THE IMPORTANT ROLE OF ICP-MS IN UNDERSTANDING THE TOXICOLOGICAL LINK BETWEEN LEAD CONTAMINATION AND HUMAN DISEASE

This year (2023) marks the 40th anniversary of the commercialisation of ICP-MS. At the 1983 Pittsburgh Conference, SCIEX introduced the ELAN 250 quadrupole-based ICP Mass Spectrometer. It was another 12 months before its joint venture with PerkinElmer Inc. was announced, but the event was the start of the meteoric rise of ICP-MS as the dominant multielement technique used for ultra-trace elemental analysis and the beginning of a competitive race which would see a number of other vendors and other mass spectrometer technologies come and go over the next 40 years. It was also the year that I 'cut my teeth' on the technique when I ran the PerkinElmer ICP-MS application/demo lab in the UK.

Today, there are close to 2,000 ICP-MS systems installed worldwide every year, representing around $400M in annual sales, performing a wide variety of applications, from routine, high-throughput multielement analysis to more complex tasks such as trace element speciation studies with high-performance liquid chromatography and monitoring of nano particles. As more and more laboratories invest in the technique, the list of applications is getting significantly larger and more diverse.

In my recent book on ICP-MS, I have written about the various ICP-MS and atomic spectroscopy (AS) application sectors being carried out by the user community **(1)**. However, 40 years after the commercialisation of the technique, it would be almost impossible to capture all of them. The most common ones include environmental monitoring, geochemical, metallurgical, petrochemical, food, clinical, toxicology, semiconductor, industrial, energy, agricultural, nuclear, pharmaceuticals, and cannabis consumer products, but every year it seems that a new market has woken up and realised the full potential of the capabilities of ICP-MS.

I am often asked if there was one application area which the technique has made the most important contribution over this time. It's a very difficult question to answer, but if pressed I would have to say it is in the field of human health and safety. Understanding the effects of toxic metals on the human body is as complex as it is fascinating. We know that too low or too high a concentration of essential trace elements in our diet can affect our quality of life. On the other hand, metallic contamination of the air, soil and water supplies can have a dramatic impact on our well-being. There are many examples that highlight both the negative and positive effects of trace metals on our lives. The effect of lead toxicity is well documented, as was demonstrated by the negligence of public health officials in Flint, Michigan who didn't adequately treat the drinking water supply when it changed from Lake Huron to the Flint River and as a result contaminated the water supply with abnormally high levels of lead. The movie Erin Brokovich alarmed us all to the dangers of hexavalent chromium (Cr VI) in drinking water, but how many of the audience realised that trivalent chromium (CRIII) metal is necessary for the metabolism of carbohydrates and fats? A few years ago, Dr. Oz, the infamous TV doctor in the US alarmed his viewers about high levels arsenic in apple juice, but what he failed to say was that it was not the highly toxic inorganic form of arsenic, but the arsenic that had been metabolised by the apple tree to the less toxic organic form.

ICP-MS has played a pivotal role in getting a much better understanding of metal toxicity on human health, and without it, we would not have been able to further our knowledge on many of these critical issues. However, there is one application that stands out and that is the dramatic reduction of blood lead levels in young children.

Lead Toxicity

Lead has no known biological or physiological purpose in the human body, but is avidly absorbed into the system by ingestion, inhalation and to a lesser extent by skin absorption **(2)**. Inorganic lead in submicron size particles in particular can be almost completely absorbed through the respiratory tract, whereas larger particles may be swallowed. The extent and rate of absorption of lead through the gastrointestinal tract depend on characteristics of the individual and on the nature of the medium ingested. It has been shown that children can absorb 40–50% of an oral dose of water-soluble lead compared to only 3–10% for adults **(3)**. Young children are particularly susceptible, because of their playing and eating habits and typically have more hand-to-mouth activity than adults **(4)**. Lead is absorbed more easily if there is a calcium/iron deficiency, or if the child has a high fat, inadequate mineral and/or low protein diet. When absorbed, lead is distributed within the body in three main areas – bones, blood and soft tissue. About 90% is distributed in the bones, while the majority of the rest gets absorbed into the bloodstream where it gets taken up by porphyrin molecules (complex nitrogen-containing organic compounds providing the foundation structure for hemoglobin) in the red blood cells **(5)**. It is therefore clear that the repercussions and health risks are potentially enormous, if humans (especially young children) have a long-term exposure to high levels of lead.

Health Effects

Lead poisoning affects virtually every system in the body, and often occurs with no distinctive symptoms. It can damage the central nervous system, kidneys, and reproductive system and, at higher levels, can cause coma, convulsions, and even death. Even low levels of lead in children are harmful and are associated with lower intelligence, reduced brain development, decreased growth and impaired hearing **(6)**. The level of lead in someone's system is confirmed by a blood-lead test, which by today's standards is considered elevated if it is in excess of 3.5 µg/dL (microgram per deciliter).

