# Application of chemical vapor generation in ICP-MS: A review

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Chemical vapor generation (CVG) is an important sample introduction technique, and is widely used for atomic spectrometry for its enhanced sensitivity and selectivity. In the past 30 years, inductively coupled plasma mass spectrometry (ICP-MS) has become a widely used and the most sensitive instrument for (ultra-)trace element determination and elemental speciation. A review of applications of this state-of-the-art coupling of CVG and ICP-MS is presented. Discussion is focused on its applications for both element determination and speciation, including hydride generation, cold vapor generation, photochemical vapor generation, alkylation, and electrochemical vapor generation. In addition, recent studies undertaken isotope dilution calibration in CVG-ICP-MS for achieving improved accuracy and precision are summarized, and the future perspectives are discussed.

**chemical vapor generation, inductively coupled plasma mass spectrometry, isotope dilution, trace element determination, speciation**

The increasing demand of the highest possible sensitivity and precision, and fast and simultaneous multi-elemental detection capabilities are continuously driving the developments of techniques in analytical chemistry. Among various atomic spectrometry techniques, inductively coupled plasma mass spectrometry (ICP-MS) is, undoubtedly, one of the most powerful analytical techniques for trace element determination [1]. It offers low LODs, wide linear dynamic range, multi-element detection capability, high sample throughput and the ability of isotopic analysis. However, the low sample introduction efficiency associated with classical pneumatic nebulizer and low tolerance to organic solvent of ICP limit its applications. Therefore, many efforts have been devoted to further improve its detection power.

Chemical vapor generation (CVG) is an important sample introduction technique, and is widely used for atomic spectrometry for its enhanced sensitivity and selectivity. Nonvolatile analytes can be transformed to volatile or semi-volatile species through chemical reaction. The generated gaseous analyte compounds can be separated from the sample matrix by a gas-liquid separator and subsequently transferred to the detector i.e. ICP-MS for detection, largely eliminating spectral and non-spectral interferences caused by matrix elements [2,3]. If the analyte is quantitatively transformed into vapor, CVG is able to provide essentially 100% analyte transport efficiency and leads to lower LODs compared to the conventional nebulizer and spray chamber arrangement. Moreover, severe memory effects for elements such as mercury and iodine encountered with the conventional nebulization process of ICP-MS are significantly reduced, which in turn improves the sample throughput and reduces analysis cost. Consequently, various CVG schemes were developed during the last decades.

This review addresses major developments in CVG including hydride generation (HG), cold vapor generation (CV), electrochemical vapor generation (EVG), recent developed photo chemical vapor generation (PVG) and alkylation with a focus on its applications with ICP-MS as powerful analytical tools for trace or ultratrace element determination and speciation. In addition, recent developments in isotope dilution (ID) based CVG-ICP-MS methods are also discussed. Nonetheless, the detailed discussion on mecha-

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nisms of different chemical vapor generation systems is out of the scope of this review. Since Yang [4] has reviewed the state-of-the-art methodologies for high precision and accuracy isotope ratio measurements by multicollector (MC) ICP-MS in 2011, which covers the application of CVG in MC-ICP-MS based techniques, advancements in MC-ICP-MS related techniques for the determination of isotope ratios are not covered in this review.

# 1   Hydride generation

HG using tetrahydroborate (III) (THB) is so far the most widespread and successful CVG technique for the determination of trace and ultratrace elements such as As, Sb, Bi, Se, Te, Ge, Sn and Pb. Recently, the application scope of HG has been significantly expanded to several transition and noble metals [5,6]. However, few applications of the HG-ICP-MS for the determination of those elements have been reported. Condition dependent vapor generation efficiencies and the unstable characteristics of generated volatile species from transition and noble elements may account for their limited applications [6]. Wibetoe group [7] proposed a dual mode sample introduction using a commercial multi-mode sample introduction system for the simultaneous determination of hydride forming and non-hydride forming elements by ICP-MS, as shown in Figure 1. Aerosols formed from the nebulizer and vapor generated from $NaBH_4$ reduction were introduced simultaneously into the plasma (Figure 1). This novel sample introduction method provided significant improvements in sensitivities for As, Bi and Sb, achieving 77-, 33- and 56-fold improvements, respectively, compared to the conventional pneumatic nebulization. There was no significant change in sensitivities for elements such as Cd, Co, Cu, Ni and Zn, probable due to the above mentioned reasons. Over the last a couple of decades,
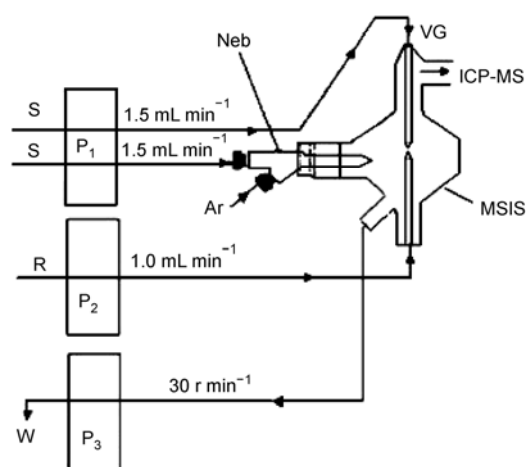


