes (743)	0.13	0.19	0.35	0.61	1.00	1.56	2.00	5.13	0.78	0.56	0.53-0.60

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

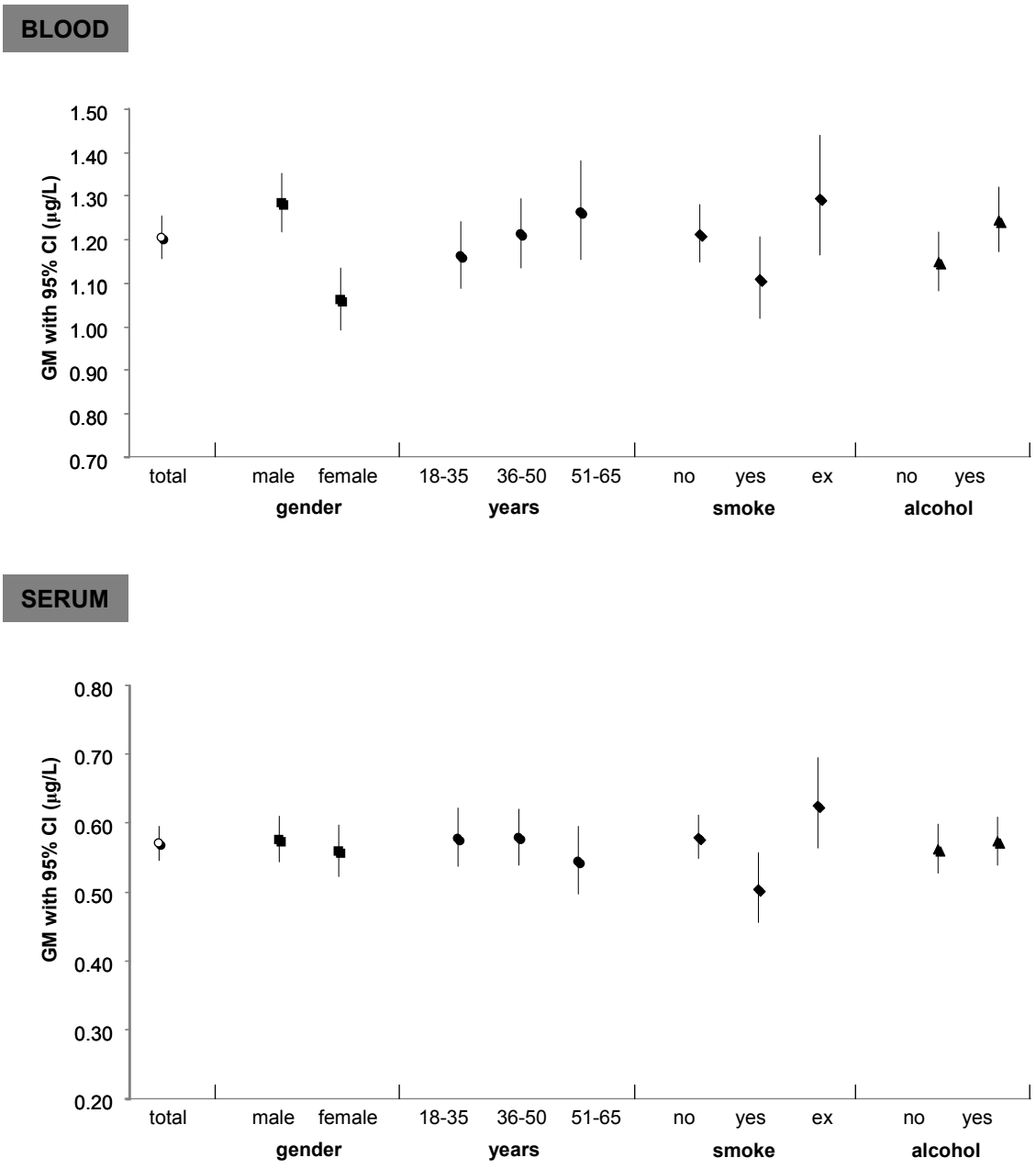


Figure A10. Mercury: GM concentrations in different classes

MOLYBDENUM (Mo)

Table A11. Molybdenum: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.31, N<LoD: 0)											
Total (1423)	0.69	0.79	0.99	1.22	1.52	1.79	2.05	5.13	1.28	1.21	1.19-1.23
Gender (1423)											
Male (953)	0.70	0.80	0.99	1.24	1.53	1.78	2.04	4.02	1.29	1.22	1.19-1.24
Female (470)	0.67	0.78	0.97	1.21	1.51	1.81	2.08	5.13	1.27	1.20	1.16-1.24
Age, years (1423)											
18-35 (516)	0.70	0.80	0.98	1.23	1.56	1.86	2.10	4.02	1.31	1.23	1.20-1.27
36-50 (582)	0.71	0.78	1.00	1.25	1.52	1.75	1.96	3.63	1.72	1.21	1.18-1.24
51-65 (325)	0.63	0.78	0.97	1.19	1.46	1.75	2.06	5.13	1.25	1.18	1.14-1.22
Smoking (1389)											
No (831)	0.69	0.81	1.01	1.25	1.54	1.82	2.05	5.13	1.30	1.23	1.20-1.26
Yes (315)	0.67	0.77	0.96	1.20	1.46	1.72	2.09	2.90	1.25	1.18	1.14-1.23
Ex (243)	0.70	0.78	0.95	1.20	1.51	1.78	1.94	3.20	1.25	1.19	1.14-1.24
Alcohol (1384)*											
No (617)	0.71	0.83	1.04	1.26	1.54	1.79	2.03	3.63	1.31	1.24	1.21-1.28
Yes (767)	0.68	0.78	0.95	1.19	1.49	1.78	2.09	5.13	1.26	1.19	1.16-1.22
SERUM (LoD 0.05, N<LoD: 0)											
Total (1344)	0.43	0.53	0.68	0.90	1.17	1.48	1.83	9.21	0.90	0.89	0.87-0.91
Gender (1344)											
Male (890)	0.42	0.51	0.66	0.89	1.16	1.48	1.86	7.13	0.97	0.88	0.85-0.90
Female (454)	0.48	0.56	0.71	0.93	1.19	1.49	1.77	9.21	1.01	0.92	0.89-0.96
Age, years (1344)											
18-35 (479)	0.49	0.56	0.70	0.92	1.15	1.48	1.85	2.90	0.99	0.91	0.88-0.95
36-50 (558)	0.45	0.54	0.69	0.90	1.19	1.49	1.81	9.21	1.01	0.91	0.87-0.94
51-65 (307)	0.37	0.45	0.63	0.84	1.15	1.47	1.83	7.13	0.94	0.83	0.79-0.88
Smoking (1319)**											
No (783)	0.46	0.54	0.70	0.91	1.19	1.49	1.87	9.21	1.01	0.92	0.89-0.94
Yes (300)	0.48	0.57	0.69	0.90	1.15	1.49	1.78	7.13	1.00	0.90	0.86-0.94
Ex (236)	0.33	0.43	0.61	0.83	1.10	1.38	1.53	3.91	0.89	0.80	0.75-0.85
Alcohol (1315)*											
No (572)	0.49	0.58	0.73	0.96	1.21	1.51	1.85	9.21	1.04	0.95	0.92-0.98
Yes (743)	0.40	0.49	0.65	0.85	1.10	1.42	1.80	7.13	0.94	0.85	0.82-0.87

