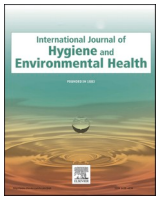
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Biomonitoring for workplace exposure to copper and its compounds is currently not interpretable

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ABSTRACT

This paper sets out to explore the requirements needed to recommend a useable and reliable biomonitoring system for occupational exposure to copper and its inorganic compounds. Whilst workplace environmental monitoring of copper is used to measure ambient air concentrations for comparison against occupational exposure limits, biological monitoring could provide complementary information about the internal dose of workers, taking into account intra-individual variability and exposure from all routes. For biomonitoring to be of reliable use for copper, a biomarker and the analytical ability to measure it with sufficient sensitivity must be identified and this is discussed in a range of matrices. In addition, there needs to be a clear understanding of the dose-response relationship of the biomarker with any health-effect (clinical or sub-clinical) or, between the level of external exposure (by any route) and the level of the copper biomarker in the biological matrix being sampled, together with a knowledge of the half-life in the body to determine accurate sampling times. For many biologically non-essential metals the requirements for reliable biomarkers can be met, however, for 'essential' metals such as copper that are under homeostatic control, the relationship between exposure (short- or long-term) and the level of any copper biomarker in the blood or urine is complex, which may limit the use and interpretation of measured levels. There are a number of types of biomarker guidance values currently in use which are discussed in this paper, but no values have yet been determined for copper (or its inorganic compounds) due to the complexity of its essential nature; the US The American Conference of Governmental Industrial Hygienists (ACGIH) has however indicated that it is considering the development of a biological exposure index for copper and its compounds. In light of this, we present a review of the reliability of current copper biomarkers and their potential use in the occupational context to evaluate whether there is value in carrying out human biomonitoring for copper exposure. Based on the available evidence we have concluded that the reliable use of biomonitoring of occupational exposure to copper and its application in risk assessment is not possible at the present time.

1. Introduction

Human biomonitoring is a widely acknowledged method to assess human systemic exposure to chemicals, including metals, at both occupational and environmental concentrations (Bevan et al., 2013). While environmental monitoring is a useful tool to collect information about the metal concentration in the ambient air of a workplace, biological monitoring can provide important complementary information about the internal dose of individuals, taking into account the intra-individual variability (Campo et al., 2020) and exposure from all routes, including the skin and gut, as well as that inhaled from the workplace air.

The biomonitoring of some metals, such as lead and chromium, has been well-established and for these there are guideline or regulatory values based on levels in the blood or urine that can be used as part of worker exposure-control measures (Morton et al., 2022; Verdonck et al., 2021). However, for any biomonitoring to be of reliable use, for metals or other substances, there are a number of essential requirements. These include: the existence of a biomarker (or metabolite) of the substance and the analytical ability to measure it with sufficient sensitivity; an understanding of the dose-response relationship of the biomarker with any health-effect (clinical or sub-clinical) or, between the level of

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external exposure (by any route) and the level of the biomarker in the blood or urine; and a knowledge of the half-life of the substance in the body to determine the most accurate sampling time (blood or urine) for comparison with any guideline value (Vorkamp et al., 2021).

For many metals, these requirements can be met as highly sensitive analytical techniques, such as inductively coupled plasma mass spectrometry (ICP-MS) are readily available. In addition, the toxicokinetics of many metals in humans by most routes of exposure, are also well understood (Santonen and Schoeters, 2022). However, we consider that for a number of 'essential' biological trace elements, including manganese, iron, copper and zinc that are regulated within the body by various forms of homeostatic control, the situation is more complicated. This is because the relationship between exposure (short- or long-term) and the level of biomarkers in the blood or urine may be far from simple; this may limit the use of some metal biomarkers, particularly for workplace exposures which are predominantly airborne and generally limited to the working day. For many essential metals, including copper, biomonitoring is usually performed for clinical or nutritional reasons to aid in the clinical diagnosis of certain diseases or nutritional deficiencies (ATSDR, 2022).

In the case of copper, a review was published by Danzeisen et al. (2007) which looked at the reliability and robustness of current biomarkers for copper status. The focus of this paper was environmental exposure of the general population following oral exposure through the diet and drinking water. The authors reported that although some blood markers may indicate moderate and severe Cu deficiency (ceruloplasmin (Cp), erythrocyte superoxide dismutase (SOD)1, peptidylglycine α mono-oxygenase (PAM), diamine oxidase (DAO)), there is no good marker for Cu excess, even at a level where symptoms such as acute nausea and abdominal pain are reported. The potential relevance of the blood markers identified to monitor occupational exposures via inhalation was not discussed. Expression of copper metallothioneins (Cu-MTs) in the liver was also discussed by Danzeisen and colleagues as a potential biomarker, as this has been shown to be regulated by Cu status. More recently Calvo et al. (2017) have reported that MTs have a number of biological functions with essential roles in Cu(I) homeostasis and in metal detoxification. Whilst we could find examples of the use of metallothioneins as biomarkers in the aquatic environment (Kadim and Risjani, 2022), their use for human biomonitoring was not apparent.

Harvey and McArdle (2008) published an update to the review by Danzeisen et al. (2007) to include discussion of the Cu chaperone for superoxide dismutase (CCS) as a potential biomarker. Although unvalidated at the time of publication, CCS was considered to potentially be an accurate and sensitive biomarker of copper status, but not discussed as a possible biomarker in the context of occupational exposure to copper.

