The interpretation of trace element analysis in body fluids

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The clinical interpretation of trace element analysis has lagged behind the technology available to measure the elements in body fluids. Reports can be difficult to interpret and requires knowledge of toxicokinetics, the dynamics of how the trace metals accumulate and pass through the body. Trace element analysis is best used for specific applications, such as establishing levels of exposure, biological exposure indices, biomonitoring of populations, and to confirm an association following a compatible diagnosis. It is not well suited for screening individual patients. Chelation treatment may follow inappropriate trace element determinations and may carry a risk of side effects, some life-threatening. Trace element analysis should be used sparingly and with full understanding of what the results are likely to mean. The physician should only order the test with a clear idea of why he or she is doing so and what he or she will do with the result.

Key words Biomonitoring - body fluids - chelation - metals - test interpretation - trace element analysis

The clinical interpretation of trace element analysis has lagged behind the technology available to measure the elements in body fluids. Trace element analysis conducted on body fluids can be difficult to interpret and requires knowledge of toxicokinetics, the dynamics of how the trace metals accumulate and pass through the body. Trace element analysis is best used for specific applications, such as establishing levels of exposure, biological exposure indices, and to confirm an association following a compatible diagnosis. Trace element analysis should be used cautiously. The physician should only order the test with a clear idea of why he or she is doing so and what he or she will do with the result.

This review is an update of a previous contribution1 that has served many physicians as a popular guide to the interpretation of trace element analysis. Because this is a vast subject with abundant documentation, references are restricted to easily accessible sources, to explanatory material or to the earlier contribution1.

By definition, trace elements are normally present in very low concentrations in the body. Iron and magnesium, for example, are not trace elements because substantial quantities are normally present in the body. Many such metals are essential elements for various metabolic functions (e.g., cobalt, manganese, selenium), however they are needed and present only in minute quantities. There are many sources of exposure for these trace elements in daily life, particularly in foods, but only at extremely low amounts.

Trace metal analysis of body fluids reflects the body burden, or internal dose, of the individual being tested.
That is, it examines the amount of the metal that has actually entered the body and remained there, compared to environmental measurements which measure external levels to which a worker might potentially but not actually be exposed. Thus, it is best considered as a reflection of the “real” level in the body of the trace elements, or internal dose, as opposed to the potential exposure that is measured by occupational hygienists. This type of internal dosage measurement is called biological monitoring, or biomonitoring.

Biological monitoring is the measurement of a substance or its metabolites in the bodily fluids or tissues (generally the blood and the urine) in an attempt to assess the potential health risk the substance may induce. The unit being measured is termed a biological marker, or biomarker. Biomarkers are physiological, cellular or molecular indicators used to evaluate xenobiotic exposures and potential population effects. There are biomarkers of exposure, effect and susceptibility. Molecular epidemiology is the approach that identifies and assesses the relationship between biomarkers and health outcomes.

Biomarkers of exposure identify and measure xenobiotic residues in tissue or body fluids, metabolites of the xenobiotic or physiological outcomes that are effects of exposure often unrelated to the toxic effect of concern in humans. For example, a biomarker might be the concentration of a chemical in urine over twenty four hours, or the degree of inhibition of an enzyme known to be affected by the chemical. These data provide information on an individual’s total exposure from all sources, proceeding the time of the analysis. Biomarkers cannot distinguish between the contribution of various absorption pathways to the internal dose that is reflected in the biomarker level. Samples over time are used to identify population trends. Biomarker data can be used to compare exposures in different subpopulations, such as children, adolescents, or the elderly, or residents of different geographical areas. Ultimately, better information about a population’s exposure results in better decisions to protect public health and assist in the prioritization of research and intervention programmes.

Biomarkers of effect characterize the impact of exposure to chemicals or contaminants on a targeted system such as the blood. As a result, molecular, cellular, or even systemic effects can be observed before clinical symptoms occur. For example, recovery of DNA adducts from blood or urine may reflect the risk of genotoxicity. Not all individuals with a given biomarker of effect will develop the disease.