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

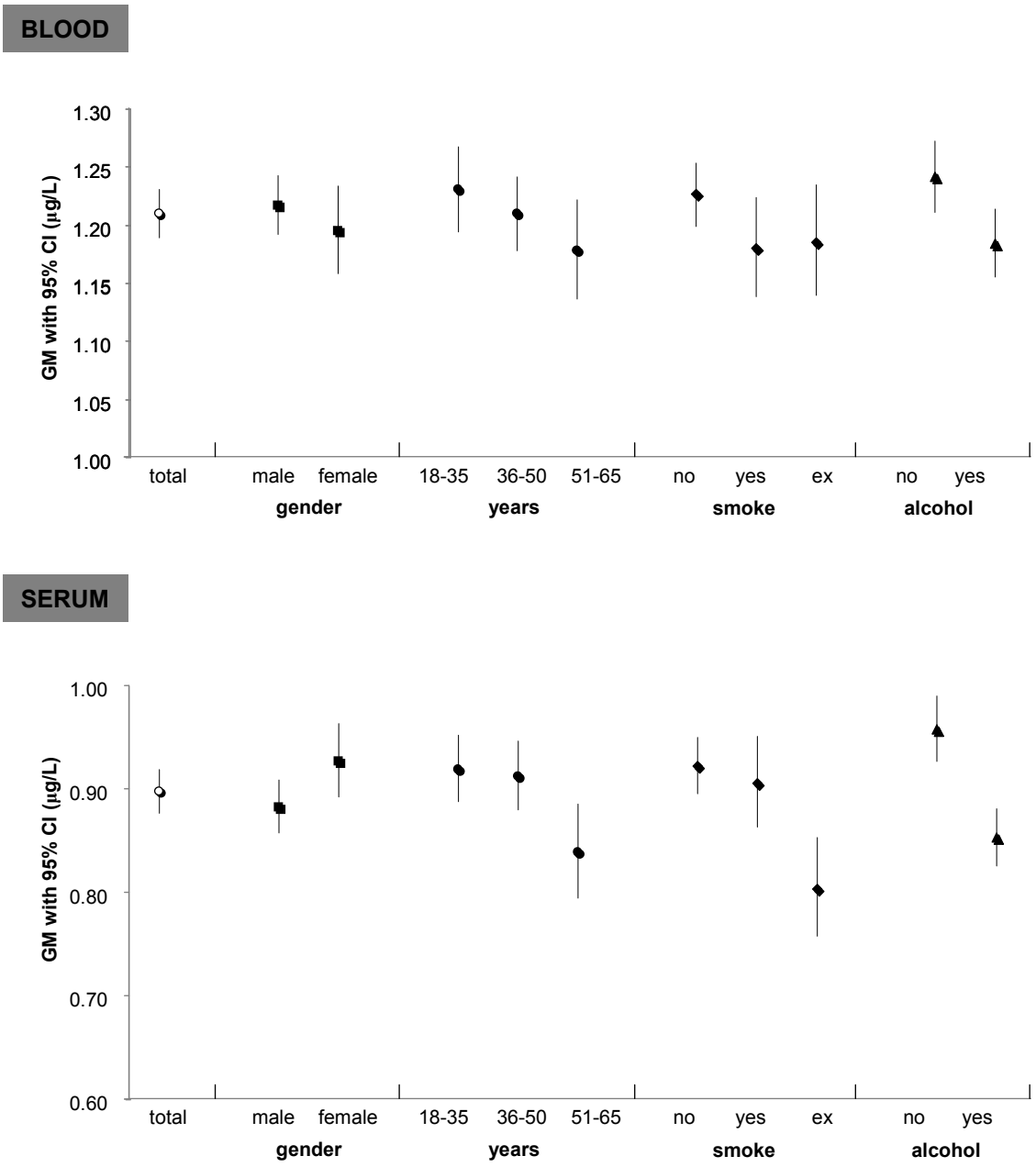


Figure A11. Molybdenum: GM concentrations in different classes

NICKEL (Ni)

Table A12. Nicke:l concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.35, N<LoD: 80)											
Total (1422)	<LoD	0.41	0.58	0.90	1.38	1.95	2.62	50.5	1.23	0.89	0.86-0.92
Gender (1422)											
Male (952)	<LoD	0.41	0.58	0.90	1.38	2.02	2.61	50.5	1.27	0.89	0.85-0.94
Female (470)	<LoD	0.42	0.57	0.89	1.39	1.86	2.65	36.6	1.16	0.88	0.83-0.94
Age, years (1422)											
18-35 (516)	<LoD	0.42	0.60	0.90	1.36	1.88	2.46	32.8	1.13	0.88	0.84-0.94
36-50 (581)	0.35	0.42	0.56	0.86	1.34	1.89	2.73	47.8	1.21	0.88	0.83-0.93
51-65 (325)	<LoD	0.38	0.55	0.93	1.45	2.38	3.01	50.5	1.43	0.91	0.84-1.00
Smoking (1388)											
No (830)	<LoD	0.41	0.58	0.91	1.40	1.97	2.72	50.5	1.32	0.90	0.86-0.95
Yes (315)	<LoD	0.39	0.55	0.89	1.32	1.81	2.51	7.07	1.07	0.85	0.79-0.92
Ex (243)	0.36	0.43	0.61	0.89	1.43	2.15	2.78	10.1	1.15	0.90	0.83-0.95
Alcohol (1383)											
No (617)	0.37	0.43	0.56	0.90	1.35	1.77	2.46	36.6	1.12	0.88	0.84-0.92
Yes (766)	<LoD	0.39	0.58	0.89	1.41	2.30	3.01	50.5	1.33	0.90	0.85-0.95
SERUM (LoD 0.03, N<LoD: 19)											
Total (1343)	0.09	0.14	0.27	0.39	0.58	0.82	0.94	10.5	0.45	0.35	0.34-0.37
Gender (1343)											
Male (889)	0.07	0.12	0.26	0.39	0.55	0.82	0.95	10.5	0.45	0.34	0.33-0.36
Female (454)	0.09	0.17	0.28	0.39	0.61	0.81	0.90	1.56	0.45	0.37	0.35-0.40
Age, years (1343)											
18-35 (479)	0.09	0.15	0.26	0.38	0.57	0.81	0.95	10.5	0.46	0.35	0.33-0.38
36-50 (558)	0.08	0.13	0.27	0.39	0.58	0.84	0.98	9.74	0.46	0.35	0.33-0.38
51-65 (306)	0.09	0.17	0.27	0.40	0.58	0.79	0.85	2.03	0.44	0.36	0.34-0.39
Smoking (1318)											
No (782)	0.09	0.14	0.27	0.39	0.57	0.82	0.95	10.5	0.45	0.35	0.34-0.37
Yes (300)	0.08	0.13	0.27	0.40	0.62	0.83	0.95	9.74	0.48	0.36	0.33-0.40
Ex (236)	0.07	0.14	0.26	0.39	0.56	0.76	0.88	1.33	0.42	0.34	0.31-0.38
Alcohol (1314)*											
No (572)	0.13	0.18	0.29	0.41	0.60	0.82	0.99	9.74	0.48	0.39	0.37-0.41
Yes (742)	0.07	0.11	0.25	0.38	0.55	0.81	0.90	10.5	0.44	0.33	0.31-0.35

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

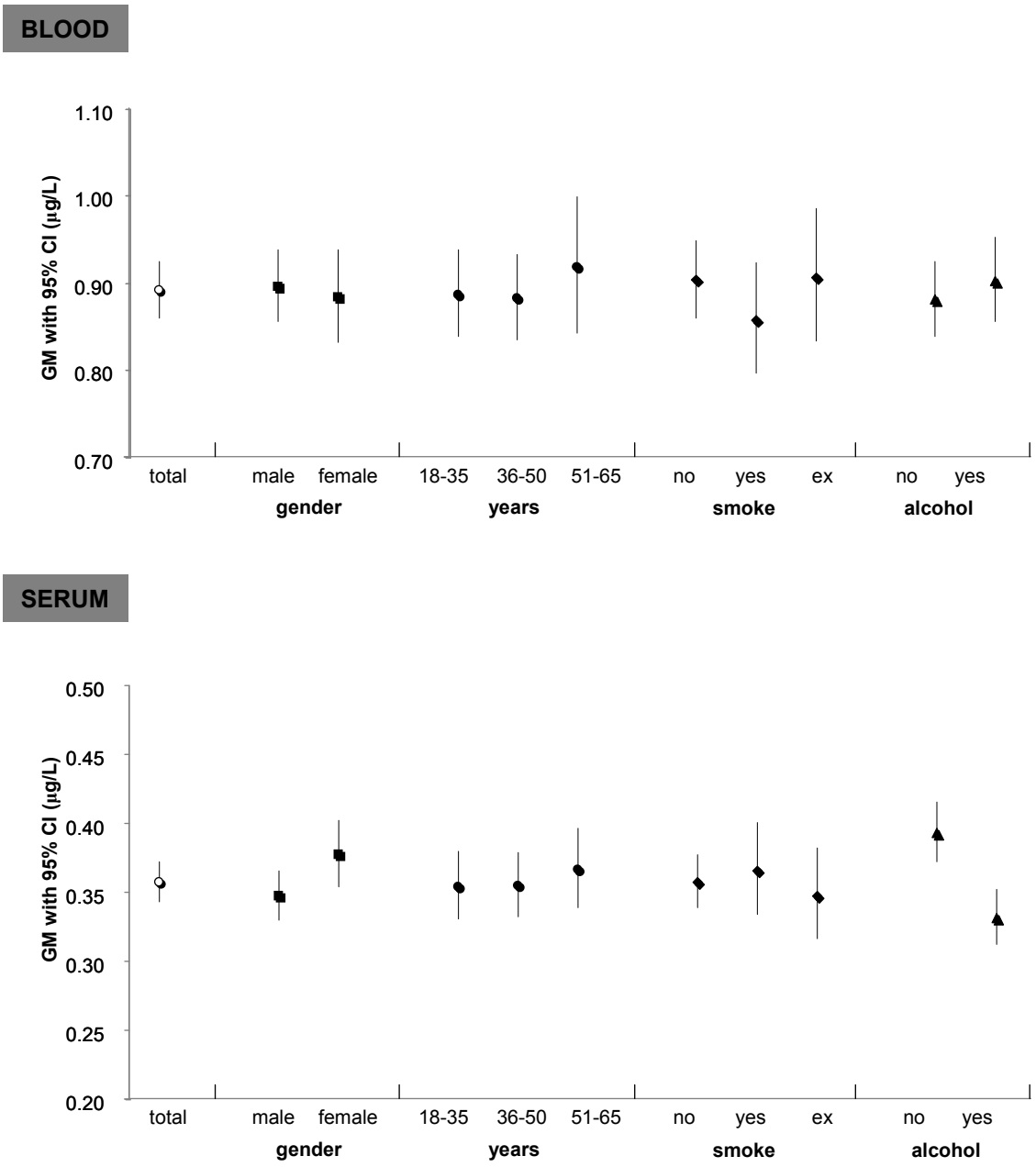


Figure A12. Nickel: GM concentrations in different classes

PALLADIUM (Pd)