In a systematic review, Harvey et al. (2009) assessed the usefulness of copper status biomarkers in the general population in identifying moderate deficiencies. Due to the essential nature and wide-ranging roles of copper, deficiency results in a large number of symptoms derived from perturbations in cuproenzyme activities. While severe copper deficiency is easily diagnosed, moderate deficiency is difficult to identify and may have adverse health consequences throughout the life span. As previously mentioned, determination of copper status is complicated by the fact that it is under tight homeostatic control and that there is a large degree of variation in background levels of copper in biological media, including blood and urine (EC, 2014).

This current paper discusses how the essential nature of copper in humans impacts the feasibility, usefulness and interpretation of occupational copper exposure biomonitoring for risk assessment purposes. It is intended to give an overall perspective of the "state of the art" by the authors and should not be considered to be a systematic review of the subject.

2. Copper as an essential metal in humans

Environmentally, copper is found in a number of minerals including: native copper metal, copper sulfides (chalcopyrite, bornite, digenite, covellite, chalcocite), copper sulfosalts (tetrahedite-tennantite, and enargite), copper carbonates (azurite and malachite), and as copper(I) or copper (II) oxides (cuprite and tenorite, respectively) (ATSDR, 2022). Copper can exist in the elemental form or as a redox metal, it can also cycle between its biologically active oxidized cupric (Cu2+) and reduced cuprous (Cu+) forms. The main form of copper present intracellularly is Cu+ and, under normal pathology, Cu2+ is the main extracellular form; once taken up into a cell, Cu2+ is reduced to Cu + due to the reducing intracellular environment (ATSDR, 2022). As the redox potential of Cu+ is higher than that of Cu2+, all copper present *in vivo* is linked to enzyme prosthetic groups or tightly bound to Cu transport or chaperone proteins that minimize the chance for reactions to occur and ensure that the Cu ions are delivered to their specific target proteins (Burkitt, 2001; Evans and Halliwell, 1994; Rosenzweig, 2001; Prohaska, 2008; Boal and Rosenzweig, 2009).

Copper is an essential micronutrient in humans and animals, playing a key role in the activity of several enzymes involved with the normal biological functions of the respiratory, immune, reproductive, endocrine, and central nervous systems (ATSDR, 2022). The absorption of copper via the gastrointestinal tract is determined by how much copper is stored in the body, with increased relative absorption occurring with low dietary intake and decreased relative absorption with increased intakes (Taylor et al., 2020; Danzeisen et al., 2007; Nieboer et al., 2007). Following absorption, copper is transported in the blood bound predominantly to ceruloplasmin (Cp) but also to albumin. Copper is mainly transported to the liver, and to a lesser extent to the kidney (Bost et al., 2016; Danzeisen et al., 2007) for storage and redistribution to all other organs (Danzeisen et al., 2007). Cu absorbed in excess of metabolic requirements is normally excreted through bile. EFSA Scientific Committee et al., (2023) estimates that overall, copper is present in the adult human body at levels between 1.4 and 2.1 mg/kg bw (around 50–150 mg), with 40% of this being located in muscles. Copper is also found in the liver, brain, heart, kidney and skeleton at levels between 4.8 and 12 μg/g and in lung, spleen and intestine at lower levels of between 1 and 2 μg/g. In red blood cells it is estimated that 60% of the copper present is within superoxide dismutase. No studies were located that provide data on the rate or extent of absorption following inhalation exposure in humans (ATSDR, 2022; Campo et al., 2020). Although physiologically-based pharmacokinetic (PBPK) models can be used to predict the levels of a chemical potentially reaching target tissues in humans following exposure via different routes, a copper specific PBPK model is not currently available (Health Canada, 2019).

Limits have been identified for copper homeostasis (Gaetke et al., 2014; Pal, 2014; Stern, 2010; Araya et al., 2006; Turnlund et al., 2004). While copper intakes are within the homeostatic range, a high intake does not cause an equivalent high body load, making it difficult to establish copper status following exposure. Indeed, it is considered that only liver copper levels can be used to precisely indicate copper status (Danzeisen et al., 2007; HBM4EU, 2018). A number of biomarkers have also been used and/or proposed as indicators of copper status, including both deficiency and excess.

As with other essential metals, both a deficiency of and excess exposure to copper, can lead to harm (EFSA Scientific Committee et al., (2023)) which is best described by a U-shaped dose-response curve (Chambers et al., 2010). The purpose of the U-shaped curve is to balance any harm due to a deficiency of copper against any toxicity from excess exposure (Taylor et al., 2020). It is considered that a steeper dose response will exist for a deficiency of copper than for an excess, as adaptation is possible in the presence of an excess, but persistent deficiencies of copper cannot be mitigated against (Farrell et al., 2022). The health-related consequences of copper deficiency are illustrated by Menkes disease, which is an inherited, X-chromosomal-linked disorder

caused by mutations in ATP7A, a copper-transporting enzyme in which patients have connective tissue disorders, severe neurodegeneration and early death. Copper deficiency is also associated with anaemia, which can present as microcytic or normocytic or macrocytic types. The mechanism for this is not known but the effects are reversible following copper supplementation (EFSA Scientific Committee et al., 2023). The toxicity of excess copper exposure has been reported following acute ingestion of a high dose of copper with symptoms including gastrointestinal symptoms, haemolysis and damage in the gut, kidney and liver. The effects of excess chronic exposure can be seen in patients with Wilson's disease who have a deficiency in plasma ceruloplasmin; this leads to an excess of copper that mainly accumulates in the liver and brain. In the liver, excess copper can lead to hepatic diseases ranging from mild hepatitis to acute liver failure or cirrhosis, and in the brain to the development of neurological symptoms such as dystonia, tremor, dysarthria, and psychiatric disturbances. Wilson's disease is a rare disorder that affects males and females in equal numbers. The disease is found in all races and ethnic groups. Although estimates vary, it is believed that Wilson's disease occurs in approximately one in 30,000 to 40,000 people worldwide, though not all will present clinical symptoms. The treatment of Wilson's disease includes supplementation with zinc, which reduces the GI uptake of copper (EFSA Scientific Committee et al., (2023)). There is currently uncertainty as to the levels at which copper becomes toxic, and biological effects associated with mild to moderate deficiency or excess have not been investigated (HBM4EU, 2018).

