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Interpretation of the trace metal analysis profile for patients occupationally exposed to metals

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Trace element profile analysis detects and quantifies the presence of several metals simultaneously at low concentrations in the body. In occupational medicine, it may be used to monitor exposure or to evaluate suspected toxicity. Clinical interpretation is often difficult because, with the exception of lead and possibly cadmium, there is little firm information on toxicity thresholds. For these tests, the reference ranges typically reflect low levels of exposure in the general population and it is expected that workers handling metals in occupations such as welding and industries such as steelmaking will have higher levels. Interpretation requires some knowledge of the toxicokinetics of the metal of interest and the preferred medium for analysis for each: serum, whole blood or urine (preferably 24-hour collection). Trends are often more informative than concentrations at one time. Trace element values are reported together with a reference range which must be distinguished from the normal range of other clinical tests. As a practical matter, the greatest interpretation problems tend to be found with manganese because serum levels have a poor correlation with both recent exposure and neurological symptoms. Molybdenum and vanadium are often found to be elevated among workers exposed to metals who show no evidence of clinical illness. Interpretation of the trace element profile analysis overall when an elevation occurs generally requires close attention to the pattern of elevation, clinical context, absolute and relative magnitude of the elevation and knowledge of the exposure history.

Key words: Biological monitoring; clinical interpretation; metal; trace element.

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INTRODUCTION

Trace element profile analyses detect and quantify the presence of metals at low to very low concentrations in body fluids. The clinical interpretation of trace element analysis has lagged behind the technology. This paper is intended to serve as a guide to the interpretation of trace element profile analysis in workers exposed to metals. These analyses typically report on a profile of several metals simultaneously and are often difficult to interpret. Even marked elevations may lack clinical or toxicologic significance.

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Originally, the determination of trace elements as a routine clinical analysis was intended for three specific indications: (1) trace element deficits, particularly from nutritional defects; (2) extreme exposure associated with clinical presentations suggesting acute toxicity and (3) monitoring personal internal dose for purposes of monitoring compliance with biological exposure indices such as those promulgated by the American Conference of Governmental Industrial Hygienists (ACGIH). The clinical issues driving the effort in these applications were selenium deficiency, dialysis-associated dementia involving accumulation of aluminium, and the evolving interest in lead toxicity at lower levels of exposure, respectively. However, once these tests were introduced, they became widely used where they were available as screening tests to identify exposure with the potential for possible toxicologic conditions.

Instead of working backwards from the disease state to identify evidence for massive exposure, the method has been used to document exposure in an effort to assess risk. Unfortunately, the empirical experience to date only supports the assessment of risk from trace element analysis in very few circumstances, such as lead and possibly cadmium exposures. The profile as a whole cannot readily be used in this way.

This paper is intended to be a guide to occupational clinicians concerned with the proper interpretation of trace element analysis. The method may be exceedingly useful in some situations but its potential and limitations must be well-understood before the test is ordered. Otherwise, the interpretation is confused and may be misleading. It is difficult to make sense of an arbitrarily ordered trace metal analysis in the absence of a clinical context, even with knowledge of the subject's occupation.

Trace element profile analysis in occupational medicine

Trace element profile analysis conducted on body fluids can be a very useful tool for following the exposure levels of groups of workers, for monitoring the exposure of individual workers and for establishing the diagnosis of toxicity in an individual patient. However, the findings from trace element profile analysis are difficult to interpret and require a detailed knowledge of the toxicokinetics of each metal.

For several years, the Occupational Health Consultation Clinic of the University of Alberta Hospitals has performed trace element profile analysis on selected workers. The measurement of most trace elements remains to be validated as an investigative technique and therefore cannot supplant to any degree the conventional work-up of occupational diseases. Rather, the aim of this testing has been to build a database of trace element values encountered in different occupational settings and to explore and gain experience on its clinical role. This short paper is intended to explain the general principles of trace element analysis, as applied at the University of Alberta Hospitals, and to describe a systematic procedure for interpreting the findings.