Biomarkers of susceptibility can potentially characterize how populations respond to exposures. In addition, biomarkers of susceptibility can identify potentially sensitive population subgroups. For example, studies of genetic polymorphism can identify persons with enzyme types more likely to be affected by a chemical. Susceptibility biomarkers can be used to identify population subgroups potentially at greater risk from a given exposure so that protective measures can be taken. They may also be important in assessing the mechanism of toxicity.

The limitations of using biomarkers in a workplace setting include characterizing the specificity and sensitivity of the biomarker for the xenobiotic, understanding the metabolism of the xenobiotic and accounting for individual differences within a population. The primary objective of molecular epidemiology is to identify associations between biomarkers and potential risk. As more biomarkers are developed and data collected, these associations increasingly will be able to provide risk decision makers with a better understanding of worker risk.

Biomonitoring that is undertaken in a population sample, in order to determine the distribution of exposure in a population and to monitor how it changes over time, has come to be called “tracking”. This term is in many ways unfortunate and inadequate, but it describes the process of following the population over time.

Trace element analysis

Trace element analysis reflects absorption from all sources, including occupational exposure, diet, hobbies, medication, smoking, and local soil-containing dust. It may also reflect characteristics of the host in retaining or accumulating the trace element, as in the case of patients on dialysis (aluminium), receiving parenteral nutrition (with a variety of possible deficiencies) with inborn errors of metabolism such as Wilson’s disease (copper), or with impaired excretion (lead).

The state of the art for trace element analysis is a highly accurate and sophisticated technology called inductively-coupled plasma mass spectroscopy (ICP-MS) to analyze the concentration of minute amounts of metals in a sample. The metal atoms are literally heated to such temperatures that they are stripped of their electrons and reduced to atomic nuclei, which are then analyzed by atomic weight. It is an exceptionally accurate method for low concentrations of trace elements, in the nmol/l or pmol/l range. Metals that are
present at higher concentrations, such as iron, overwhelm the system and are better determined using traditional methods. The accuracy of ICP-MS is very high, on the order of plus or minus 5 per cent of the true reading. This compares with errors of 20 per cent or more for conventional methods. Quality assurance testing is essential for confidence in laboratory reports: this involves splitting samples and comparing results on the same sample with determinations at a reference laboratory.

The technology works equally well for biological fluids and for water samples and is used routinely for both. Three biological fluids are assayed on a routine basis: serum, whole blood, and urine. These analyses typically report on a profile of several metals simultaneously.

Testing is performed on serum (the liquid fraction of blood) for metals that are carried in the blood in dissolved form or that are bound onto proteins that circulated in the blood. These include aluminium, antimony, barium, beryllium, copper, manganese, nickel, selenium, vanadium, and zinc. Serum samples cannot be used for lead or arsenic and are inaccurate for some trace elements such as bismuth.

Testing is performed on whole blood for metals that are present in serum and also for those that concentrate in the red cell fraction of blood. Concentrations in serum and whole blood for those metals present in serum are usually similar but in some cases, as for copper, the serum assay result may be somewhat higher because there is less in the red cells that make up approximately 40 per cent of the volume of whole blood. Those metals that accumulate preferentially in red cells are not accurately reflected in serum concentrations and only whole blood concentrations are valid for these metals such as cadmium, cobalt, molybdenum, lead, and thallium.

Urine is tested to determine the excretion of metals over a 24 h period. This is usually the most accurate reflection of the total body burden of the metal. Many factors affect excretions of metals over short periods: state of hydration, renal function, intake with foods, short-term exposures from other sources, renal blood flow. Over a longer period of time, however, these variations even out and excretion is then generally directly related to the average serum concentration during this period (in equilibrium with red cell concentration, in the case of those metals that accumulate in red cells). For this reason, spot urine samples are not very useful in determining whether an excessive exposure has occurred, particularly close to the reference range. Compliance is much more difficult to achieve in collecting a 24 h urine specimen but it is essential for an accurate and valid result. Urinary excretion over 24 h is used to determine aluminium, antimony, arsenic, barium, beryllium, bismuth, cadmium, manganese, selenium, lead, thallium, vanadium, and zinc.