Thus, there is both toxicological and clinical interest in the biomonitoring of copper levels and intake but, these are primarily to ensure that there is a sufficiency of copper, via homeostatic and other mechanisms, to maintain a wide range of essential biological functions, or for treatment purposes in the case of Wilson's disease, rather than to consider potential excesses due to occupational exposures.

3. Establishment and use of guideline values for the biomonitoring of occupational exposure to copper

To be of value, any biomarker used for workplace assessment needs to be capable of being applied in a systematic and repeatable fashion to provide reliable information that can inform the risk assessor, safety manager or occupational health professional towards worker protection. To this end, there are a number of types of occupational biomarker guidelines which have been established by various bodies over the years, against which any measured worker exposure can be compared. These are briefly described in Table 1. Broadly, as can be seen from these descriptions, there are four kinds of biomonitoring guidance values. The first of these is where there is a known relationship between the level of the substance (or its metabolite), usually measured in blood or urine, and some known harmful (clinical or pre-clinical) effect. The second type is where there is a well-established relationship, usually linear, between the level of the substance (or metabolite) in blood or urine and the airborne exposure to the substance in the breathing zone of workers. Clearly, it is necessary to take into account the half-life of the substance and the pattern of exposure (short-term or long-term) during the working week to know when, during the working week, the biomarker (urine or blood sample) needs to be collected from the exposed workers. The third form is where a guideline cannot be set on the above two criteria and an arbitrary value, based on perhaps a percentage of the level found in the general, non-occupationally exposed population, can be used as a trigger for investigation. An example of this is the German Biologische Arbeitsstoff-Referenzwert (BAR) value described in Table 1. The fourth approach is also where there is insufficient information or relationship and an arbitrary value, based on 95th percentile of the available biomonitoring data for that substance from industries using it in well-controlled conditions, is used as a target value as a guide for "good practice". These are used by the UK Health and Safety Executive (HSE) and described as BGVs in Table 1.

If an occupational biological monitoring value for copper-exposed

Table 1
Occupational biomonitoring guidance values and their definitions.

Setting body	Guideline value type	Definition	Essential metals (examples)
American Conference of Industrial Hygienists (ACGIH)	Biological Exposure Indices (BEIs®).	BEIs® are guidance values for assessing human biomonitoring (HBM) data based on a direct correlation, where supported by the data, with the corresponding TLV®[a], i.e., the concentration of that substance, in the blood or urine, that would be reached if that person were exposed to the TLV® for a normal 8-hr working day. Where the adverse effect for a chemical is well defined, for example for lead, the BEI® definition is analogous to that of the ICOH BLV (https://www.acgih.org/science/tlv-bei-guidelines/biological-exposure-indices-bei-introduction/[accessed October 2023]).	cobalt (and inorganic compounds)
The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area in Germany (MAK Commission)	Biological tolerance (Biologische Arbeitsstoff-Toleranzwerte; BAT) values	BAT values are the occupational-medical and toxicological derived concentration for a substance, its metabolites, or a biological effect parameter in the corresponding biological matrix (urine or blood) at which the health of an employee generally is not adversely affected, even when the person is repeatedly exposed during long periods. BAT values are based on a relationship between external and systemic exposure or between the systemic exposure and the resulting effect of the substance (https://series.publisso.de/sites/default/files/documents/series/mak/lmbv/Vol2022/Iss2/Doc002/mbwl_2022_eng.pdf [accessed October 2023]).	none relating to essential metals
	Biological Guidance (Biologische Leit-Werte; BLW) values	BLW values relate to the amount of a chemical substance or its metabolites or the deviation from the norm of biological parameters induced by the substance in exposed humans	cobalt (and cobalt compounds)

(continued on next page)

Table 1 (*continued*)

Setting body	Guideline value type	Definition	Essential metals (examples)
		which serves as an indicator for necessary protective measures. BLW values are specifically derived for carcinogenic substances and suspected carcinogens (Categories 1 to 3) and for non-carcinogens for which the toxicological data are inadequate to determine a BAT value. BLW values are generally established on the assumption that persons are exposed at work for at most 8 h daily and 40 h weekly during their working lives (https://series.publisso.de/sites/default/files/documents/series/mak/lmbv/Vol2022/Iss2/Doc002/mbwl_2022_eng.pdf [accessed October 2023]).	
	Biological Reference (Biologische Arbeitsstoff-Referenzwerte; BAR) values	BAR values are used where there is insufficient data to set a BAT and are usually based on the 95th percentile of concentrations of that substance (or its metabolite) in the non-occupationally exposed general population. These might be particularly important for substances where there is no clear relationship between airborne exposure and level on biomarker, even when well-studied and no clear relationship between any health effect and known level of biomarker (https://series.publisso.de/sites/default/files/documents/series/mak/lmbv/Vol2022/Iss2/Doc002/mbwl_2022_eng.pdf [accessed October 2023]).	cobalt (and cobalt compounds), manganese (and inorganic manganese compounds), molybdenum (and molybdenum compounds)
French Agency for Food, Environmental and Occupational Health & Safety (ANSES)	BLVs	Two types of BLV are derived, depending on the type and availability of data (https://www.anses.fr/en/content/biological-limit-values-chemicals-used-workplace [accessed October 2023]):	cobalt (and cobalt compounds)
		• where a dose-response relationship has been established, the BLV is defined on the basis of health data (i.e., a threshold of effect, or acceptable risk level for non-threshold carcinogens); • where such data are not available, the BLV is calculated as the concentration of biomarker that is expected following exposure at the 8-h OEL[b]. In the case of non-threshold carcinogens, a pragmatic BLV may need to be defined if these is insufficient quantitative data, that aims to limit exposure to such chemicals. Biological reference values (BRV) are also recommended which correspond to 'concentrations found in a general population of adults whose characteristics are similar to those of the French population (preferentially for the biological indicators of exposure) or, by default, in a non-worker control population exposed to the substance being studied (preferentially for the biological indicators of effects)'. BRV's thus provide a very useful reference point when BLVs cannot be determined. These are thus quite similar to the principle behind German BAR values.	
UK Health and Safety Executive (UK HSE)	Health guidance values (HGV)	HGVs are set at a level at which there is no indication, from the scientific evidence available, that the substance being monitored is likely to be injurious to health. Values not greatly in excess of an HGV are unlikely to produce serious short or long-term effects on health.	none relating to essential metals