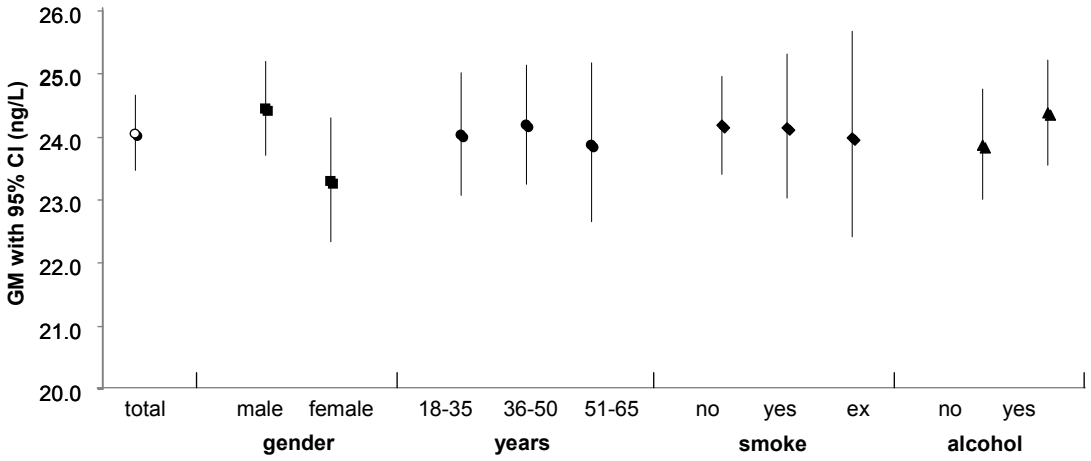
Table A13. Palladium: concentrations (ng/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 15.0, N<LoD: 125)											
Total (1423)	<LoD	15.5	19.4	25.2	32.2	40.7	47.6	390	26.9	24.0	23.4-24.6
Gender (1423)											
Male (953)	<LoD	15.6	19.8	25.4	32.4	41.0	49.1	390	27.4	24.4	23.6-25.2
Female (470)	<LoD	15.2	18.7	24.7	31.5	39.6	45.3	79.0	25.7	23.2	22.2-24.2
Age, years (1423)											
18-35 (516)	<LoD	15.4	19.2	25.5	32.2	40.0	46.4	111	26.6	24.0	22.9-25.0
36-50 (582)	<LoD	15.5	19.9	25.1	32.2	40.8	49.7	207	26.9	24.1	23.2-25.1
51-65 (325)	<LoD	15.6	18.9	25.0	32.1	41.2	47.3	390	27.2	23.8	22.6-25.1
Smoking (1389)											
No (831)	<LoD	15.5	19.7	25.3	32.4	40.6	47.5	207	26.8	24.1	23.3-24.9
Yes (315)	<LoD	16.3	19.1	24.6	31.3	40.9	47.3	75.7	26.3	24.1	22.9-25.3
Ex (243)	<LoD	<LoD	19.4	25.6	34.2	41.1	51.3	390	28.2	23.9	22.3-25.7
Alcohol (1384)											
No (617)	<LoD	15.4	19.3	25.4	31.9	40.2	44.4	207	26.4	23.8	22.9-24.7
Yes (767)	<LoD	15.7	19.6	25.2	32.6	41.3	50.7	390	27.4	24.3	23.5-25.2
SERUM (LoD 2.85, N<LoD: 40)											
Total (1343)	3.69	5.00	7.32	11.2	16.0	22.5	29.4	130.5	12.9	10.6	10.2-10.9
Gender (1343)*											
Male (889)	4.05	5.15	7.89	11.7	17.0	24.4	31.5	64.8	13.7	11.2	10.8-11.8
Female (454)	3.07	4.30	6.44	9.70	14.6	19.3	24.2	130.5	11.4	9.36	8.81-9.95
Age, years (1343)*											
18-35 (479)	3.18	4.59	6.65	10.0	15.0	20.3	25.5	64.8	11.7	9.68	9.13-10.3
36-50 (558)	4.34	5.52	7.79	11.6	16.7	24.4	30.6	63.9	13.6	11.2	10.6-11.8
51-65 (306)	3.02	4.69	7.75	11.9	17.1	23.4	30.2	130.5	13.6	10.9	10.1-11.8
Smoking (1318)											
No (782)	3.77	5.02	7.32	10.8	15.8	21.7	29.0	64.8	12.7	10.5	10.0-10.9
Yes (300)	3.93	5.04	7.26	10.9	15.6	21.0	26.3	50.1	12.4	10.3	9.64-11.1
Ex (236)	<LoD	4.87	7.97	12.5	18.5	27.4	36.0	130.5	14.8	11.5	10.5-12.7
Alcohol (1314)											
No (572)	4.24	5.60	7.80	11.3	16.0	22.2	28.9	130.5	13.2	11.0	10.2-11.5
Yes (742)	3.13	4.65	7.16	11.1	16.3	23.1	30.1	64.8	12.8	10.4	9.86-10.9

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

BLOOD



SERUM

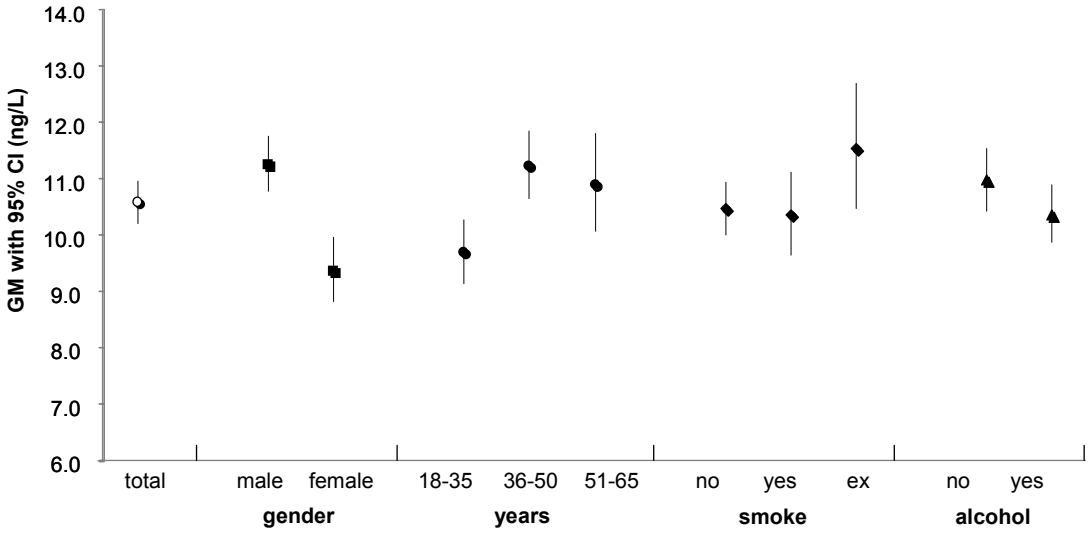


Figure A13. Palladium: GM concentrations in different classes

PLATINUM (Pt)

Table A14. Platinum: concentrations (ng/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 5.00, N<LoD: 59)											
Total (1423)	5.28	6.88	10.2	15.1	20.6	27.3	31.6	95.0	16.4	14.1	13.6-14.5
Gender (1423)*											
Male (953)	5.56	7.49	10.8	16.0	21.7	28.7	35.1	95.0	17.5	14.9	14.4-15.5
Female (470)	<LoD	6.49	9.26	13.9	18.9	23.4	28.3	57.7	14.5	12.5	11.8-13.2
Age, years (1423)											
18-35 (516)	7.50	15.4	19.2	25.5	32.2	40.0	46.4	95.0	17.2	14.7	14.0-15.5
36-50 (582)	7.50	15.5	19.9	25.1	32.2	40.8	49.7	56.8	16.2	14.1	13.5-14.8
51-65 (325)	7.50	15.6	18.9	25.0	32.1	41.2	47.3	75.5	15.5	12.9	12.0-13.8
Smoking (1389)											
No (831)	5.33	6.86	10.2	15.1	20.3	26.3	30.2	75.5	16.1	13.9	13.4-14.5
Yes (315)	<LoD	7.32	10.2	14.8	20.1	27.7	33.8	95.0	16.4	14.0	13.1-14.9
Ex (243)	5.13	6.23	9.62	15.6	21.8	30.2	37.9	74.6	17.2	14.3	13.2-15.5
Alcohol (1384)**											
No (617)	5.06	6.64	9.86	14.5	19.5	24.4	28.6	74.6	15.3	13.3	12.7-13.9
Yes (767)	5.27	7.13	10.3	15.6	21.8	29.6	35.5	95.0	17.2	14.6	14.0-15.2
SERUM (LoD 0.74, N<LoD: 6)											
Total (1344)	1.64	2.21	3.62	5.64	7.97	10.8	13.3	475	6.79	5.23	5.04-5.42
Gender (1344)											
Male (890)	1.58	2.14	3.44	5.50	7.94	10.8	13.7	475	6.94	5.14	4.91-5.38
Female (454)	1.74	2.30	3.93	5.87	8.12	10.8	12.5	60.6	6.50	5.41	5.10-5.73
Age, years (1344)											
18-35 (479)	1.63	2.31	3.77	5.66	8.52	11.6	14.1	60.6	6.76	5.40	5.08-5.75
36-50 (558)	1.51	2.17	3.60	5.85	8.03	10.6	13.0	475	7.15	5.23	4.94-5.54
51-65 (307)	1.74	2.19	3.35	5.13	7.41	9.69	12.6	121	6.19	4.96	4.62-5.31
Smoking (1319)											
No (783)	1.70	2.30	3.75	5.79	8.30	11.0	13.5	475	7.14	5.38	5.13-5.64
Yes (300)	1.83	2.42	3.73	5.81	7.89	10.4	12.4	32.4	6.40	5.32	4.95-5.72
Ex (236)	1.32	1.78	2.88	5.18	7.87	10.6	13.3	121	6.28	4.66	4.24-5.13
Alcohol (1315)*											
No (572)	2.00	2.56	4.27	6.15	8.67	11.6	14.4	60.6	7.05	5.88	5.60-6.19
Yes (743)	1.43	1.96	3.22	5.09	7.55	10.4	12.5	475	6.62	4.77	4.53-5.02