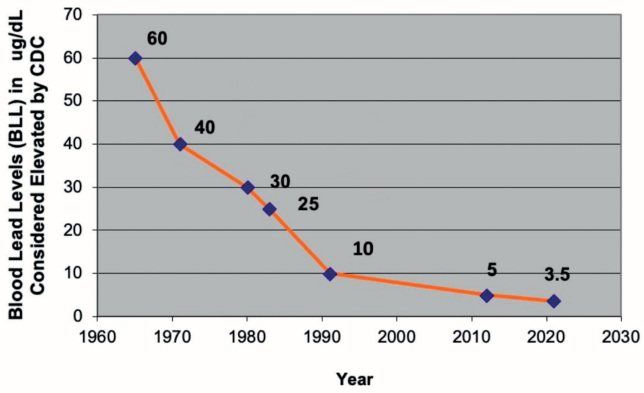

Figure 1: The trend in blood lead levels (µg/dL) in children considered elevated by the Centers for Disease Control and Prevention (CDC), since the mid-1960s

Note: On October 28, 2021, CDC lowered the blood lead reference value (BLRV) from 5.0 µg/dL to 3.5 µg/dL. A BLRV is intended to identify children with higher levels of lead in their blood compared with levels in most children. The value is based on the 97.5th percentile of the blood lead distribution in U.S. children ages 1–5 years. (for comparison purposes 1 µg/dL = 10 ppb) (7).

However, the long-term effects of lead poisoning have not always been well- understood. In the early-mid 1960s, remedial action would be taken if a blood lead level (BLL) threshold value was in excess of 60 µg/dL. As investigators discovered more sensitive detection systems and designed better studies, the generally recognised level for lead toxicity has progressively shifted downward. In 1970 it was lowered to 40 µg/dL and by 1978 the level had been reduced to 30 µg/dL. In 1985 the CDC published a threshold level of 25 µg/dL, which they eventually lowered to 10 µg/dL in 1991. It stayed at this level until it was reduced to 5 µg/dL in 2012 and eventually ended up at 3.5 µg/dL in 2021. However, as our understanding of disease improves and measurement technology gets more refined, this level could be pushed even lower in the future **(10)**. Figure 1 shows the trend in blood lead levels considered elevated by the Centers for Disease Control (CDC), since the mid-1960s.

Major Source of Lead

Currently the major source of lead poisoning among children comes from lead-based household paints, which were used up until they were banned in 1978 by the Consumer Product Safety Commission. Prior to this, leaded gasoline was the largest pollutant before it was completely removed from the pumps in 1995. Other potential sources include lead pipes used in drinking water systems, airborne lead from smelters, clay pots, pottery glazes, lead batteries, household dust and some processed foods made from natural plants and crops. However, awareness of the problem combined with preventative care and regular monitoring, have reduced the percentage of children aged 1–5 years with elevated blood levels (≥3.5 µg/dL) in the US from 26% in the early-mid 1990s to less than 2.5% today. These data were taken from a recent National Health and Nutrition Examination Survey (NHANES) report **(8)**.

Routine Monitoring of Lead Using Atomic Spectroscopic Techniques

There is no question that the routine monitoring of lead has had a huge impact in reducing the number of children with elevated blood levels. Lead assays were initially carried out using the dithizone colorimetric method, which was sensitive enough, but very slow and labour intensive. It became a little more automated when anodic stripping voltammetry was developed **(9)**, but blood-lead analysis was not considered a truly routine method until AS techniques became available. Let's take a more detailed look at how improvements in atomic spectroscopy instrumentation detection capability have helped to lower the number of children with elevated blood lead levels, since atomic absorption was first commercialised in the early 1960s.

Flame AA

When FAA was first developed, the BLRV was 60 µg/dL (600 ppb). Even though this is well above the detection limit of ~20 ppb at the time, it struggled to meet this level when sample preparation and dilution of the blood samples was taken into consideration, which typically involved acid digestion followed by dilution and centrifuging/filtering. When sample preparation was factored, the concentration of lead in the sample was in the order of 20 ppb – virtually the same as the FAA detection limit.

Delves Cup AA

To get around this limitation, an accessory called the Delves Cup was developed in the late 1960s to improve the detection limit of FAA **(10)**. The Delves Cup approach uses a metal crucible, which was positioned over the flame. The sample is pipetted into the crucible, where the heated sample vapour is passed into a quartz tube, which was also heated by the flame. The ground state atoms are concentrated in the tube and therefore resident in the optical path for a longer period of time, resulting in much higher sensitivity and about 100x lower detection limits. The Delves Cup became the standard method for carrying out blood lead determinations for many years, because of its relative simplicity and low cost of operation.

Electrothermal Atomization

The Delves Cup approach eventually got phased out with the commercialization of electrothermal atomization (ETA) or graphite furnace AA in the early-1970s. This new breakthrough technique offered a detection capability for lead of ~ 0.1 ppb – approximately 200x better than FAA. However, its major benefit for the analysis of blood samples was the ability to dilute and inject the sample automatically into the graphite tube with very little off-line sample preparation. This result was that blood lead determinations could now be carried out in an automated fashion with relative ease, even at very low levels.