(*continued on next page*)

Table 1 (*continued*)

Setting body	Guideline value type	Definition	Essential metals (examples)
		However, regularly exceeding the HGV does indicate that control of exposure may not be adequate. Under these circumstances, employers will need to look at current work practices to see how they can be improved to reduce exposure.	
	Benchmark guidance values (BGV):	BGVs are not health based but rather, they are considered to be practicable, achievable levels set at the 90th percentile of the current available biological monitoring results collected from a representative sample of workplaces with good occupational hygiene practices. If a result is greater than a BGV it does not necessarily mean that ill health will occur, but it does indicate that control of exposure may not be adequate. Under these circumstances, employers will need to look at current work practices to see how they can be improved to reduce exposure (https://www.hse.gov.uk/pubns/priced/eh40.pdf [accessed October 2023]).	none relating to essential metals
EU HBM4EU	Human biomonitoring guidance values (HBM-GVs)	HBM-GVs can be derived for the general population ($HBM\text{-}GV_{GenPop}$) or for occupationally exposed adults ($HBM\text{-}GV_{Worker}$) (https://www.hbm4eu.eu/what-we-do/[accessed October 2023]). Of relevance here are the $HBM\text{-}GV_{Worker}$ values which represent 'a concentration of a substance, or its relevant metabolite (s), in human biological media aiming to protect workers exposed to the respective substance regularly (each workday), and over the course of a working life from the adverse effects related to medium- and long-term exposure'.	none relating to essential metals

[a] TLVs® act as OELs and represent a level of exposure that can be experienced by a typical worker without adverse health effects.

[b] Protect workers from harmful effects related to exposure to the chemical in question, over the medium- or long-term. These take into account repeated exposure throughout a worker's working life.

workers is going to be derived, it will be important to consider which of these four well-established types of guideline value could be adopted. The approach must also take into account the fact that the homeostatic control of copper levels in the body is likely to preclude the use of any clear relationship for the first two types described above, and even compromise interpretation the potential use of the two arbitrary types, based on population distributions, described in Table 1. There are interesting parallels in this respect for copper to the extensive efforts that have been undertaken over the last few decades to identify a reliable biomarker for use in occupational settings for exposure to manganese and its inorganic compounds (discussed later) another essential metal that the body keeps under tight homeostatic control (Bevan et al., 2017).

4. Occupational exposures to copper

Occupational exposure to copper may occur during the mining, smelting and refining of copper and, potentially, as a consequence of the downstream uses of copper powder (Haase et al., 2022). Commonly used copper and inorganic copper compounds in industry include: copper metal; copper (I) chloride; copper (II) acetate; copper (II) carbonate; copper (II) chloride; copper (II) hydroxide; copper (II) nitrate; copper (II) oxide; copper (II) oxysulfate; copper (II) sulfate; and copper (II) sulfate pentahydrate. Due to its unique conductive properties, copper and its compounds are produced and used in large quantities for the manufacture of electrical devices including wire, cables, transformers, and generators. ICSG[1] reports additional uses of copper and copper compounds in: metallic paints; coatings/lubricants/plastics; as a catalyst; in brazing paste; coating and electroplating; spray coating agent; and cosmetic, cleaning and body care products. In the main, occupational exposure to copper via inhalation is not associated with adverse health effects. Acute exposure in humans causes respiratory irritation with symptoms such as coughing, sneezing, thoracic pain, and a runny nose being reported; this is also referred to as 'Metal fume fever' and is an acute self-limiting systemic inflammatory response (ATSDR, 2022). Whilst these effects are largely attributed to zinc oxide, copper has been suggested to play a contributory role (Markert et al., 2016; Brand et al., 2020); no causal relationship has been found however, despite the extensive use of copper across widespread industries (Poland et al., 2022). Similar local effects on the respiratory tract, including reversible immunomodulatory effects, have been reported in animal studies following inhalation exposure to copper (ATSDR, 2022; Haase et al., 2022; Poland et al., 2022).