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

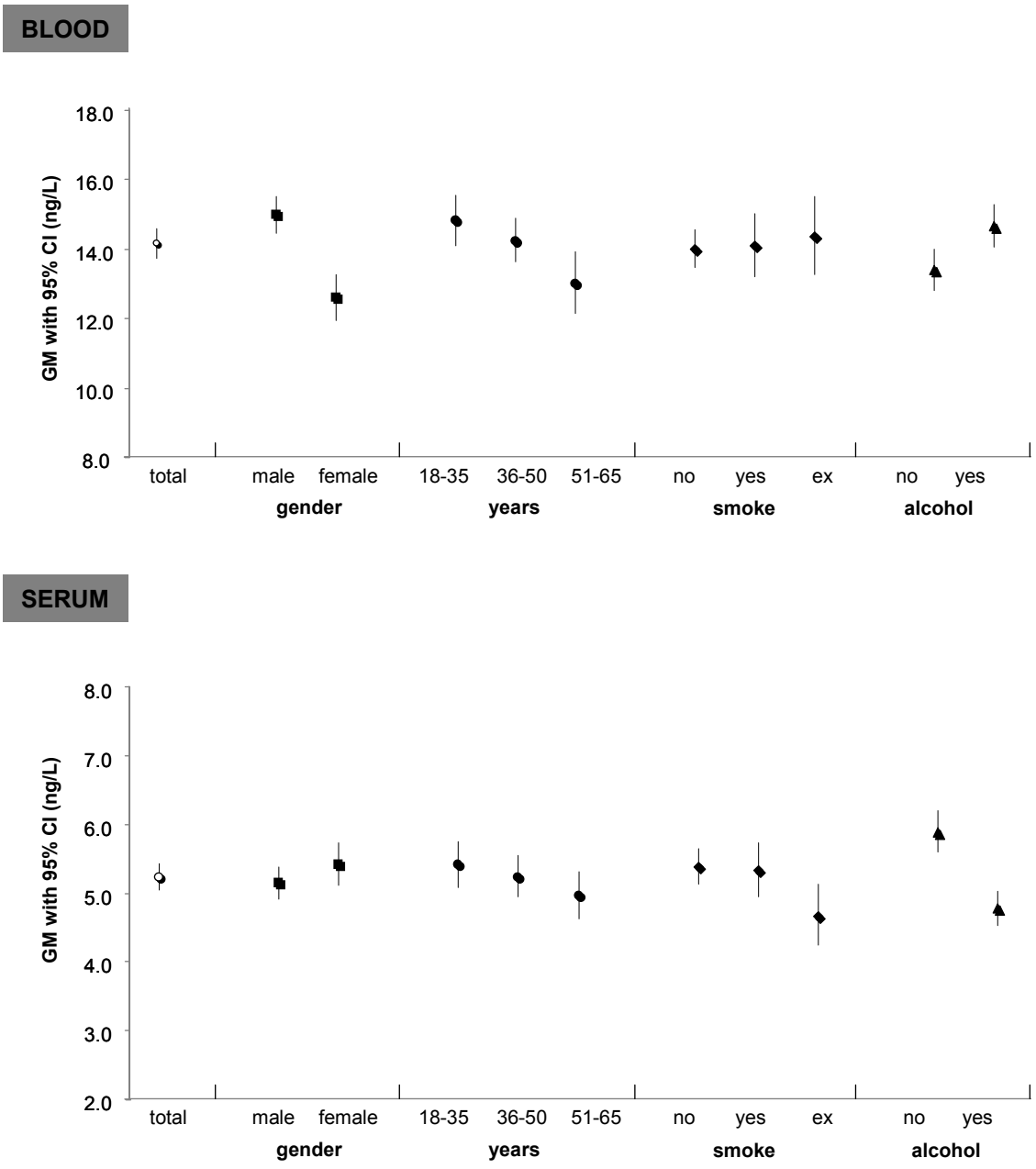


Figure A14. Platinum: GM concentrations in different classes

RHODIUM (Rh)

Table A15. Rhodium: concentrations (ng/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 15.0, N<LoD: 220)											
Total (1423)	<LoD	<LoD	16.2	18.9	24.0	28.8	32.2	59.3	19.6	18.0	17.6-18.4
Gender (1423)*											
Male (953)	<LoD	<LoD	15.8	18.5	22.9	28.3	31.0	46.0	18.9	17.3	16.8-17.8
Female (470)	<LoD	<LoD	16.7	19.8	25.5	30.5	33.6	59.3	21.0	19.5	18.8-20.2
Age, years (1423)											
18-35 (516)	<LoD	<LoD	16.3	19.3	24.7	30.3	33.8	59.3	20.3	18.7	18.0-19.4
36-50 (582)	<LoD	<LoD	16.1	18.8	24.0	29.0	31.8	51.9	19.4	17.8	17.2-18.4
51-65 (325)	<LoD	<LoD	15.9	18.3	22.8	27.0	29.6	38.7	18.7	17.3	16.6-18.2
Smoking (1389)											
No (831)	<LoD	<LoD	16.2	19.2	24.4	29.6	32.4	59.3	19.9	18.3	17.8-18.9
Yes (315)	<LoD	<LoD	15.9	18.5	22.9	27.0	29.8	40.7	18.8	17.4	16.6-18.2
Ex (243)	<LoD	<LoD	16.0	18.2	23.1	28.6	32.2	51.9	19.0	17.4	16.4-18.4
Alcohol (1384)*											
No (617)	<LoD	<LoD	16.5	19.7	25.0	29.9	33.1	59.3	20.4	18.9	18.3-19.5
Yes (767)	<LoD	<LoD	15.8	18.3	22.6	28.3	30.8	59.2	18.8	17.2	16.7-17.7
SERUM (LoD 2.05, N<LoD: 32)											
Total (1343)	3.21	4.29	6.56	10.2	14.1	18.8	23.1	56.4	11.1	9.28	8.97-9.60
Gender (1343)*											
Male (889)	2.98	3.98	6.17	9.73	13.2	16.9	19.7	56.4	10.3	8.73	8.38-9.10
Female (454)	3.86	4.86	7.36	11.0	15.6	22.9	27.3	43.0	12.5	10.4	9.84-11.1
Age, years (1343)											
18-35 (479)	2.81	3.97	6.31	10.0	14.4	19.3	25.0	56.4	11.1	9.07	8.52-9.66
36-50 (558)	3.36	4.32	6.73	10.1	13.8	18.8	21.8	43.0	11.0	9.34	8.89-9.82
51-65 (306)	3.60	4.63	6.79	10.6	14.0	18.4	21.7	47.8	11.1	9.48	8.85-10.2
Smoking (1318)											
No (782)	2.95	4.20	6.55	10.3	14.0	19.0	24.5	56.4	11.2	9.27	8.85-9.71
Yes (300)	3.35	4.42	6.47	10.2	14.7	18.5	21.3	33.7	11.0	9.32	8.68-10.0
Ex (236)	3.34	4.26	6.88	9.74	13.2	18.9	21.3	47.8	10.8	9.28	8.61-10.0
Alcohol (1314)											
No (572)	3.33	4.24	6.57	10.2	14.3	19.3	24.2	56.4	11.2	9.33	8.85-9.84
Yes (742)	3.16	4.30	6.50	10.2	13.9	18.4	21.8	47.8	11.0	9.23	8.82-9.67