Hair analysis has been very popular among some practitioners because of its convenience in sampling. However, hair is a difficult matrix for trace element determinations because it is contaminated by dust, hair products, and other environmental exposures and is in the solid rather than liquid phase, which makes it more difficult to handle. Concentrations may also vary along the length of the hair. As a consequence, hair analysis is not recommended for trace element analysis except in highly controlled settings, where there is no other sample available, and when forensic studies are conducted (for example, assessing changes over time as indicated by the length of the hair). Hair analysis should not be used as a routine clinical screening tool.

The final product of a trace element analysis is a profile of metal concentrations in any or all of the three body fluids, expressed in micromoles per litre for those in relatively higher concentrations and in nanomoles per litre for those in lower concentrations.

Interpreting trace element analyses

The absolute value of the concentration is the first consideration in interpretation. Is it in the expected order of magnitude? Technology other than ICP-MS may be prone to error in measurement at such low concentrations, so anomalous values should normally be repeated if they might be clinically significant. A single elevation may be an outlier or questionable significance in itself.

The absolute value of trace element concentration is usually definitive only for lead, where an action level of 2.0 µmol/l (40 mcg/dl in the United States) has been established and 3.0 µmol/l is considered presumptive toxicity for adults.

The reported value is compared against a reference range which is usually derived from the authoritative literature, matched against the experience of the local laboratory. Table I presents the reference ranges used for analysis at the Trace Element/Environmental Toxicology Laboratory at the University of Alberta, which has been a leader in trace element analysis. A
Table I. Trace elements (metals) and their reference ranges as used by the Trace Element and Environmental Toxicology Laboratory at the University of Alberta Hospitals

<table>
<thead>
<tr>
<th>Trace metal</th>
<th>Units</th>
<th>Serum (per litre)</th>
<th>Whole blood (per litre)</th>
<th>Urine (24 h total volume)</th>
<th>Toxicity of primary concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>µmol</td>
<td>0.00-0.37</td>
<td>NA</td>
<td>0.00-1.18</td>
<td>Dementia in context of renal failure</td>
</tr>
<tr>
<td>Antimony</td>
<td>nmol</td>
<td>0-50</td>
<td>NA</td>
<td>0-10</td>
<td>Respiratory irritant, cardiac toxicity (very rare)</td>
</tr>
<tr>
<td>Arsenic</td>
<td>µmol</td>
<td>NA</td>
<td>NA</td>
<td>0.00-1.35</td>
<td>Cancer risk, neuropathy</td>
</tr>
<tr>
<td>Barium</td>
<td>µmol</td>
<td>0.00-2.11</td>
<td>NA</td>
<td>0.02-0.05</td>
<td>Muscle toxicity (free Ba⁺⁺ ion only)</td>
</tr>
<tr>
<td>Beryllium</td>
<td>µmol</td>
<td>0.22-0.55</td>
<td>NA</td>
<td>0.00-0.22</td>
<td>Beryllium disease (similar to sarcoidosis)</td>
</tr>
<tr>
<td>Bismuth</td>
<td>nmol</td>
<td>NA</td>
<td>NA</td>
<td>0-96</td>
<td>Very low toxicity</td>
</tr>
<tr>
<td>Cadmium</td>
<td>nmol</td>
<td>NA</td>
<td>0-50</td>
<td>0-10</td>
<td>Pulmonary, renal, systemic, cancer risk</td>
</tr>
<tr>
<td>Cobalt</td>
<td>nmol</td>
<td>NA</td>
<td>0-20</td>
<td>NA</td>
<td>Pulmonary, cardiac, asthma sensitization*</td>
</tr>
<tr>
<td>Copper</td>
<td>µmol</td>
<td>11-28</td>
<td>NA</td>
<td>0.1-0.8</td>
<td>Neurotoxic, hepatic in context of Wilson’s disease, MFF*</td>
</tr>
<tr>
<td>Lead</td>
<td>µmol</td>
<td>NA</td>
<td>0.30-1.95</td>
<td>0.00-0.40</td>
<td>Neurotoxic, renal, systemic (protein)</td>
</tr>
<tr>
<td>Manganese</td>
<td>nmol</td>
<td>9-20</td>
<td>NA</td>
<td>0-20</td>
<td>Neurotoxic</td>
</tr>
<tr>
<td>Mercury</td>
<td>nmol</td>
<td>NA</td>
<td>NA</td>
<td>0-50</td>
<td>Neurotoxic, renal</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>nmol</td>
<td>NA</td>
<td>5-50</td>
<td>NA</td>
<td>Very low toxicity</td>
</tr>
<tr>
<td>Nickel</td>
<td>nmol</td>
<td>0-100</td>
<td>NA</td>
<td>NA</td>
<td>Cancer risk, sensitization</td>
</tr>
<tr>
<td>Selenium</td>
<td>µmol</td>
<td>1.29-2.60</td>
<td>NA</td>
<td>0.00-1.00</td>
<td>Systemic*</td>
</tr>
<tr>
<td>Thallium</td>
<td>nmol</td>
<td>NA</td>
<td>0-49</td>
<td>0-49</td>
<td>Systemic, neurotoxic</td>
</tr>
<tr>
<td>Vanadium</td>
<td>nmol</td>
<td>0-200</td>
<td>NA</td>
<td>0-160</td>
<td>Pulmonary irritant (rare)**</td>
</tr>
<tr>
<td>Zinc</td>
<td>µmol</td>
<td>8-20</td>
<td>NA</td>
<td>2.0-12.0</td>
<td>MFF*</td>
</tr>
</tbody>
</table>