Workplace airborne exposure to copper dust and fumes are monitored according to standard methods from National Institute for Occupational Safety and Health (NIOSH) (method 7302) and Occupational Safety and Health Administration (OSHA) (Method ID-125G) in which air samples are collected onto cellulose ester membrane filters (0.8 μm). The NIOSH method then utilises digestion with nitric acid, sulfuric acid and hydrogen peroxide, with dissolution of the elements achieved using hydrochloric acid. OSHA adopts a microwave digestion approach with nitric acid to digest the filters and achieve dissolution of the elements. For both methods, analysis is performed using Inductively Coupled Argon Plasma-Atomic Emission Spectroscopy (ICAP-AES) with quality assurance/quality control (QA/QC)achieved using certified reference materials.

No standardised human biomonitoring protocols have currently been

[1] The International Copper Study Group (https://icsg.org/).

established to monitor copper exposure in the workplace. However, biomonitoring of copper in urine using inductively coupled plasma–mass spectrometry (ICP–MS) for research and survey purposes (e.g., NHANES, 2016) has been described.

5. Biomarkers of exposure

Human biomonitoring assesses the uptake of a chemical from all routes of exposure and increased copper levels have been reported in a number of biological matrices following exposure to copper, including whole blood, serum, urine, faeces, hair and liver. Exposure of the general population to copper occurs predominately via the oral route, whereas the inhalation route is of greater importance in certain occupational settings, where higher airborne copper occurs. Uptake following dermal exposure is considered to be low due the poor absorption of copper through intact skin. Excretion of copper in humans is bi-phasic and a biological half-life has been determined for plasma of 2.5 and 69 days for the first and second phases respectively (HMB4EU, 2018). In liver and kidney respectively, half-lives of 3.9 and 21 days and 5.4 and 35 days for the first and second phases have been determined. For lung, the half-life of copper sulfate has been estimated to be 7.5 h after intratracheal instillation in rats (ATSDR, 2022). As discussed in the previous section, analytical methods are available for quantification purposes for a number of sample types (ATSDR, 2022) with tested methods including electrothermal (graphite furnace) atomic absorption spectrometry (GF-AAS) or inductively coupled plasma quadrupole mass spectrometry (ICP/MS) (MAK, 2018).

A small number of occupational studies have used air and biological monitoring of copper to investigate the extent to which the two parameters are correlated. Some studies collected air and post-shift urine concentrations for different categories of workers at a socket manufacturing plant (n = 34 participants in total; Wu and Liu, 2014), a copper refinery (n = 127 participants in total; Nieboer et al., 2007) and a copper smelter (n = 293 participants in total; NIOSH, 1981). In addition, airborne copper measurements were collected alongside serum samples in workers employed in copper dust sieving and copper electrolysis (Suciu et al., 1981) and alongside blood, urine and hair samples in a copper processing facility (Finelli et al., 1981). Findings from the studies as a group were inconsistent with regard to biological measures reflecting excess exposure to copper, and no suitable biomarker relationship to airborne exposure can be identified from these studies (Gradient, 2020).

6. Blood components

Total copper has been investigated as a potential biomarker in a number of blood components, including serum, plasma, erythrocytes, and platelets. In serum, levels of copper are raised in all individuals following copper supplementation, with the largest changes seen in copper-deficient individuals; as such it may not reflect minimal changes in copper status which are anticipated to occur following recent occupational exposure. It has also been reported that serum copper levels are affected by age, sex, pregnancy and the use of oral contraceptives. In addition, as ionic copper levels in serum have a short half-life following an acute bolus dose, it is considered that serum copper may only reflect recent exposures (ATSDR, 2022; Ellingsen et al., 2015).

A small number of studies have evaluated total copper levels in plasma as a biomarker for increased copper exposure. When the studies were grouped, a meta-analysis showed no significant increase in plasma copper levels following oral supplementation. However, a study in severely copper-deficient infants showed a significant increase in plasma copper levels following supplementation. It is considered that, as for serum copper measurements, plasma copper levels may be useful in showing copper repletion in depleted individuals after supplementation but does not reflect medium and low level long-term exposure; the evidence base for this, however, is much more limited that for serum (HBM4EU, 2018).

Ceruloplasmin protein concentration in serum/plasma has been proposed as a copper status biomarker. Harvey et al. (2009) reported the findings of a meta-analysis of data from 8 supplementation and 2 depletion studies. The authors' findings showed that, as a whole, ceruloplasmin responded significantly ($p < 0.03$) to changes in copper intake. When evaluated in terms of copper status, ceruloplasmin was not found to be a useful biomarker in copper replete adults. However, a significant increase ($p < 0.00001$) in ceruloplasmin concentration after supplementation was found in copper-deplete individuals suggesting that ceruloplasmin protein may be a useful biomarker in deficient individuals.

Erythrocyte and leucocyte Cu/Zn superoxide dismutase (SOD) activities have been investigated in several studies as possible biomarkers of copper status. A larger number of studies addressed erythrocyte activity in replete and copper depleted individuals, with no clear effect of copper supplementation on measured activity. A smaller number of studies were available that assessed leucocyte activity, with no effect seen following copper supplementation. These are not, therefore, considered to be useful biomarkers of copper status (Bost et al., 2016).

7. Urine, hair and nails

Among the various types of biological specimen used in human biomonitoring, blood (including whole blood, plasma and serum) is the most widely adopted sample of choice. However, as blood collection is an invasive procedure, the preferable use of non-invasive samples such as urine, hair and nails has also been developed (Lum et al., 2021).

Urine is the most common non-invasive sample used in human biomonitoring studies. In general, urinary measurements of copper are used for the diagnosis of diseases affecting copper homeostasis and the liver, in which copper levels are raised. In healthy individuals, the concentrations of copper in urine are much less (50–60 times) than those in blood (ATSDR, 2022) mainly due to the favoured excretion of excess copper via bile and faeces. It has also been reported that, due to homeostatic control, the urinary concentration of copper is not related to the level of exposure (Letzel et al., 2018; ATSDR, 2022). Additionally, it has been suggested that as the concentrations of a number of elements, including copper, in urine varies over time, the commonly used practice of taking a single time point sample (spot urine) to estimate levels may result in error (Wang et al., 2023).