Zeeman Correction GFAA

The next major milestone in AA was the development of Zeeman background correction (ZBGC) in 1981, which compensated for non-specific absorption and structured background produced by complex biological matrices, like blood and urine **(11)**. This, in conjunction with the STPF (stabilised temperature platform furnace) concept, allowed for virtually interference-free analysis of blood samples, using aqueous calibrations and as a result became the recognised way of analysing most types of complex matrices by ETA **(12)**.

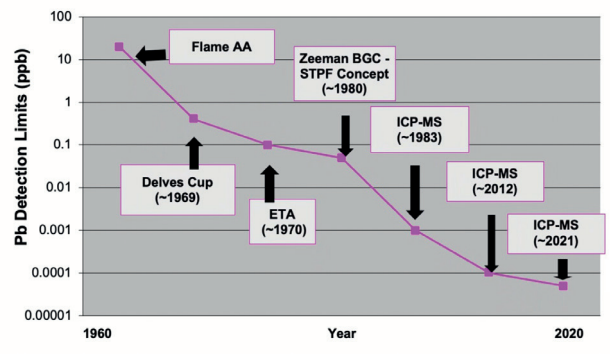

Figure 2: Comparison of detection capability of AS techniques (ppb) for lead and the approximate year they were developed, or improvements were made

ICP-MS

Even though ETA had been the accepted way of doing blood lead determinations for over 15 years, the commercialisation of quadrupole-based ICP-MS in 1983 gave analysts a tool that was not only 100x more sensitive but suffered from less severe matrix-induced interferences. In addition, ICP-MS offered multielement capability and much higher sample throughput. These features made ICP-MS very attractive to the clinical community, such that many labs converted to ICP-MS as their main technique for trace element analysis. Then as the technique matured, utilising advanced mass separation devices, performance enhancing tools, powerful interference reduction techniques and more flexible sampling accessories, detection limits in real-word samples improved dramatically for some elements. Figure 2 shows the improvement in lead detection capability (in ppb) of ICP-MS compared the other AS techniques.

It should also be emphasised these are instrument detection limits (IDLs), which are based on simplistic calculations of aqueous blanks carried out by manufacturers and not realistic method detection limit (MDL) into consideration the sample preparation procedure, dilution steps and multiple analytical measurements **(13)**. For that reason, a 10-50 x degradation in IDL is quite common for a real-world method limit of quantitation (LOQ).

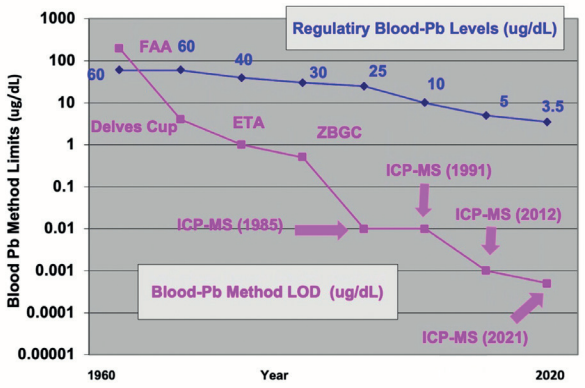

Figure 3: The improvement in real-world detection capability (in µg/dL) offered by AS techniques for blood-lead determinations compared to the trend in blood-lead levels set by the CDC

Figure 3 is a combination of figures 1 and 2 and shows the improvement in detection capability (in µg/dL) offered by AS techniques for blood-lead determinations compared to the trend in blood-lead levels set by the CDC. Both plots are shown in log scale, so they can be viewed on the same graph.

Final Thoughts

There is no question that developments in atomic spectroscopy have helped us better understand the toxicity effects of lead over the past 50 years. As Figure 3 clearly demonstrates, there is a direct correlation between the lowering of the CDC blood-lead levels and the detection capability of ICP-MS. It has allowed us to lower the clinical practice threshold level of 60 µL/dL in the mid-1960s to the current blood lead reference value (BLRV) of 3.5 µL/dL. More importantly, it has helped to reduce elevated blood levels of children in the U. S., from 26 % in the early-mid-1990s to less than 2.5% today, as well as allowing us to get a much better understanding of the environmental sources of lead contamination. However, such is the power and versatility of modern atomic spectroscopy instrumentation and its accessories, that it has also dramatically improved our understanding of other trace metal-related human diseases. The toxic effects of trivalent/pentavalent arsenic and hexavalent chromium would still be relatively unknown, if it wasn't for the continual improvements in ICP-MS and in particular, its use as a very sensitive detector for trace element speciation studies using chromatographic separation technology. Even though ICP-MS has been successfully applied to many application areas since it was first commercialised in 1983, its use as a biomedical, clinical and toxicological research tool has had a direct impact on the quality of many people's lives.

Further Reading

1. Practical Guide to ICP-MS and Other Atomic Spectroscopy Techniques A Tutorial for Beginners, 4th Edition, R.J. Thomas, CRC Press, Boca Raton, FL, ISBN – 978-1-032-03502-4

2. Preventing Lead Poisoning in Young Children, Chapter 2: Absorption of Lead, Centers for Disease Control and Prevention (CDC), 1991, https://www.cdc.gov/nceh/lead/publications/books/plpyc/contents.htm

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