*Equal or greater interest in role as essential trace element in nutrition; **Equal or greater interest as dietary supplement or medicinal use

MFF, may cause metal fume fever; NA, not applicable

Published reference range is commonly used because it is usually not practical for individual laboratories to develop their own reference ranges on large populations. The individuals who make up the reference sample are usually selected to be generally representative of the population as a whole and are usually a “convenience sample” of people accessible to the investigators, such as health workers. In recent years, however, data have become available from large cross-sectional surveys, such as the National Health and Nutrition Examination Survey. Such surveys are very expensive and are rarely conducted except as research projects. Subjects included in the reference range are rarely chosen to be representative of occupationally-exposed groups. As a result, one usually has much more information on the distribution of trace element levels in the general population than in occupationally exposed populations.

Reference ranges for occupational exposure are often benchmarked against a standard reference work first prepared in 1983 by Robert Lauwerys, of the Catholic University of Louvain in Belgium, which is now in its third and last edition⁵. A new reference work is in preparation by a team of North American authors and may be available in 2009⁶.

Trace element analyses can be compared with the reference range only as a very rough guide. In practice, accuracy on the distribution of trace element levels in the population is not essential. For most applications,
it is enough to know approximately what the range is for people who are not occupationally exposed to metals and to know that the local laboratory is getting similar results.

The reference range for trace elements means something very different from the “normal range” of a clinical test. The normal range of a clinical test represents the range of a biochemical parameter representative of healthy people and is normally set to include 95 per cent of the distribution for subjects in presumptive good health, without indication of a clinical disorder. A finding outside this range suggests a deviation from the normal homeostatic mechanisms of the body that keep the internal chemistry on an even keel. The reference range for trace element analysis, in contrast, has no such intrinsic physiological meaning. It only suggests the range of levels of a trace element that would be expected from the usual exposure sources encountered in daily life. Occupational exposure may result in much greater body fluid concentrations, sometimes an order of magnitude greater, without implying toxicity. The further away one is from the toxicity threshold, the better, in theory.