**Figure 1**   Schematic diagram of dual mode sample introduction ICPMS. Reprinted with permission from Ref. [7], Copyright (2006) The Royal Society of Chemistry.

the development of HG-ICP-MS system has focused on the conventional HG forming elements (e.g. As, Bi, Ge, Pb, Se, Sn and Te) for their determination and speciation.

In many cases, the presence of high concentrations of transition metals (e.g. Ni, Co, Cu and Fe) severely suppresses the formation and releasing of the analyte hydrides. As a result, several means have been exploited to overcome interferences arising from these elements in sample matrix, such as the use of various masking reagents or separation of analyte from the matrix by ion exchange prior to HG [8]. However, these methods involve additional sample preparation steps and thus could introduce more uncertainties, affecting the final results. Based on the fact that the HG reaction for analyte is usually faster than that of interfering elements, modified HG devices with very short reaction time and rapid separation of the gaseous products have been successfully developed to minimize the interferences from transition and noble elements. Sturgeon and co-workers [9,10] have made great efforts in this field. In their HG system, an additional inner capillary was inserted in the concentric nebulizer to simultaneously introduce the sample and the reductant, and wherein a spray chamber was used as a gas-liquid separator for the separation of the product, virtually eliminating signal suppression from high transition metals presented in sample matrix [10]. Similarly, a modified Scott spray chamber and cross-flow nebulizer containing very limited reaction zone was developed [11]. By mixing the acidified sample and the reductant solution at the tip of a cross-flow nebulizer, the reaction time was reduced to 60 ms. This viable sample introduction technique was successfully demonstrated for the determination of Se in two biological certified reference materials. Kumar et al. [12] and Long et al. [8] presented overviews of interferences in HG atomic spectrometric techniques. The mechanisms of liquid-phase and gas-phase interferences, and various approaches used to minimize these interferences were discussed in detail. As the gas-liquid separator (GLS) is one of the most important components in the HG system, the development of new GLS configurations is the focus in HG-ICP-MS applications. Double stage GLSs [13] and GLS closed with an electromagnetic pinch valve [14] were proposed to replace the consumable membrane GLS and to reduce the consumption of reagent or waste, respectively.

Toxicity and bioavailability of an element greatly depend on its species rather than its total concentration, for example methylmercury is more toxic than inorganic Hg. Elemental speciation is thus indispensable to evaluate the biological risks and benefits associated with elements. Chromatographic separations using high performance liquid chromatography (HPLC), gas chromatography (GC), capillary electrophoresis (CE) in combination with ICP-MS for detection are currently the most powerful and widely used approaches for elemental speciation. Among these hyphenated techniques, HPLC-ICP-MS dominates the field. Although the chromatographic separation is helpful in remov-

ing the sample matrix related interferences [15], the use of HG as an interface between HPLC and ICP-MS can greatly improve the LODs of element species and reduce organic compounds introduced to ICP. Nonetheless, due to the species dependent HG efficiencies of different elements, analyte species generally need to undergo reduction, oxidation or UV irradiation after elution from chromatography column to achieve high HG efficiencies [16–18]. To enhance sensitivity, Nakazato et al. [17] designed a photo reactor by irradiation with vacuum ultraviolet light at 185 nm instead of the conventional 254 nm for the efficient decomposition of persistent organic arsenicals without any other oxidation reagents, resulting in extremely short decomposition time and high decomposition efficiencies of analyte species compared to the conventional photooxidation procedure. Good detection limits for 10 arsenic species including the persistent organic arsenicals by LC-HG-ICP-MS were in a range of 2.3 to 1.8 ng $L^{-1}$ as As. Chen et al. [19] developed a method using a combination of ion pair, cation exchange, and anion exchange columns for efficient separation and HG ICP-MS detection for the quantitative determination of As(III), monomethylarsonic acid [MMA(V)], dimethylarsinic acid [DMA(V)], As(V), and arsenobetaine (AsB) at sub-microgram per liter levels in human urine samples. Instead of using commercial column, Chandrasekaran et al. [20] utilized an in-house PTFE micro-column loaded with polyaniline for the separation of arsenite and arsenate, and subsequent determination of these species by flow injection HG-ICP-MS within 3 min.