The 'trace elements' in a trace elements profile analysis are metals that 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 present only in minute quantities. There are many sources of exposure for these trace elements in daily life, particularly in foods, but only in extremely low amounts. Occupational exposures by inhalation or ingestion are usually significant because they typically occur in much higher amounts than dietary intake.

The metals of concern vary greatly in their toxicokinetic behaviour. For example, lead is absorbed efficiently 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 1 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, while there is a very poor correlation for manganese.[1] 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 profile analysis.

Trace metal analysis of body fluids reflects the body burden, or internal dose, of the individual being tested. That is, the clinical sample 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, the clinical sample is best considered as the 'real' level in the body of the trace elements, compared to the potential exposure that is measured by occupational hygienists. This type of internal dosage measurement is called biological monitoring.

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.[2] An absolute requirement for an acceptable BEI is that it correlate closely with documented exposure in the workplace for individuals. This is true for many metals such as lead and cadmium but not for others such as manganese. Manganese levels do reflect workplace exposure on an average, group basis, but for any one individual the levels can be highly variable despite constant exposure.[3]

In Canada, many unions have opposed biological monitoring on the grounds that it invades the privacy of workers and may lead to questionable applications in the future, such as intrusive genetic screening or drug testing without reasonable cause. However, in Japan and Germany, biological monitoring is rapidly becoming the norm and is replacing environmental monitoring as the 'gold standard' for regulatory purposes in some situations.[4,5]

Biological monitoring is a reflection of several different processes. It primarily reflects exposure from all sources, including occupational sources, 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), with inborn errors of metabolism such as Wilson's disease (copper), or with impaired excretion (lead); however, such cases are uncommon in the occupational setting.

It is a cardinal principle of medicine that tests should

not be ordered unless the requesting physician knows how to interpret the result. However, trace element analysis has been used as a screening tool without a clear picture of its appropriate application. This must be corrected if trace element analysis is to become a useful supplementary tool in medical evaluation.

METHODS AND TECHNOLOGY

The Trace Elements/Environmental Toxicology Laboratory at the University of Alberta Hospitals uses a highly accurate and sophisticated technology called inductively-coupled plasma mass spectroscopy (ICP-MS) to simultaneously analyze the concentration of minute amounts of metals in a sample. The metal atoms are literally heated in a hot plasma to such temperatures that they are stripped of their electrons and reduced to positively charged atomic nuclei, which are then analyzed by atomic weight in a mass spectrometer. It is an exceptionally accurate and specific method for low concentrations of trace elements, in the nmol/L or μmol/L range. Metals that are present at higher concentrations, such as iron, calcium and magnesium are generally better determined using traditional methods. The accuracy of ICP-MS is very high, on the order of plus or minus 1–5% of the true reading. This compares with errors of 5–10% or more for conventional methods. A further advantage of ICP-MS is its ability to analyze several different elements from the same sample.

The technology works equally well for biological fluids and for water samples and is routinely used for both. Three biological fluids are assayed on a routine basis: serum, whole blood and urine. Clinical testing is performed on serum for metals that are carried in the blood in dissolved form or that are bound to serum proteins which includes aluminium, antimony, barium, beryllium, copper, manganese, nickel, selenium, vanadium and zinc. Concentrations in serum and whole blood for those metals present in serum are usually similar but in some cases, as for copper, the measured serum concentration may be somewhat higher because less copper is found in the red cell fraction. Clinical testing is performed on whole blood for metals that, while present in serum, are mainly concentrated in the red cell fraction. 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: cadmium, cobalt, molybdenum, lead and thallium.

Urine is tested to determine the excretion of metals — ideally over a 24-hour 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 and 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). Urinary excretion over 24-hours is used to determine these metals: aluminium, antimony, arsenic, barium., beryllium, bismuth, cadmium, copper, manganese, selenium, lead, thallium, vanadium and zinc.