Ideally, one would like to place an elevated finding on a trace element analysis on a continuum between the reference range, representing the “background” level in the general population, and the toxicity threshold, the concentration at which toxic effects may be expected. Published toxicity levels are approximate and need to be interpreted in context. Thresholds have not been established for most trace elements and probably vary according to the age and genetic susceptibility of the individual, whether the accumulation took place over sufficient time for tolerance to develop, intake from foods, whether other exposures have occurred, whether there is a co-existing clinical disorder.

Applications to screening for health risk

Trace element analysis has become widely used as a screening test to identify exposure with the potential for possible toxicological conditions. However, that is not necessarily the most appropriate use of the test. It is difficult to make sense of an arbitrarily ordered trace metal analyses in the absence of a clinical context, even with knowledge of the subject’s occupation. The use of trace element analysis by alternative medical practitioners and its conduct by questionable laboratories have somewhat discredited the method and is a frequent source of confusion in medical diagnosis.

Instead of working backwards from the disease state to identify evidence for massive exposure, the method has often been used to document exposure in an effort to assess risk prospectively. Unfortunately, the empirical experience to date supports the assessment of risk from trace element analysis in a few circumstances, such as lead exposure and possibly cadmium. Trace element profiles as a whole cannot be readily used for purposes of assessing future risk.

Applications in occupational medicine

Trace element analysis is a useful tool for monitoring the exposure levels of groups of workers, for the primary purpose of monitoring the exposure of individual workers. Occupational exposures by inhalation or ingestion reflect exposure in part because of the elements involved and in part because exposure typically occurs at much higher amounts than dietary intake and so is apparent against background levels. The elevations observed do not necessarily represent toxicity, however.

The routine use of biological monitoring to evaluate exposure to workplace hazards is the basis of “biological exposure indices” (BEIs), such as those developed by the American Conference of Governmental Industrial Hygienists. An absolute requirement for an acceptable BEI is that it correlate closely with documented exposure in the workplace for individuals. This is true.

Standard laboratory tests
(e.g., glucose, creatinine, electrolytes)

Fig. 1. Normal distribution (may be log-normal in practice) and appropriate interpretations based on statistical frequency in a standard clinical test.

Trace element analysis

Fig. 2. Distributions of trace element levels in the general population (solid curve) and an occupationally exposed population (hatched curve).
for many metals such as lead and cadmium but not for others such as manganese. Manganese levels reflect workplace exposure on an average, group basis but for any one individual the levels can be highly variable, making it difficult to use for diagnostic purposes.

**Toxicokinetics of metals**

The metals of concern vary greatly in their toxicokinetic behaviour. For example, lead is efficiently absorbed through inhalation but only inefficiently through ingestion, accumulates in red blood cells (90%), is sequestered in bone and soft tissues, and is only slowly excreted primarily by the kidney, with a half-life for practical purposes of about one month. Manganese is also only efficiently absorbed by inhalation and also accumulates in red cells (96%), but is predominantly excreted in bile and faeces and has a very short half-life, just days. There is a very close correlation between intake of lead and concentration in body fluids, with more recent exposures better reflected in urine, and a very poor correlation for manganese. Thus, it is necessary to know as much as possible about the specific behaviour of the metals in question before attempting to interpret the toxicological significance of an elevated trace metal analysis.

Oxidation potential is a critical factor for chromium and some other metals. This complicates interpretation because the exposure of potential interest is only CrIV, not the more common CrIII. Fluctuations of urinary levels generally reflect CrVI-exposure during the last 24-48 h, while the individual “base” level more generally reflects cumulative past exposure to Cr in any valence state. Currently there is not sufficient information in the literature to recommend as guidelines certain levels of chromium in whole blood, plasma or urine - total chromium or CrVI - below which current CrVI-exposure may be considered as safe or not hazardous7.

As for nickel (Ni), it has been found that urinary levels of this element corresponds quite well to airborne exposure levels2,5. The above limitations must be taken into consideration when attempting to monitor Ni in blood or urine among stainless steel (SS) welders.