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

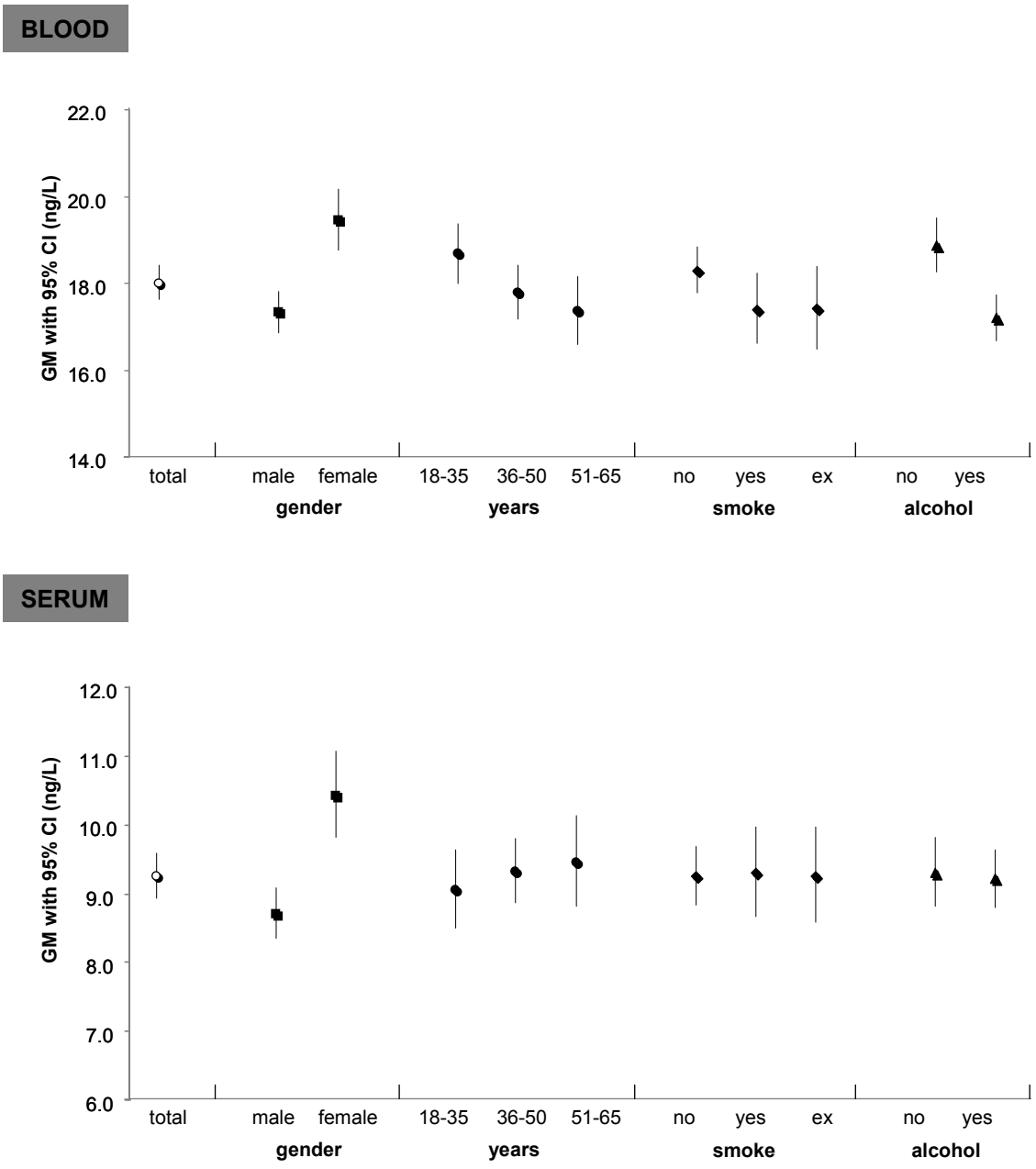


Figure A15. Rhodium: GM concentrations in different classes

THALLIUM (Tl)

Table A16. Thallium: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.015, N<LoD: 21)											
Total (1423)	0.018	0.020	0.026	0.034	0.048	0.074	0.098	0.74	0.045	0.037	0.035-0.038
Gender (1423)											
Male (953)	0.017	0.020	0.026	0.034	0.048	0.073	0.095	0.47	0.043	0.036	0.035-0.037
Female (470)	0.018	0.021	0.025	0.033	0.049	0.077	0.121	0.74	0.049	0.037	0.035-0.039
Age, years (1423)											
18-35 (516)	0.018	0.021	0.026	0.034	0.050	0.079	0.106	0.74	0.048	0.038	0.036-0.040
36-50 (582)	0.018	0.020	0.026	0.034	0.048	0.073	0.093	0.47	0.043	0.036	0.035-0.038
51-65 (325)	0.017	0.019	0.024	0.033	0.048	0.073	0.113	0.37	0.043	0.035	0.033-0.037
Smoking (1389)											
No (831)	0.017	0.020	0.026	0.035	0.050	0.077	0.097	0.62	0.045	0.037	0.036-0.038
Yes (315)	0.018	0.020	0.025	0.032	0.045	0.073	0.105	0.69	0.045	0.035	0.033-0.038
Ex (243)	0.017	0.020	0.025	0.030	0.043	0.070	0.094	0.74	0.043	0.034	0.032-0.037
Alcohol (1384)*											
No (617)	0.018	0.020	0.026	0.036	0.056	0.080	0.103	0.69	0.049	0.039	0.037-0.040
Yes (767)	0.017	0.020	0.025	0.031	0.044	0.065	0.092	0.74	0.041	0.034	0.033-0.036
SERUM (LoD 0.005, N<LoD: 1)											
Total (1344)	0.012	0.014	0.018	0.024	0.034	0.050	0.071	1.79	0.034	0.026	0.025-0.026
Gender (1344)											
Male (890)	0.012	0.014	0.018	0.024	0.034	0.049	0.066	1.79	0.031	0.025	0.024-0.026
Female (454)	0.013	0.014	0.019	0.024	0.035	0.057	0.090	1.51	0.038	0.027	0.025-0.028
Age, years (1344)											
18-35 (479)	0.013	0.014	0.018	0.024	0.035	0.050	0.072	1.79	0.035	0.026	0.025-0.027
36-50 (558)	0.012	0.014	0.018	0.024	0.034	0.050	0.065	1.51	0.032	0.026	0.024-0.027
51-65 (307)	0.010	0.013	0.017	0.023	0.033	0.052	0.085	0.62	0.034	0.025	0.023-0.027
Smoking (1319)*											
No (783)	0.012	0.014	0.019	0.025	0.036	0.055	0.072	0.62	0.032	0.027	0.025-0.028
Yes (300)	0.010	0.014	0.017	0.023	0.030	0.046	0.084	1.79	0.036	0.024	0.023-0.026
Ex (236)	0.012	0.014	0.017	0.021	0.030	0.046	0.065	1.51	0.034	0.024	0.022-0.026
Alcohol (1315)*											
No (572)	0.012	0.014	0.019	0.026	0.039	0.056	0.078	1.51	0.036	0.028	0.026-0.029
Yes (743)	0.012	0.014	0.017	0.022	0.030	0.047	0.066	1.79	0.031	0.024	0.023-0.025

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

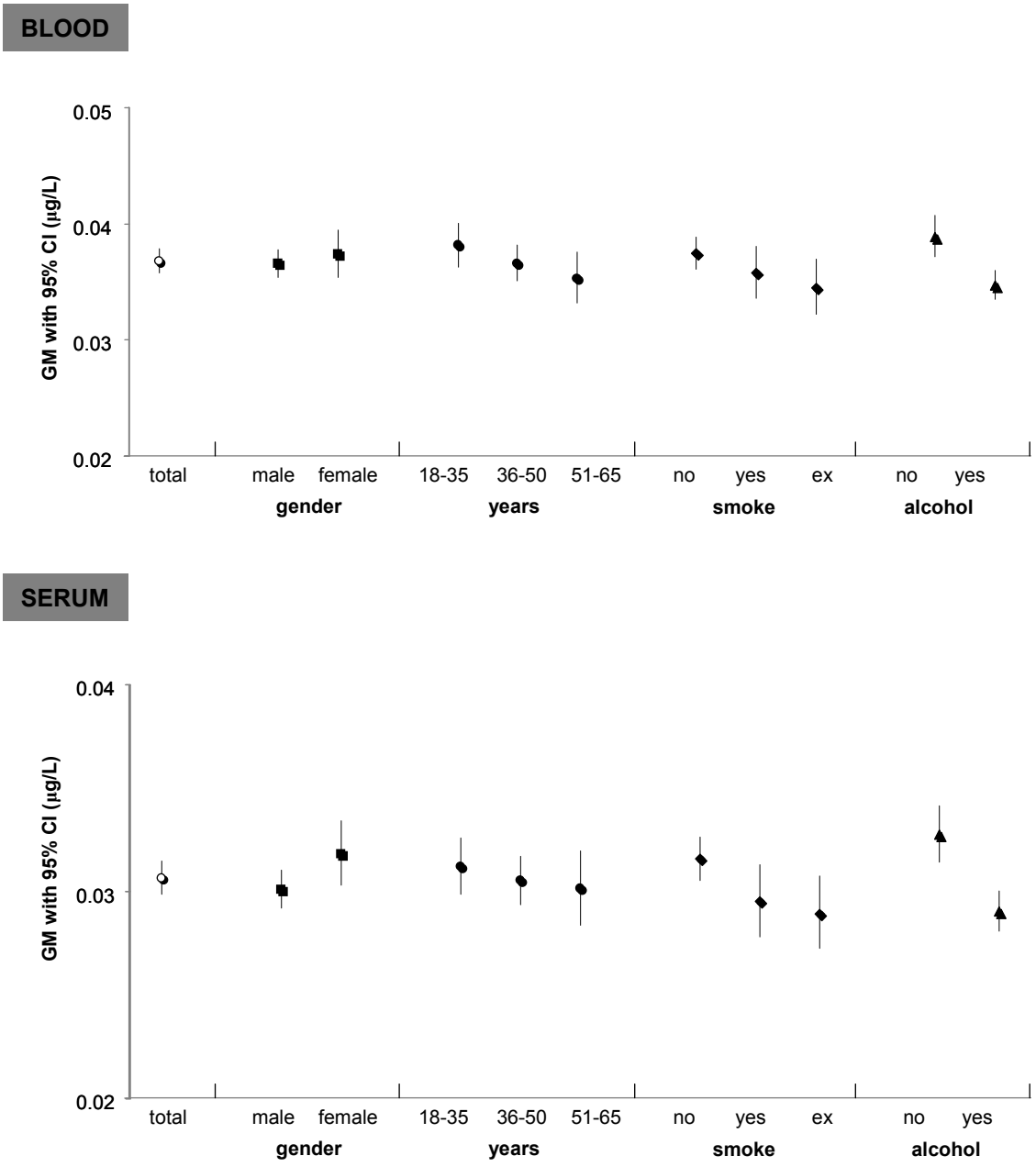


Figure A16. Thallium: GM concentrations in different classes

TIN (Sn)