A 24-hour urine collection is usually not practical in the workplace. Therefore, the BEIs established by the ACGIH are based on random spot urine samples, often collected at a specific time in relation to exposure (pre- or post-shift).[2] To compensate for variable urine output, the measured concentration of the trace metal is divided by the concentration of creatinine in the sample. Thus, the BEI for cadmium in urine using a creatinine correction is expressed as 5 μg cadmium/g creatinine.

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 SI units of micromoles per litre for those in relatively higher concentrations and in nanomoles per litre for those in lower concentrations.

Interpretation of clinical findings

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 primary concern from an occupational perspective are usually lead, cadmium, arsenic and manganese. Cadmium is a particularly controversial issue since there is evidence to suggest that renal effects are not only irreversible but progressive long after exposure ceases.[6]

Absolute value

The absolute value of the concentration is the first consideration. Is it in the expected order of magnitude (nmol or μmol/L)? The absolute value by itself is definitive only for lead, where an action level of 2.0 μmol/L has been established and 3.0 μmol/L is considered presumptive toxicity. When available, it is also very useful to compare the value to previous values for the same individual. When exposure has not changed but the values are highly variable, a single elevation may be an outlier or of questionable significance in itself.

Reference ranges

The reported value is compared against a reference range which is usually derived from the authoritative literature taking into consideration clinically relevant

geographic distributions of some metals (*e.g.*, selenium) or age factors and are matched against the experience of the local laboratory. Table 1 presents the reference ranges used for analysis at the Trace Elements/Environmental Toxicology Laboratory at the University of Alberta Hospitals. A published reference range may be used if the preliminary findings of a local laboratory on normal subjects is consistent. It is usually not practical for individual laboratories to develop their own reference ranges on large populations, but laboratories typically test their methods on smaller samples of lab personnel in order to ensure that the findings are consistent with other laboratories. (This is in addition to quality assurance testing that involves splitting samples and comparing results on the same sample from different laboratories.) The individuals who make up the reference sample are selected to be at least generally representative of the population as a whole and are usually a 'convenience sample,' picked because they happen to be around the hospital rather than in some systematic fashion, such as a cross-sectional survey. Such broader surveys are very expensive and are rarely conducted except as research projects. In practice, this level of certainty on the distribution of trace element levels in the population is hardly ever very useful. For most applications, it is enough to know approximately what the range is for healthy people who are not occupationally-exposed to metals and to know that the local laboratory is getting similar results.

Subjects in the reference range rarely include occupationally-exposed individuals. As a result, when the test is introduced, one usually has much more information on the distribution of trace element levels in the general population than in occupationally-exposed populations. That comes later, after sufficient clinical experience has accumulated to determine what values are found in patients who actually have symptoms of disease and after research projects have been conducted to determine what levels are found in groups of exposed workers. This is especially true when such exposures are unusual or uncommon except in certain jobs, as in the case of workers exposed to metals.

The results from trace element analyses on occupationally-exposed populations can be compared with the reference range only as a very rough guide. The reference range for trace elements means something very different from the 'normal range' of a clinical test as it applies to a specific population group.

The normal range of a clinical test is highly meaningful; it represents the range of a biochemical parameter representative of healthy people and is normally set to include 95% 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. Figure 1 illustrates the usual statistical interpretation of a clinical test.

The reference range for a trace element analysis, in

Table 1. Trace elements (metals) and their reference ranges as used by the Trace Element and Environmental Toxicology Laboratory at the University of Alberta Hospitals