Hair and nails are increasingly being evaluated for use in longer-term human biomonitoring as they involve non-invasive sampling, and are stable and easily stored; however the reliability of these for assessing copper exposure has not yet been established. Both hair and nail samples allow information about long-term exposure to be retrieved and there is an association between the elemental profiles of the samples and that in blood, but there are differences in the profiles due to the chemical nature and affinity of different elements and their related species in the two tissues (Gutiérrez-González et al., 2019).

The US Environmental Protection Agency (EPA) considers hair analysis to play a key role in the monitoring of heavy metals in the general population (Liang et al., 2017). Excreted heavy metals are able to accumulate in human hair and, as metabolic products, heavy metals can be incorporated into hair structure during growth (Morton et al., 2002; Liang et al., 2017), meaning that levels in hair can reflect exposure levels (Liang et al., 2017). Human biomonitoring studies to date have generally obtained hair samples from the occipital region of the head, although it is not known how elements vary in hair collected from different sites. Hopps (1977) determined that, assuming a hair growth rate of 10 mm per month, the first 2 cm of hair proximal to the scalp would represent copper intake over the previous 2 months. Levels of copper in scalp hair are higher than those in serum (10–100 x) with values ranging from 7 to 95 μg/g reported in the general population (Bost et al., 2016; Wilhelm et al., 1991). In oil distribution workers exposed to copper from fossil fuel combustion, copper levels in hair were

seen to be significantly higher than in controls (69.6 μg/g and 36.8 μg/g respectively) (Jaccob, 2020). Similarly, Finelli et al. (1981) reported increased hair copper levels in workers exposed to airborne copper compared to non-exposed workers (705.7 μg/g and 8.9 μg/g respectively). Although the hair matrix presents a number of advantages for the determination of copper exposure, there are only a few studies that have evaluated the relationship between dietary copper intake and copper content of hair, and the results from these are contradictory (Chan et al., 2023; Suliburska, 2011). In addition, there are a number of uncertainties regarding the use of hair for human biomonitoring related to the mechanism of incorporation in the hair, correlation with internal organ concentrations, the rate of hair growth, pigment effects, and the potential uptake of copper from exogenous sources such as shampoos which becomes tightly bound to the hair matrix (Wilhelm et al. 1989, 1994; Pozebon et al., 2017). Some of these issues may be overcome due to improvements in analytical methodologies, as discussed below.

Fingernails and toenails can be utilised for human biomonitoring, including for monitoring exposure to metals which readily bind from the blood to the growing keratinous tissue (Christensen et al., 2017). In comparison to fingernails however, toenails are less exposed to the environment and grow more slowly and so represent a longer exposure window of an individual for the same length of nail sample. Due to their slow growth rate of around 1 mm/month, toenail samples are considered to represent copper intakes over the previous 12–18 months (Fleckman, 1985). A study in preschool children reported concentrations of 7.5 mg/kg (range 3.0–18.6 mg/kg) copper in toenail samples and mean levels of 132 mg/kg have been found in residents who lived in copper-mining towns (Ndilila et al., 2014). Gutiérrez-González et al. (2019) reviewed the current evidence regarding the validity of toenail clippings for use as exposure biomarkers for trace metals including copper. From a total of 139 studies identified by the authors, 32 focused on copper. Mean Cu levels were usually below 10 μg/g, with the highest Cu concentrations (average mean of 26.2 mg/kg) being found among subjects living in rural areas near a highly industrialized city in Pakistan (Gutiérrez-González et al., 2019).

8. Analytical challenges

There are a number of analytical difficulties associated with the measurement of metals in hair and nail matrices. ICP-MS is the most commonly used method in human biomonitoring studies to measure copper levels in serum and urine because, compared to AAS, it is faster, more precise and has greater sensitivity (Martinez and Baudelet, 2020). The analysis of solid biological samples such as hair and nail offers several advantages over conventional solution analysis as there is no or limited dilution, minimal sample preparation, and the sample size required is much smaller. As such, laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) and laser-induced breakdown spectroscopy (LIBS) are techniques that have been increasingly used for the detection of metals and metalloids in biological samples in the last decade (Martinez and Baudelet, 2020).

LA-ICP-MS has been developed to combine the direct solid sampling of laser ablation with the excellent analytical performance of ICP-MS, to allow spatial resolution of elemental distribution in samples including hair and nails. However, at present, the lack of standardised analytical protocols and reference materials hinders the application of LA-ICP-MS, although some developments of the methodology are being undertaken (Noël et al., 2015; Martinez and Baudelet, 2020). Chan et al. (2023) reported improved ablation scanning and sample cleaning and preparation for the elemental analysis of hair and nail samples. In the absence of a commercially-certified reference material, the authors developed a dried droplet calibration using element-enriched filter paper as calibration standards for the quantification of elements. For all the elements measured, including copper, there was a significant correlation between the concentrations obtained from the improved LAICP-MS method and the ICP-MS (solution-based) method. The concentration of copper in hair and nail samples obtained from seven volunteers ranged between 2.27 ± 0.14 and 4.75 ± 2.87 μg/g in hair samples and between 1.11 ± 0.08 and 2.75 ± 0.14 μg/g in nail samples. The authors concluded that the data 'demonstrates that LA-ICP-MS can be used for high throughput of hair and nail samples, and has potential application in future HBM studies'.