Table A17. Tin: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.095, N<LoD: 32)											
Total (1423)	0.124	0.169	0.289	0.501	0.975	1.754	2.250	86.5	1.261	0.539	0.512-0.568
Gender (1423)											
Male (953)	0.130	0.172	0.286	0.524	0.976	1.825	2.255	86.5	1.305	0.552	0.518-0.588
Female (470)	0.109	0.164	0.296	0.476	0.963	1.725	2.164	57.1	1.172	0.514	0.469-0.563
Age, years (1423)											
18-35 (516)	0.129	0.171	0.292	0.489	0.997	1.667	2.218	70.3	1.019	0.527	0.486-0.571
36-50 (582)	0.116	0.158	0.280	0.504	0.926	1.725	2.145	42.8	0.912	0.506	0.468-0.547
51-65 (325)	0.142	0.184	0.299	0.511	1.111	1.992	3.206	86.5	2.270	0.625	0.552-0.708
Smoking (1389)											
No (831)	0.130	0.181	0.291	0.496	0.948	1.696	2.222	86.5	1.240	0.534	0.500-0.570
Yes (315)	0.109	0.145	0.272	0.458	0.866	1.705	2.089	48.0	1.102	0.488	0.437-0.546
Ex (243)	0.132	0.176	0.299	0.557	1.305	2.067	3.075	43.5	1.514	0.610	0.531-0.700
Alcohol (1384)											
No (617)	0.129	0.164	0.272	0.473	0.893	1.650	2.107	78.1	1.183	0.507	0.469-0.547
Yes (767)	0.120	0.177	0.299	0.521	1.012	1.920	2.292	86.5	1.320	0.561	0.522-0.603
SERUM (LoD 0.06, N<LoD: 23)											
Total (1344)	0.11	0.14	0.21	0.34	0.51	0.85	1.27	5.19	0.46	0.34	0.32-0.35
Gender (1344)*											
Male (890)	0.11	0.15	0.23	0.36	0.56	0.94	1.37	5.19	0.49	0.36	0.34-0.38
Female (454)	0.10	0.13	0.19	0.30	0.46	0.75	1.15	3.37	0.40	0.30	0.28-0.32
Age, years (1344)											
18-35 (479)	0.11	0.14	0.21	0.32	0.48	0.75	1.20	4.28	0.43	0.32	0.30-0.34
36-50 (558)	0.11	0.14	0.21	0.34	0.51	0.82	1.14	5.19	0.45	0.34	0.32-0.36
51-65 (307)	0.09	0.14	0.23	0.36	0.62	1.07	1.52	4.72	0.53	0.37	0.33-0.41
Smoking (1319)**											
No (783)	0.11	0.14	0.21	0.32	0.49	0.85	1.19	5.19	0.44	0.33	0.31-0.34
Yes (300)	0.11	0.13	0.21	0.33	0.52	0.80	1.21	4.28	0.44	0.34	0.31-0.36
Ex (236)	0.10	0.16	0.25	0.39	0.60	0.93	1.48	3.79	0.52	0.38	0.34-0.42
Alcohol (1315)											
No (572)	0.11	0.14	0.21	0.32	0.46	0.75	1.10	3.11	0.41	0.32	0.30-0.34
Yes (743)	0.11	0.14	0.21	0.35	0.57	0.94	1.40	5.19	0.49	0.35	0.33-0.37

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

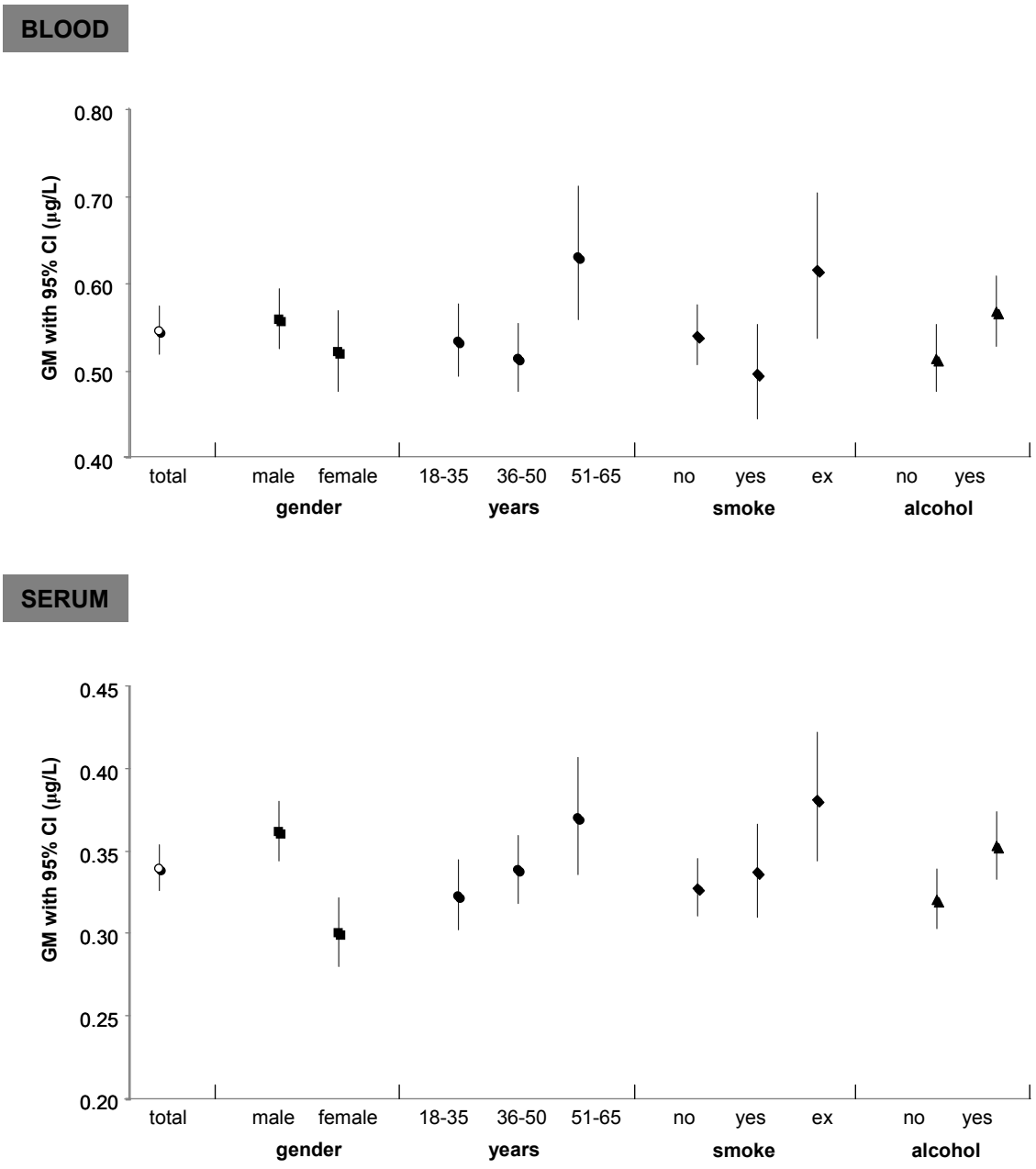


Figure A17. Tin: GM concentrations in different classes

TUNGSTEN (W)