Trace metal	*Units*	*Serum (per litre)*	*Whole blood (per litre)*	*Urine (24-hour total volume)*	*Toxicity of primary concern*[7]
Aluminium	µmol	0.00–0.37	NA	0.00–1.18	Dementia in context of renal failure
Antimony	nmol	0–50	NA	0–10	Respiratory irritant, cardiac toxicity (very rare)
Arsenic	µmol	NA	NA	0.00–1.35	Cancer risk, neuropathy
Barium	µmol	0.00–2.11	NA	0.02–0.05	Muscle toxicity (free Ba^{++} ion only)
Beryllium	µmol	0.22–0.55	NA	0.00–0.22	Beryllium disease
Bismuth	nmol	NA	NA	0–96	Very low toxicity
Cadmium	nmol	NA	0–50	0–10	Pulmonary, renal, systemic, cancer risk
Cobalt[a]	nmol	NA	0–20	NA	Pulmonary, cardiac, sensitization
Copper	µmol	11–28	NA	0.1–0.8	Neural, hepatic in context of Wilson's disease, MFF*
Lead	µmol	NA	0.30–1.95	0.00–0.40	Neural, renal, systemic (protean)
Manganese[a]	nmol	9–20	NA	0–20	Neural
Mercury	nmol	NA	NA	0–50	Neural, renal
Molybdenum[a]	nmol	NA	5–50	NA	Very low toxicity
Selenium[a,b]	µmol	1.29–2.60	NA	0.00–1.00	Systemic
Thallium	nmol	NA	0–49	0–49	Systemic, neural
Vanadium[a]	nmol	0–200	NA	0–160	Pulmonary (very rare)
Zinc[a,b]	µmol	8–20	NA	2.0–12.0	MFF

MFF = May cause metal fume fever; NA = Not applicable.

[a] Proven or suspected essential trace element.

[b] Consumed as dietary supplement or taken for medicinal use.

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

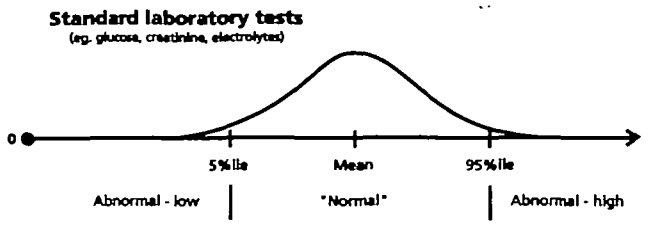
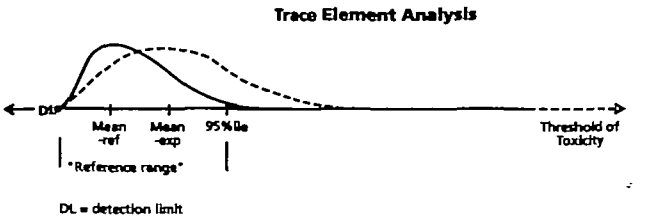


Figure 2. Distributions of trace element levels in the general population (solid curve) and an occupationally exposed population (hatched curve).



general, has no such 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, without occupational or other unusual exposures. Figures 2 illustrates the appropriate interpretation of a trace element analysis. The solid curve represents the distribution of trace element levels encountered in the general population from whom the reference range is established. Although the true distribution of trace element values in the general population is usually not known, it is probably positively skewed toward lower values. The distribution of trace element levels in an occupationally-exposed group is depicted by the hatched curve. Note that a significant portion of this curve extends beyond the upper limit of the reference range but still represents values obtained from healthy individuals.

Toxicity thresholds

Ideally, one would like to place an elevated finding from 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. The further away one is from the toxicity threshold, the better, in theory.

Toxicity thresholds have not been established for most trace elements and probably never will be. Thresholds may 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 coexisting clinical disorder, *etc.* Published toxicity levels are approximate and need to be cautiously interpreted in context.

For example, manganese toxicity is among the most heavily studied exposure-related disorder involving light metals. The neurological effects of manganese toxicity are well-documented but the published literature on exposure–response is almost exclusively based on environmental exposure data, not on body fluid levels. The correlation between blood levels of manganese and environmental exposure even in workers with evidence of neurological effects is poor[8] but most of these studies have been done near the reference range. Therefore, as a practical matter, one cannot use body fluid levels near the reference range as anything but the most general guide to exposure: if the blood or urine level is much above the reference range, it only indicates that the person was exposed more than would be the case for the general population. However, the published reports of manganese toxicity suggest that it occurs only at very high levels of environmental exposure, not within the range usually seen in most industries with acceptable hygiene practices. This means, logically, that a blood or urine level of manganese associated with toxicity would probably be far above the reference range, but may not relate in a one-to-one correspondence with the degree of exposure. Since one commonly encounters manganese levels that are up to several times the reference levels among workers who are occupationally exposed to metals but show no symptoms of neurological disease, one applies the rule of thumb that an isolated elevation of less than an order of magnitude (factor of 10) over the reference range is probably not significant in the absence of symptoms but may suggest an excessive exposure that should be controlled to avoid future risk.