**Application to clinical medicine**

Trace element analyses yield a profile that must be interpreted in context. The toxicity threshold for most trace elements is unknown and is probably highly variable, depending on the susceptibility of the individual. An exception is lead, where a level of 3.0 or 3.5 µmol/l is generally accepted as indicative of toxicity. The interpretation of a trace element analysis also depends on the specific metals of concern. As a practical matter, the metals of greatest concern with respect to clinical toxicity are usually lead, mercury, arsenic, and manganese.

Smoking status is an important factor in interpreting trace element analysis. Cadmium and nickel are often elevated in smokers. Welders who smoke may show elevated levels of nickel and chromium compared to those welders who do not.

**Patterns of elevations**

Another useful clue to interpreting trace element analyses is the pattern of elevations in the profile. Certain elevations clearly go together: molybdenum, vanadium, and selenium, for example, are usually elevated or relatively elevated together in welders compared to the reference range1. There is no obvious toxicological significance to this observation. Rather, it probably reflects the combined exposure encountered in certain industrial processes and alloys.

Certain elevations above the reference range have well-described associations that have no toxicological significance. Arsenic, for example, is often elevated following a meal of seafood because shellfish accumulate the metal. Nickel may be elevated among cigarette smokers. Selenium and zinc may be elevated when the subject is taking supplements, usually from health food stores. Aluminium is sometimes observed to be elevated in individuals in renal failure and on dialysis. Substantial elevations of thallium would be very unusual in the general population, for example, and might suggest ingestion of rat poison9. Isolated elevations may also relate to occupational exposures. Nickel, cadmium, and lead, in particular, may reflect occupational exposures well below the levels probably associated with toxicity.

The preferred approach to using trace element analysis for diagnosis is to work backward from the presumptive diagnosis. An elevation known to be associated with a particular disorder, such as manganese and movement disorders, is much more convincing in the context of a patient with the clinical suggestion of Parkinson’s disease than as an isolated finding. The “post hoc” (after the fact) probability of the association being real is much greater than speculating on future risk in an asymptomatic individual after observing a single elevated level. This is especially true for those metals, such as manganese, for which the association between body fluid levels and the disease in question has not been documented.

Another factor in interpreting the clinical context is whether an elevation is likely to be stable or to represent a
single value captured during an increase or decrease. If the subject has not been exposed for several months to a metal with a short half-life in the body (such as manganese) and yet has a markedly elevated level, this is presumptive evidence that the initial level was much higher. Because the toxicokinetic models that describe the behaviour of metals at low concentrations are not simple logarithmic decay curves, one should not make a simple extrapolations to the original value. On the other hand, if there has been little or no change in the overall pattern of exposure, the level obtained is probably representative despite variation.

**Specific trace elements**

The trace elements generally considered to be essential are copper, cobalt, iodine, iron, manganese, molybdenum, selenium and zinc. A balanced and regular diet generally keeps these trace elements roughly constant and consistent but there is no homeostatic mechanism that does so. Deficiencies in the uptake or metabolism could result to sustained imbalance of trace elements. In addition, an excess intake could result in disease. Other trace elements, such as arsenic, cadmium, lead and mercury, have no known human body function and exposure to these elements could result in both immediate and delayed adverse health effects.