Preconcentration of analyte prior to HG ICP-MS determination can further improve the sensitivity. As reported by Alonso and co-workers [21], a pre-concentration/separation system using tandem columns was integrated with HG-ICP-MS for the determination of Sb(III) and Sb(V) in aqueous environmental samples. In this system, Sb(III) was collected on a [1,5-bis(2-pyridyl)-3-sulfophenyl methylene] thiocarbonohydrazide immobilized aminopropyl-controlled pore glass (PSTH-cpg) column, whereas Sb(V) was collected on the Amberlite resin. The collected species were sequentially eluted by 0.04% thiourea solution in 5% $HNO_3$ and measured by HG-ICP-MS. The method allowed for the simultaneous determination of antimony species in various types of water samples.

GC-ICP-MS is another widely used and powerful technique for elemental speciation. Use of HG in combination with GC-ICP-MS has been reported. However multi-elemental speciation was limited due to the pH dependent derivatization efficiencies of analytes and significantly different optimum conditions for each reaction. To overcome this problem in analysis of non-volatile methylated metal(loid) species by HG, Diaz-Bone et al. [22] developed a semi-automated HG procedure with a gradient pH for the multi-elemental speciation. Within this approach, pH was changed from 7 to 1 whereas $NaBH_4$ solution was continuously introduced, and the determination of methylated element species of Ge, As, Sn Sb, Te and Hg were successfully obtained.

The species-depended HG efficiencies of elements can be an advantage which provides the possibility for the determination of different species using non-chromatographic methods [23]. Based on the different HG efficiencies of arsenic species, Buckley group [24] developed a method for the selective determination of toxic arsenic species in urine samples. Under optimized conditions of 1% $NaBH_4$, 0.2 mol $L^{-1}$ HCl and 0.05 mol $L^{-1}$ L-cysteine, the toxic arsenic species (e.g. As(III) ) were effectively separated from non-toxic species (e.g. AsB), and the resultant volatile species were transferred to ICP-MS for detection. A LOD of 6 ng $L^{-1}$ was obtained by the proposed method. Major applications for CVG-ICP-MS techniques in the literatures are outlined in Table 1.

## 2   Cold vapor generation systems

Cold vapor generation is a traditional approach of CVG systems, which has been used for the determination of mercury and cadmium. THB is normally used as a redundant for the determination of cadmium whereas both THB and $SnCl_2$ are used for mercury measurement. Compared to the strong reduction ability of THB with many elements and their species, $SnCl_2$ is a mild reductant which is only capable of reducing inorganic Hg. $SnCl_2$ is considered as a selective reagent for mercury reduction and widely used for mercury determination. Consequently, $SnCl_2$ based methods suffer less interferences from transition metals than those in THB based methods. Furthermore, no excess hydrogen generated during $SnCl_2$ reduction makes it more compatible with ICP-MS, maintaining stable plasma.

In 2007, Wu et al. [27] published a review article that outlined mercury determination by ICP-MS after cold vapor generation. Very recently, Gao et al. [28] presented major developments since 2008 in mercury determination and speciation analyses by atomic spectrometry, including cold vapor generation ICP-MS technique. In recent years, more attention has been given to the development of methods for Hg speciation, due to the high toxicity and biomagnification of methylmercury. The use of cold vapor generation as an interface between LC and ICP-MS with $NaBH_4$ reduction has been frequently reported to achieve higher sensitivity. In the case of using $SnCl_2$, a weak reductant, post-column sample preparation to decompose organic mercury species is needed. For example, UV/nano-$TiO_2$ system was successfully implemented to decompose organic mercury after column separation, facilitating the vaporization of $MeHg^+$ in $SnCl_2$ based VG techniques [29]. Selective reduction of inorganic mercury by $SnCl_2$ or by low concentration of $NaBH_4$ [30] in combination with selective absorption of mercury species by solid phase extraction (SPME) [31] were proved to be feasible alternative approaches for Hg