LIBS is an alternative analytical approach to LA-ICP-MS that utilises a laser to ablate the sample surface, and the signal from the generated plasma is detected to provide information of element type and concentration in the sample. The advantages of the technique are that it is simple to use, requires minimal sample pre-treatment, and is a rapid, *in-situ* multi-element analysis. Zhang et al. (2020) described some improvements to the LIBS method by using ultrasound-assisted alkali dissolution (UAAD) to assist hair dissolution. The R2 value of the calibration curve for copper was 0.9918, with a limit of detection of 0.0146 μg/g. Measurement of copper in sampled hair of volunteers (n = 3) were reported at levels between 1.14 (±0.04) and 1.80 (±0.08) μg/g, which compared well (<5% variation) with levels measured using inductively coupled plasma optical emission spectrometry (ICP-OES). The authors concluded that 'UAAD-LIBS is an accurate and reliable method for determining trace elements in human hair'.

9. Occupational guidance values for copper and its inorganic compounds

Occupational guidance values have been established for copper dusts and fumes based on health risk. At present, the US American Conference of Governmental Industrial Hygienists (ACGIH) has two Threshold Limit Values (TLVs®)[2] for copper – 0.2 mg/m^3 (200 μg/m^3) for copper fume (adopted in 1975) and 1 mg/m^3 (1000 μg/m^3) for dusts and mists (adopted in 1965), both as 8-h time-weighted average (TWA) concentrations. Both values are based on the prevention of local irritative ocular, dermal, respiratory tract and mucus membrane effects, and the systemic gastrointestinal effects reported in workers. The ACGIH also develops biological exposure indices (BEIs®) used as 'guidance values for evaluating biological monitoring results' (i.e., measurements of a chemical determinant in biological media, including urine, blood, and exhaled air). Wordwide, other occupational exposure limits of similar values are published for copper and its inorganic compounds, as collated on the Gestis[3] database, but with no examples of established biological exposure values.

The German MAK Commission evaluated copper and its inorganic compounds in 2013 and derived a Maximale Arbeitsplatzkonzentration [maximum workplace concentration] (MAK) value of 0.01 mg/m^3 (10 μg/m^3) for the respirable fraction. This was based on the critical local effects on the respiratory system following occupational inhalation exposure (MAK, 2014). This recommendation is currently under discussion within the German regulatory system that sets OELs.

In 2014, the European Commission's (European Commission) Scientific Committee on Occupational Exposure Limits (SCOEL) recommended an occupational exposure limit (OEL) for copper and its inorganic compounds, defined as 'an upper limit on the acceptable air concentration of a hazardous substance in workplace air for a particular substance or group of substances to which workers can be exposed throughout their working lifetime (for 8 h per day, 5 days per week, for 40 years) without developing adverse health effects'. SCOEL recommended an OEL of 0.01 mg/m^3 (10 μg/m^3; respirable fraction) 8-h TWA for copper, based on its local action on the respiratory tract, including an immunosuppression effect attributable to the disturbance of alveolar

[2] TLVs® are defined as 'airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects'.

[3] https://gestis-database.dguv.de.

macrophage function (European Commission, 2014). They made no mention of a biological monitoring guidance value (see below). This recommendation has not yet been evaluated for implemented into EU regulations.

ACGIH is currently considering the development of a biological exposure index (BEI®) for copper and its compounds. A BEI® 'generally indicates a concentration below which nearly all workers should not experience adverse health effects' and in some cases corresponds to TLVs® of the respective chemical, defined as 'airborne concentrations of chemical substances [that] represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects'. It is unclear from the assessments carried out by other authoritative bodies, what toxicity endpoint a BEI® for copper and its compounds could be based on. In their evaluation, SCOEL (EC, 2014) considered that a biological limit value[4] could not be derived due to the large inter-individual variation in the levels of copper in blood and/or urine, which are commonly used matrices for biological monitoring. In addition, increased exposure to copper via inhalation or the oral route is not reflected in an increase in serum or urinary levels, which is thought to be a result of homeostatic control (Finelli et al., 1981; Kossowska et al., 2010; Minoia et al., 1990; ATSDR, 2022).

The MAK Commission evaluated whether a biological tolerance (BAT[5]) value could be derived for copper and its inorganic compounds. Following an evaluation of occupational data, it was concluded that 'due to homoeostatic regulation over a wide exposure range, there is no relationship between external exposure to copper and its concentrations measurable in biological materials. Neither increased inhalation exposure much higher than the currently valid MAK value of 0.01 mg copper/m^3, nor increased oral supply led to an increase of copper in possible biological exposure indicators. In addition, the main effect is a local toxicity which cannot be demonstrated by a systemic effect (increased copper concentration). It was thus considered not possible to differentiate an additional occupational burden from physiological levels of copper by biological monitoring. Therefore, the evaluation of a BAT value and a biological reference value (BAR[6]) based on the copper concentrations in blood or urine is not indicated'.

In an attempt to anticipate what BEI® could be derived by ACGIH, Gradient (2020) reviewed the scientific literature to determine 'what evidence is available to inform a copper BEI®, including in occupational settings where biological monitoring for copper has been conducted, and studies and reviews of indicators of copper status in the general population'. The authors concluded that 'collectively, the relevant occupational studies we identified are few in number and inconsistent with regard to biological measures reflecting excess exposure to copper. No biomarker suitable for deriving a copper BEI® is supported by the available occupational literature'.