Until there is more information grounded on accurate trace element analyses such as ICP-MS trace element profile assessment, this is the best that can be done. This 'rule of thumb' is very crude and applies only approximately for the more toxic metals. It is probably overly conservative for the less toxic metals, because the toxicity thresholds for some of them (such as barium and molybdenum) are very high and clinical toxicity is almost never observed.

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, manganese, vanadium and selenium, for example, are often elevated or relatively elevated together in welders compared to the reference range. There is no obvious toxicological significance to this observation. Rather, it probably reflects the combined exposure encountered in certain industrial processes. Table 2 shows a representative pattern in blood and serum for a welder from our clinic.

Elevations associated with temporal changes are particularly meaningful. Table 3 presents the profile

Table 2. Representative trace element analysis profile for serum and blood in a welder

Trace element	*Units*	*Serum*	*Blood*
Aluminium	µmol/L	< 0.05	NA
Antimony	nmol/L	< 15	NA
Arsenic	µmol/L	NA	NA
Barium	µmol/L	0.47	NA
Beryllium	µmol/L	< 0.06	NA
Bismuth	nmol/L	NA	NA
Cadmium	nmol/L	NA	< 1
Copper	µmol/L	12.0	< 2
Lead	µmol/L	NA	0.11
Manganese	nmol/L	40	NA
Mercury	nmol/L	< 5	NA
Molybdenum	nmol/L	NA	< 5
Thallium	nmol/L	NA	< 4
Selenium	µmol/L	2.30	NA
Vanadium	nmol/L	218	NA
Zinc	µmol/L	7.2	NA

For reference ranges, please refer to Table 1.

Elevations beyond reference range are indicated in bold type.

NA = not applicable

of a young woman, aged 26, who worked with mercury repairing pressure gauges for oilfield instruments. Despite extensive protection, she shows consistently elevated levels, just above the reference range. Elevations in other trace elements may reflect her occupational exposure to other metals and to inhaled metal dust. None of these elevations approach toxicity, although the abrupt rise in cadmium prompted a search for the source.

Isolated elevations

Certain elevations above the reference range have well-described associations that have no toxicologic significance. Arsenic, for example, is often elevated following a meal of seafood because marine plants and animals accumulate organic compounds of the metal of low toxicity.[9] 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 routinely observed to be elevated in individuals in renal failure on dialysis. Substantial elevations of thallium would be very unusual and might suggest ingestion of rat poison.[10]

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.

A second round of analyses is essential for verification of an elevation when a clinical decision hinges on the result. A transient elevation may have no clinical significance, may represent a brief and unrepresentative exposure or may represent an error in measurement, although this is unlikely with current methods.

Table 3. Trace element analysis profile of a laboratory technician exposed to mercury and other metals during one month of observation: 26 years old, asymptomatic, referred because employer noted elevated mercury on screening evaluations