Table A18. Tungsten: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.005, N<LoD: 1)											
Total (1423)	0.011	0.014	0.019	0.027	0.039	0.059	0.075	5.14	0.038	0.028	0.027-0.029
Gender (1423)*											
Male (953)	0.012	0.014	0.019	0.028	0.041	0.063	0.082	0.63	0.036	0.029	0.028-0.030
Female (470)	0.010	0.013	0.018	0.025	0.035	0.053	0.066	5.14	0.044	0.026	0.025-0.028
Age, years (1423)*											
18-35 (516)	0.012	0.015	0.021	0.030	0.043	0.065	0.085	5.14	0.047	0.031	0.029-0.033
36-50 (582)	0.012	0.014	0.018	0.026	0.037	0.057	0.072	0.93	0.034	0.027	0.026-0.028
51-65 (325)	0.010	0.013	0.017	0.025	0.037	0.055	0.066	0.29	0.031	0.025	0.024-0.027
Smoking (1389)											
No (831)	0.011	0.014	0.019	0.027	0.038	0.058	0.070	0.93	0.036	0.028	0.027-0.029
Yes (315)	0.011	0.014	0.018	0.026	0.040	0.067	0.076	0.14	0.033	0.028	0.026-0.029
Ex (243)	0.011	0.014	0.019	0.028	0.043	0.063	0.084	5.14	0.056	0.030	0.027-0.032
Alcohol (1384)											
No (617)	0.012	0.014	0.020	0.027	0.037	0.058	0.069	0.39	0.033	0.028	0.026-0.029
Yes (767)	0.011	0.014	0.018	0.027	0.041	0.062	0.082	5.14	0.043	0.290	0.027-0.030
SERUM (LoD 0.019, N<LoD: 2)											
Total (1344)	0.055	0.064	0.079	0.102	0.138	0.190	0.235	0.570	0.117	0.106	0.103-0.108
Gender (1344)**											
Male (890)	0.057	0.066	0.079	0.104	0.142	0.200	0.247	0.570	0.121	0.109	0.106-0.112
Female (454)	0.052	0.061	0.079	0.098	0.132	0.175	0.195	0.370	0.109	0.100	0.096-0.104
Age, years (1344)											
18-35 (479)	0.055	0.063	0.080	0.107	0.145	0.191	0.216	0.350	0.118	0.108	0.104-0.112
36-50 (558)	0.057	0.066	0.079	0.101	0.138	0.192	0.250	0.570	0.119	0.107	0.103-0.111
51-65 (307)	0.049	0.061	0.074	0.099	0.127	0.186	0.243	0.420	0.113	0.101	0.096-0.106
Smoking (1319)											
No (783)	0.057	0.066	0.081	0.103	0.139	0.191	0.232	0.490	0.118	0.108	0.104-0.111
Yes (300)	0.056	0.064	0.079	0.105	0.142	0.196	0.240	0.570	0.121	0.108	0.102-0.114
Ex (236)	0.049	0.058	0.074	0.099	0.131	0.175	0.219	0.420	0.111	0.100	0.094-0.105
Alcohol (1315)*											
No (572)	0.057	0.067	0.085	0.110	0.146	0.198	0.250	0.570	0.125	0.114	0.109-0.117
Yes (743)	0.053	0.064	0.076	0.098	0.130	0.181	0.216	0.490	0.111	0.101	0.097-0.104

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

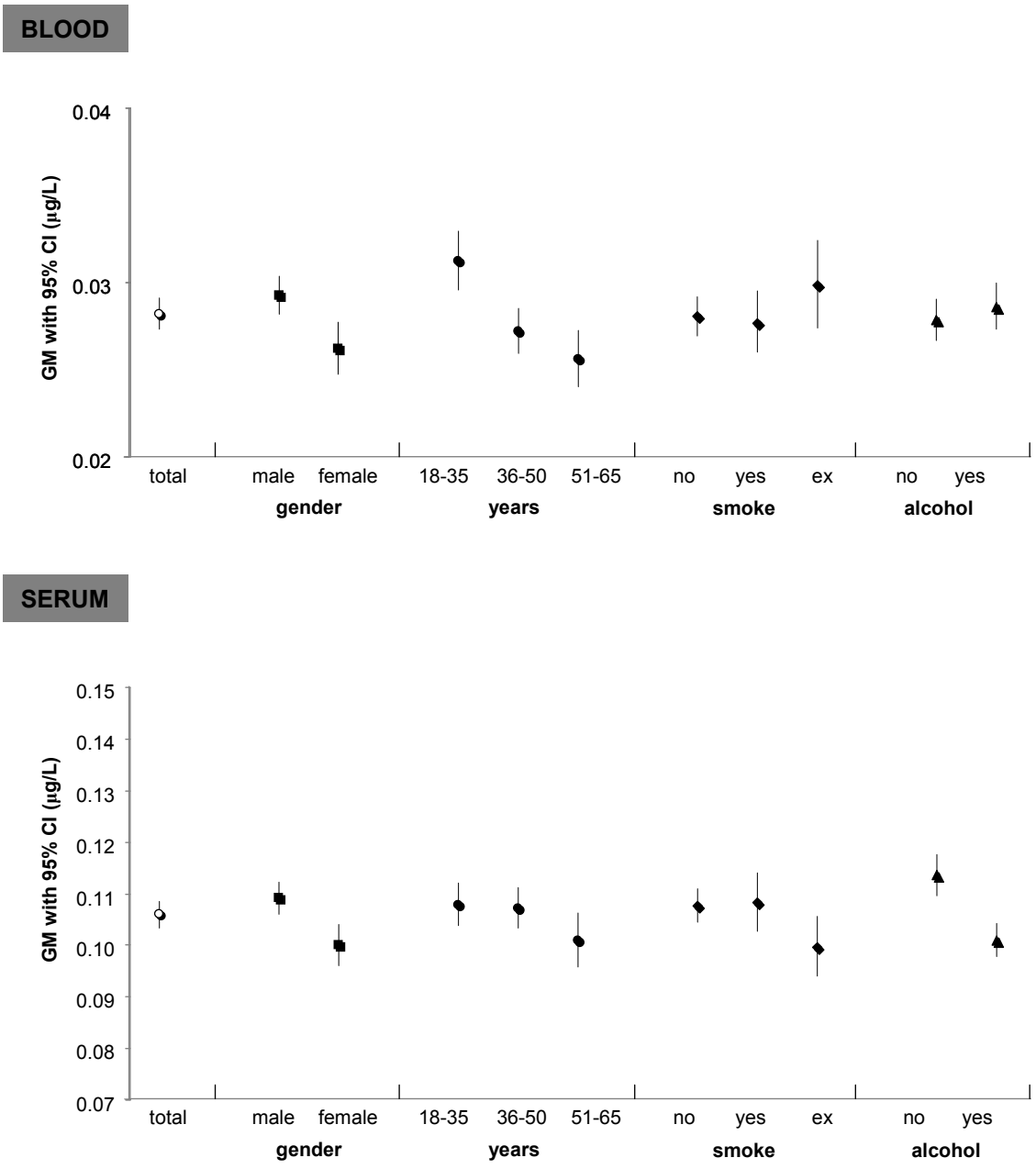


Figure A18. Tungsten: GM concentrations in different classes

URANIUM (U)

Table A19. Uranium: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.0015, N<LoD: 32)											
Total (1423)	0.0018	0.0026	0.0042	0.0059	0.0083	0.0115	0.0140	0.0898	0.0068	0.0057	0.0055-0.0058
Gender (1423)*											
Male (953)	0.0017	0.0024	0.0040	0.0058	0.0084	0.0117	0.0142	0.0436	0.0067	0.0056	0.0053-0.0058
Female (470)	0.0021	0.0032	0.0046	0.0061	0.0080	0.0108	0.0138	0.0898	0.0069	0.0059	0.0056-0.0062
Age, years (1423)*											
18-35 (516)	0.0020	0.0030	0.0048	0.0064	0.0083	0.0116	0.0142	0.0898	0.0072	0.0061	0.0057-0.0064
36-50 (582)	0.0020	0.0025	0.0041	0.0059	0.0084	0.0113	0.0139	0.0436	0.0066	0.0056	0.0053-0.0059
51-65 (325)	0.0016	0.0022	0.0037	0.0053	0.0081	0.0118	0.0139	0.0420	0.0063	0.0052	0.0048-0.0055
Smoking (1389)											
No (831)	0.0020	0.0029	0.0046	0.0061	0.0083	0.0113	0.0139	0.0898	0.0070	0.0059	0.0057-0.0061
Yes (315)	0.0016	0.0026	0.0040	0.0059	0.0083	0.0115	0.0148	0.0242	0.0065	0.0055	0.0051-0.0059
Ex (243)	0.0016	0.0021	0.0034	0.0054	0.0083	0.0125	0.0152	0.0436	0.0066	0.0052	0.0047-0.0057
Alcohol (1384)											
No (617)	0.0023	0.0033	0.0046	0.0061	0.0083	0.0113	0.0138	0.0898	0.0070	0.0060	0.0057-0.0063
Yes (767)	0.0017	0.0022	0.0039	0.0058	0.0083	0.0120	0.0145	0.0436	0.0066	0.0054	0.0052-0.0057