Table II presents commonly used reference values for trace elements, representing a range of authoritative values used by national occupational health institutes and by the World Health Organization.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Measured parameter</th>
<th>ACGIH</th>
<th>HSE</th>
<th>DFG</th>
<th>FIOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>U-AsIII + AsV + MMA</td>
<td>50 µg/g cr</td>
<td>230 µmol/mol cr</td>
<td>0.07 µmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+DMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>U-AsIII + AsV + MMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>U-Cd</td>
<td>5 µg/g cr</td>
<td>10 µmol/mol cr</td>
<td>15 µg/l</td>
<td>50 nmol/l</td>
</tr>
<tr>
<td></td>
<td>B-Cd</td>
<td>5 µg/l</td>
<td></td>
<td>15 µg/l</td>
<td>50 nmol/l</td>
</tr>
<tr>
<td>Chromium (VI), water soluble fume</td>
<td>U-Cr</td>
<td>10 µg/g creat</td>
<td>40 µg/l</td>
<td>0.6 µmol/l</td>
<td></td>
</tr>
<tr>
<td>Chromium: B-Cr</td>
<td>30 µg/g creat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkalimetal chromates</td>
<td>U-Cr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium (VI) oxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt</td>
<td>U-Cobalt</td>
<td>15 g/l</td>
<td></td>
<td>60 g/l</td>
<td>600 nmol/l</td>
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<td></td>
<td>B-Cobalt</td>
<td>1 g/l</td>
<td></td>
<td>5 g/l</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>B-Pb</td>
<td>30 g/100 ml</td>
<td>70 g/100 ml</td>
<td>70 g/100 ml</td>
<td>50 g/100 ml</td>
</tr>
<tr>
<td></td>
<td>U-Pb</td>
<td>150 g/l</td>
<td></td>
<td>50 g/l</td>
<td></td>
</tr>
<tr>
<td>Lead, organic</td>
<td>U-Lead</td>
<td>40 g/g cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>U-Hg, inorganic</td>
<td>35 µg/g cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B-Hg, inorganic</td>
<td>15 µg/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury, inorganic</td>
<td>U-Hg</td>
<td>20 µmol/mol cr</td>
<td>200 µg/l</td>
<td>250 nmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B-Hg</td>
<td>50 µg/l</td>
<td></td>
<td>90 nmol/l</td>
<td></td>
</tr>
<tr>
<td>Mercury, organic</td>
<td>B-Hg</td>
<td>100 µg/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel, soluble cmpd</td>
<td>U-Nickel</td>
<td></td>
<td></td>
<td>1.3 µmol/l</td>
<td></td>
</tr>
<tr>
<td>Nickel, insoluble</td>
<td>U-Nickel</td>
<td>45 µg/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>U-Se</td>
<td></td>
<td></td>
<td>1.25 µmol/l</td>
<td></td>
</tr>
</tbody>
</table>

ACGIH, American Conference of Government Industrial Hygienists, 1997; HSE, Health and Safety Executive, UK (Wilson, 1996); DFG, Deutsche Forschungsgemeinschaft (Deutsche Forschungsgemeinschaft, 1996); FIOH, Finnish Institute of Occupational Health (Ahlstrom, 1998); B, blood; U, urine

a, end of work week; b, benchmark value; c, end of shift; d, exposure equivalent for carcinogenic chemicals (EKA); e, increase during shift; f, does not apply to welding fumes; g, end of shift at end of work week; h, in continuous exposure, after several shifts, at the end of the exposure; i, 40 µg/100 ml for women of childbearing age; j, 30 µg/100 ml for women <40 yr of age; k, prior to the next shift; l, morning specimen
The toxicity and characteristics of each trace element is described in many handbooks and publications, among which are the Toxicology Profiles of the Agency for Toxic Substances and Disease Registry. These are comprehensive reviews, updated every few years, and contain useful summaries in lay language that can be shared with patients. They are also web-accessible.

**Chelation therapy**

The rational for chelation treatment is to mobilize for rapid excretion metal that is not rapidly bound in tissue stores. Certain metals, such as mercury and relatively light metals are relatively freely mobile and their excretion is not much enhanced by chelation so the treatment is not therapeutically valuable. Other metals, including some radionuclides, are tightly bound to bone and chelation treatment is only used in extremely unusual circumstances as in an adjuvant treatment to mobilize substances such as plutonium, where every atom virtually makes a difference in terms of future risk. These are exceptional cases and the vast majority of indications for chelation treatment in occupational medicine are for either lead or arsenic.

Chelation therapy in treating heavy metal intoxication is considered valuable but potentially dangerous and must be closely monitored. Chelation only removes about 1 or 2 per cent of the body burden of lead in the body of an adult and is not particularly effective at reducing tissue levels in the central nervous system. The danger, even in treatment for toxic metals, is that mobilization of the metals also enhances their toxicity, particularly to the nervous system and kidney. Thus, in the course of a treatment designed to enhance excretion and therefore to reduce body burden, the trade-off is to present the metal in a form that may cause greater toxicity than the heavy metal, usually lead, itself. With repeated or relatively indiscriminate treatment, there is concern regarding mobilization of calcium and future risk of osteoporosis. As well, there have been hypersensitivity reactions to chelating agents.