Interestingly, there is a parallel case in efforts to establish a possible useful biomarker for manganese, an essential metal that, like copper, that is also under tight homeostatic control in humans. In an evaluation of manganese and its inorganic compounds by SCOEL (EC, 2011), mainly based on the IEH review (IEH, 2004), it was concluded that it was not possible to recommend a health-based or exposure-based biological monitoring standard due to the poor correlation between airborne manganese and either blood or urine concentrations of manganese. However, it was noted that in Germany, a Biologischer Arbeitsstoff-Referenzwert (BAR) value of 15 mg/l blood has been established by the MAK Commission which represents manganese concentrations in the general population (95th percentile) not occupationally exposed to manganese but of working age (EC, 2011). A recent extensive review (Shilnikova et al., 2022) has confirmed that there is no still reliable biomarker for exposure to exposure to manganese and its inorganic compounds.

For any biomarker to be of use as a reference or guidance value, particularly in the occupational context, it needs to satisfy a number of criteria discussed above, so that measured values can be usefully interpreted. These have been set out in the form of a framework (Bevan et al., 2012) which also includes the various biological monitoring guidance values that have been established in the US and Europe for either regulatory or simply guidance purposes. As can be seen, there are major problems that, at present, would be difficult to overcome in the case of developing such a value for copper.

10. Summary

Overall, the findings reviewed in this paper do not suggest that total copper levels in blood and/or blood components can be used as a reliable indicator of airborne occupational exposure to copper. Although plasma and serum levels are increased following copper supplementation, the largest changes are seen in copper-deficient individuals and this level of change may not be sensitive enough to reflect that which may occur following occupational exposure. In addition, blood levels of copper show high inter-individual variability as they can be affected by a number of factors including age, sex, pregnancy status and the use of oral contraceptives. Plasma biomonitoring of ceruloplasmin protein concentration, as an indirect biomarker of copper status, is also compromised as levels may reflect regulation of the protein rather than of Cu levels *per se*.

The overall elimination of copper via urine reflects only a small portion of the daily intake (1–2%), meaning, that in healthy individuals, urinary levels of copper are lower than those in blood. Due to the influence of homeostatic control and to uncertainties regarding the extent of urinary dilution and the excretion rate of copper, urinary copper is not recommended as a biomarker of exposure. Although urinary levels in healthy individuals are much lower than those in blood, urinary measurements can be used for clinical diagnoses of diseases that result in raised copper levels.

Copper levels in hair, fingernail and/or toenail samples have been investigated for use as biomarkers of longer-term exposure, including in workers and/or residents exposed to high airborne copper. For hair, there are still considerable uncertainties that limit its current use in HBM, including knowledge of how chemicals are incorporated into the hair, whether there is any correlation of levels with internal organ concentrations, the effects of hair growth rates and pigment effects and the potential uptake of copper from exogenous sources such as shampoos which becomes tightly bound to the hair matrix. Toenails grow slowly and represent the longest exposure window of an individual. Measured levels of copper are considered to reflect the previous 12–18 months exposure, compared with 2 months for hair samples.

Thus, although both hair and nails may be useful for long-term environmental exposure or dietary research purposes, they represent difficult matrices for analysis, particularly in the context of a routine occupational monitoring tool to complement air monitoring. It is currently feasible to perform direct analysis of hair and nail samples, but

[4] Biological Limit Values (BLVs) are reference values for the evaluation of potential health risks in the practice of occupational health. They were established by SCOEL on the basis of available scientific data. For many substances, the data are too limited to support a biological monitoring method, or a metabolite or indicator cannot be defined.

[5] The BAT value describes the average occupational-medical and toxicological derived concentration for a substance, its metabolites or an effect parameter in the corresponding biological material at which the health of an employee generally is not adversely affected even when the person is repeatedly exposed during long periods. As a rule, exposure to the substance is assumed for the whole of working life. BAT values are based on a relationship between external and systemic exposure or between the systemic exposure and the resulting effect of the substance.

[6] The BAR ("biological reference value") represents the internal exposure to a substance at a particular time of a reference population of persons of working age who are not occupationally exposed to this substance (background exposure). This background exposure may (also) have an endogenous cause.

quantification can be challenging due to matrix effects and limited certified reference materials (CRM) for validation purposes.

11. Conclusions

- Current biomonitoring guidance values mainly fall into four groups. Two of these rely on a clear established relationship between the level of the substance (or its metabolite), usually in the blood or urine, and some known harmful (clinical or pre-clinical) effect or, a clear relationship between airborne exposure and the level of a measured biomarker in a matrix (e.g., blood or urine). Due to the essential nature of copper as a nutrient and its endogenous homeostatic control, an increase in exposure to copper by workers is not reflected in higher blood or urine levels. In addition, most reported effects of copper inhalation are direct local effects on eyes, skin, respiratory tract and other mucus membranes, and systematic toxicity is less evident due to homeostatic control.
- Other biomonitoring guidance values, such as the German BAR value, can be set, based on an arbitrary value estimated as a percentage of levels determined in the general, non-occupationally exposed population. Although this is potentially feasible for copper, the large inter-individual variation in blood levels within the general population may give too large a range for any meaningful increases following occupational exposure to be detected.
- The UK HSE have derived a pragmatic biomonitoring guidance value, based on the 95th percentile of available biomonitoring data obtained under well-controlled occupational conditions. However, due to the sparsity of such data for copper, this is also not an option that could be utilised for copper.

Based on available evidence, the feasibility and usefulness of monitoring occupational copper exposure via biomonitoring and its application in risk assessment and occupational health is not interpretable at the present time, for the reasons discussed above.

CRediT authorship contribution statement

Ruth Bevan: Writing – original draft. **Len Levy:** Writing – original draft.

Declaration of competing interest

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