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests

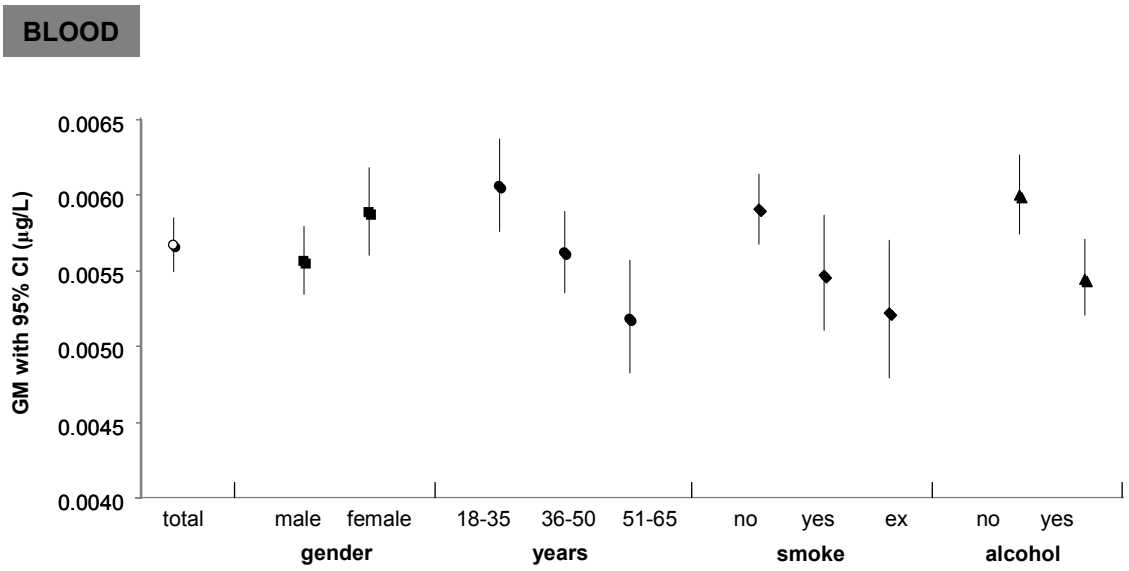


Figure A19. Uranium: GM concentrations in different classes

VANADIUM (V)

Table A20. Vanadium: concentrations (µg/L) in adults (18-65 years) in Italy

Class (sample size)	P5	P10	P25	P50	P75	P90	P95	MAX	AM	GM	CI-GM
BLOOD (LoD 0.024, N<LoD: 28)											
Total (1423)	0.027	0.030	0.045	0.067	0.092	0.120	0.146	1.41	0.076	0.064	0.062-0.066
Gender (1423)											
Male (953)	0.026	0.030	0.043	0.067	0.093	0.123	0.146	1.22	0.075	0.063	0.061-0.066
Female (470)	0.027	0.031	0.047	0.069	0.090	0.114	0.145	1.41	0.080	0.065	0.062-0.069
Age, years (1423)**											
18-35 (516)	0.028	0.032	0.050	0.072	0.092	0.118	0.151	1.41	0.082	0.068	0.064-0.071
36-50 (582)	0.025	0.030	0.043	0.065	0.093	0.120	0.138	1.06	0.074	0.062	0.059-0.065
51-65 (325)	0.027	0.030	0.041	0.061	0.087	0.121	0.167	0.55	0.072	0.061	0.058-0.065
Smoking (1389)*											
No (831)	0.027	0.031	0.046	0.069	0.094	0.124	0.152	1.22	0.080	0.066	0.063-0.069
Yes (315)	0.027	0.030	0.043	0.063	0.088	0.117	0.133	0.38	0.070	0.062	0.058-0.065
Ex (243)	0.025	0.029	0.039	0.060	0.082	0.105	0.137	1.41	0.070	0.058	0.054-0.062
Alcohol (1384)*											
No (617)	0.028	0.034	0.050	0.073	0.096	0.127	0.151	1.22	0.082	0.069	0.066-0.072
Yes (767)	0.026	0.030	0.040	0.060	0.086	0.112	0.140	1.410	0.071	0.059	0.057-0.062
SERUM (LoD 0.015, N<LoD: 4)											
Total (1343)	0.019	0.022	0.032	0.043	0.059	0.085	0.115	0.78	0.052	0.044	0.043-0.045
Gender (1343)*											
Male (889)	0.020	0.023	0.033	0.045	0.060	0.091	0.131	0.34	0.053	0.046	0.044-0.047
Female (454)	0.018	0.021	0.030	0.040	0.052	0.078	0.095	0.78	0.048	0.040	0.038-0.042
Age, years (1343)											
18-35 (479)	0.020	0.023	0.033	0.044	0.059	0.085	0.115	0.78	0.053	0.044	0.042-0.046
36-50 (558)	0.020	0.024	0.033	0.044	0.060	0.081	0.110	0.31	0.051	0.044	0.042-0.046
51-65 (306)	0.015	0.020	0.029	0.042	0.059	0.091	0.137	0.43	0.052	0.042	0.039-0.045
Smoking (1318)											
No (782)	0.020	0.023	0.032	0.042	0.055	0.077	0.100	0.78	0.050	0.043	0.041-0.044
Yes (300)	0.017	0.020	0.034	0.045	0.062	0.095	0.125	0.31	0.054	0.046	0.043-0.049
Ex (236)	0.015	0.020	0.030	0.045	0.061	0.106	0.148	0.43	0.056	0.046	0.042-0.049
Alcohol (1314)											
No (572)	0.020	0.025	0.033	0.045	0.060	0.082	0.106	0.78	0.053	0.045	0.043-0.047
Yes (742)	0.017	0.020	0.030	0.043	0.059	0.090	0.129	0.44	0.051	0.043	0.041-0.045

N: number of cases;
P5, P10, P25, P50, P75, P90, P95 = percentiles;
MAX = maximum value;
AM = arithmetic mean;
GM = geometric mean;
CI-GM = approximate 95% confidence interval for GM.

* p≤0.001, Mann-Whitney or Kruskal-Wallis tests
** p≤0.01, Mann-Whitney or Kruskal-Wallis tests

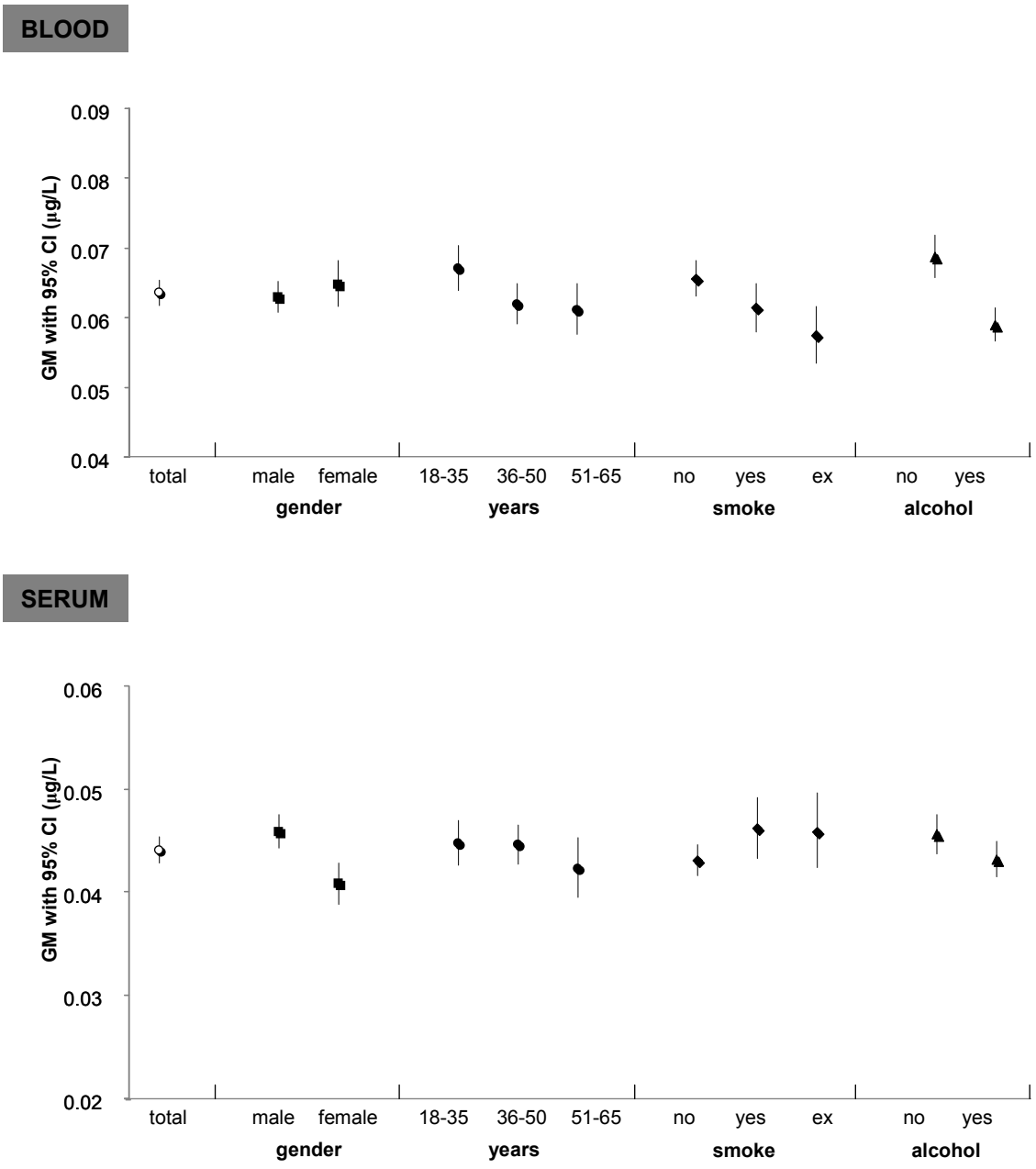


Figure A20. Vanadium: GM concentrations in different classes

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