In adults and children, the chelating agent of choice is dimercaptosuccinic acid (DMSA, trade name Succimer), which has replaced penicillamine as the chelation agent of choice for most purposes and for lead. The greatest concern over DMSA, has arisen from the finding of neurotoxicity in experimental animals without lead exposure. In other words, animals treated with lead showed improved function after chelation but animals that did not have lead toxicity actually showed signs of toxicity to the nervous system after chelation with DMSA. This suggests a potentially serious risk when DMSA is given casually of to children who have blood lead levels in the intermediate to low range and who do not have overt lead poisoning.

The criteria for chelation treatment of heavy metal toxicity are somewhat controversial. Most authorities agree, however, that chelation treatment for lead toxicity in adults is only appropriate for blood levels “well over” 80 µg/dl (and some say 100) in the clear presence of symptoms. Most authorities would not agree with chelation therapy at levels as low as 80 µg/dl or in the absence of symptoms. The primary treatment of chronic lead toxicity is always removal from exposure. In a context of treatment of lead toxicity, regular monitoring of the rate of elution of lead by serial 24 h urine collections is considered essential as well as regular urinalysis and renal function testing because soluble lead is nephrotoxic. Because blood lead levels lag well behind mobilization of lead, it is not considered worthwhile to check blood lead levels more than every week or so.

Use of chelation to treat children with acute heavy metal toxicity calls for a different protocol entirely and is generally performed using Succimer given orally. Chelation treatment in children should only be undertaken by an experienced clinician, using accepted protocols for agreed clinical indications. Chelation for lead toxicity is usually not necessary unless the child is both symptomatic and has confirmed high blood lead levels. Chelation at lower blood lead levels may reduce blood lead levels but has not been shown to improve cognitive function, which is the endpoint of treatment and as noted may carry an intrinsic risk of neurotoxicity. In most cases, removal from exposure is safer and reduces blood lead level over time. Chelation is ineffective and potentially dangerous for the treatment of autism, which some practitioners have dubiously related to mercury exposure although there is no persuasive evidence for this.

Arsenic is the third exposure for which chelation may rarely but plausibly be used by clinicians. The use of chelation treatment for other metal intoxication would be so rare as to be reportable in the medical literature. In the rare instances that “edetate”, or ethylene diamine tetracetic acid (EDTA) is used, particular care should be made to ensure that only disodium calcium EDTA salt is used (trade name Versinate in the United States), and not disodium EDTA (trade name Endrate in the United States). EDTA avidly chelates calcium and unless the calcium salt is used, EDTA can result in dangerous and even fatal levels of hypocalcaemia.
There are many ethical constraints on the use of chelation therapy in heavy metal toxicity, among the general recognition that it should never be used to suppress heavy metal levels in workers who continue to be exposed. Chelation therapy should be performed only by individuals who are trained in toxicology and familiar with the principles and it is not considered a suitable procedure to be used in primary care. Further, because of the attendant risks, very close monitoring of patients and serial measures of urinary excretion and renal function are absolutely essential. However, the criteria used as an indication for treatment do indeed vary among reputable authors. All agree, however, that chelation therapy in heavy metal toxicity, among the greater care and understanding in interpretation of trace element analysis of laboratory levels. Greater care and application to be used unless the patient is symptomatic or the body burden is extremely high. It should not be used casually or as a preventive, low-dose treatment, notwithstanding its recent popularity as an alternative treatment for cardiovascular disease risk.

The abuse of chelation treatment is intimately linked with misunderstanding of trace elements and the significance of laboratory levels. Greater care and understanding in interpretation of trace element analysis will lead to safer interventions and less potentially dangerous over-utilization of chelation.

References
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