Medium and element	*Units*	*22 June*	*6 July*	*20 July*
Serum				
Al	µmol/L	< 0.05	0.07	< 0.05
Ba	µmol/L	0.78	0.9	0.57
Be	µmol/L	< 0.06	< 0.06	0.06
Cu	µmol/L	16.4	25.7	22.5
Mn	nmol/L	11	**23**	**22**
Ni	nmol/L	67	< 5	< 5
Sb	nmol/L	< 25	< 15	< 15
Se	µmol/L	2.51	1.99	1.82
V	nmol/L	**219**	174	164
Zn	µmol/L	6.7	12.6	12.6
Blood				
Cd	nmol/L	2	NA	2
Co	nmol/L	2	NA	< 2
Mo	nmol/L	**53**	NA	19
Pb	µmol/L	0.05	NA	0.04
Th	nmol/L	< 4	NA	< 4
Urine (total in 24-hour collection)				
Al	µmol/L	< 0.02	< 0.02	< 0.13
As	µmol/L	0.34	< 0.06	1.14
Ba	µmol/L	0.01	0.01	< 0.02
Be	µmol/L	< 0.02	< 0.02	< 0.16
Bi	nmol/L	< 19	< 20	**134**
Cd	nmol/L	2	3	**26**
Cu	µmol/L	0.1	0.1	**6.6**
Hg	nmol/L	**60**	**57**	**56**
Mn	nmol/L	5	< 2	< 13
Pb	µmol/L	0	0	< 0.01
Sb	nmol/L	< 6	< 6	**< 41**
Se	µmol/L	0.67	0.53	**1.71**
Th	nmol/L	< 2	< 2	< 11
V	nmol/L	**199**	**171**	**486**
Zn	µmol/L	1.9	3.3	**18.8**

For reference ranges, please refer to Table 1.

Elevations beyond the reference range are shown in bold type.

Clinical context

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.[8]

Another factor in interpretation 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. (It is dangerous, given all the uncertainties, to make a simple extrapolation to try to calculate the original value, however.) On the other hand, if there has been little or no change in the overall pattern of exposure, the level obtained is probably representative recognizing that repeated sampling may still show considerable variation.

CONCLUSION

Trace element profile analysis is an imperfect tool for routine clinical screening. It is best used for certain specific applications such as establishing exposure, biological exposure indices and to confirm an association after a compatible diagnosis has been made. As experience with the method grows, trace element profile analysis will become increasingly useful. For the moment, however, it should be used cautiously and the occupational 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.

Trace element analysis can be a very valuable tool in evaluating patients and monitoring exposure. However, the results should be carefully interpreted with a knowledge of the kinetics of the metals involved and not treated in the same way as routine clinical tests.

REFERENCES

1. Chandra SV, Shukla GS, Srivastava RS, Singh H, Gupta VP. An exploratory study of manganese exposure to welders. *Clin Tox* 1981; **18**: 407–416.
2. American Conference of Governmental Industrial Hygienists. *Handbook of Threshold Limit Values and Biological Exposure Indices*. Cincinnati, OH (USA): 1996–1997.
3. Jarvisalo J, Olkinuora M, Kiiluenen M, Kivisto H, Ristola P, Tossavainen A, Aitio A. Urinary and blood manganese in occupationally nonexposed populations and in manual metal arc welders of mild steel. *Int Arch Occup Environ Health* 1992; **63**: 495–501.
4. Ogata M. Japanese experience in biological monitoring. Int *Arch Occup Environ Health* 1993; **65(1 Suppl)**: S15–S21.
5. Lehnert G, Schaller KH. Strategy of biological monitoring and setting of biological threshold limits (BAT values) in Germany. *Isr J Med Sci* 1995; **31**: 549–557
6. Järup L, Persson B, Edling C, Elinder CG. Renal impairment in workers previously exposed to cadmium. *Nephron* 1993; **64**: 75–81.
7. US Agency for Toxic Substances and Disease Registry. *Toxicological Profiles (Series)*. Atlanta, GA (USA): US Public Health Service, 1992.
8. Sjögren B, Iregren A, Frech W, Hagman M, Johansson L. Tesarz M, Wennberg A. Effects on the nervous system among welders with exposure to aluminum and manganese. *Occup Environ Med* 1996; **53**: 32–40.
9. Le X-C, Cullen WR, Reimer KJ. Human urinary arsenic excretion after one-time ingestion of seaweed, crab, and shrimp. *Clin Chem* 1994; **40**: 617–624.
10. Rangel-Guerra R, Martinez HR, Villarreal HJ. Thallium poisoning. Experience with 50 patients [In Spanish]. *Gaceta Medica de Mexico* 1990; **126**: 487–495.