**Table 1**   Applications of HG-ICP-MS system for element determination and speciation analyses

| Analyte | Method description | Sample matrix | Limit of detection | Ref. |
|---|---|---|---|---|
| Pb | Liquid-gas separation by a double-stage GLSs with HG-ICP-MS detection | Poplar leaves, human hair and copper ore | 0.002 µg L$^{-1}$ | [13] |
| As, Se, Hg | Ion exchange(IE) CVG-ICP-MS | Biological and geological materials | As: 0.0021 µg L$^{-1}$<br>Se: 0.0022 µg L$^{-1}$<br>Hg: 0.0007 µg L$^{-1}$ | [15] |
| As, Hg, Sb, Sn | Slurry introduction with FI CV-ICP-MS determination | Sediment and coals | As: 20 ng g$^{-1}$<br>Hg: 60 ng g$^{-1}$<br>Sb: 200 ng g$^{-1}$<br>Sn: 90 ng g$^{-1}$ | [25] |
| Se(IV), Se(VI), SeCN | LC-HG-ICP-DRC-MS | Sea water and rain water | Se(IV): 0.15 ng Se L$^{-1}$<br>Se(VI): 0.27 ng Se L$^{-1}$<br>SeCN: 0.19 ng Se L$^{-1}$ | [16] |
| As, Bi, Cd, Co, Cu, Ni, Pb, Sb, and Zn | Dual mode sample introduction with ICP MS detection | Citrus leaves, pine needles, water, bush branches and leaves, and human hair | As: 7 pg mL$^{-1}$<br>Bi: 15 pg mL$^{-1}$<br>Sb: 10 pg mL$^{-1}$ | [7] |
| Ge, As, Se | Using L-cysteine as masking reagent with FI-HG-DRC-ICP MS detection | Nickel-based alloys | Ge: 0.001 ng mL$^{-1}$<br>As: 0.001 ng mL$^{-1}$<br>Se: 0.02 ng mL$^{-1}$ | [2] |
| Selenium metabolites | HPLC-HG-ICPMS | Urine | 0.003 µg Se L$^{-1}$ | [26] |
| Total toxic arsenic species | HG-ICP MS | Human urine | 6 ng L$^{-1}$ | [24] |
| Sb(III), Sb(V) | SPME-HG-ICP MS | Water samples | Sb(III): 0.013 µg L$^{-1}$<br>Sb(V): 0.021 µg L$^{-1}$ | [21] |
| Methylated Ge-, As-, Sn-, Sb-, Te- and Hg-species | PH-gradient-HG-GC-ICP MS | Soils, sediments, organic waste and compost samples | 0.02–0.3 ng kg$^{-1}$ | [22] |
| DMA(V), MMA(V), As(V), AsB | Complementary chromatography separation with HG -ICPMS determination | Human urine | As(III): 0.197 µg L$^{-1}$<br>DMA(V): 0.116 µg L$^{-1}$<br>MMA(V): 0.161 µg L$^{-1}$<br>As(V): 0.092 µg L$^{-1}$ | [19] |
| As(III), As(V) | Microcolumn separation with FI-HG-ICP MS detection | Groundwater | As(III): 0.05 µg L$^{-1}$<br>As(V): 0.09 µg L$^{-1}$ | [20] |
| Selenium species | HPLC-UV-HG-ICPMS | Water samples | 2–8 ng L$^{-1}$ | [18] |

speciation as a non-chromatographic scheme. In addition, the development of new sample preparation techniques [32,33] (e.g. microwave assisted extraction and microwave assisted combustion) has advanced mercury speciation.

Although cold vapor generation with AAS and AFS have become mature techniques and have been widely used for the determination of cadmium in various sample matrices, application of cold vapor generation with ICP-MS has rarely been reported. In 2005, Sanz-Medel and co-workers [34] took advantage of volatile species generation and developed an alternative CE-ICP-MS interface for the speciation of Cd-metallothioneins (MTs) in rabbit liver. The analyte transport efficiency was significantly enhanced and the detection limits for Cd-MTs were almost one order of magnitude better than those obtained from a conventional nebulizer-based interface. Recently, Arslan and co-workers [35] reported an on-line cold vapor method in the presence of $K_3Cr(CN)_6$ for Cd determination. Volatile species of Cd were generated by on-line mixing of acidic $K_3Cr(CN)_6$ solution with TBH. The presence of $K_3Cr(CN)_6$ in the cold vapor system led to a 15-fold increase of sensitivity. It was

speculated that reactive intermediates formed during the interaction of $[Cr(CN)_6]^{3-}$ and TBH increased the yield of volatile Cd species. Table 2 summarizes reported cold vapor generation ICP-MS techniques for trace element determination and speciation.

## 3   Photochemical vapor generation systems

Photochemical vapor generation (PVG) which utilizes free radicals generated by photo-redox reactions in the presence of low molecular of organic compound as reductant is a powerful alternative sample introduction to the conventional cold vapor generation. Guo et al. [41] first introduced PVG in 2003, and applications of this new sample introduction quickly expanded [42,43]. A wide range of elements can be photochemically derivatized to volatile species, such as Hg [44,45], Ni [46,47], Se [43], Co [48,49], Fe [50], and I [51,52]. A typical schematic of PVG system is shown in Figure 2. In addition, PVG is a simple and environmental friendly sample introduction with high efficient and fewer

**Table 2**    Applications of cold vapor generation with ICP-MS for element determination and speciation

| Analyte | Reductant | Sample matrix | Sample preparation | Method | Limit of detection | Ref. |
|---|---|---|---|---|---|---|
| $Hg^{2+}$, $MeHg^+$, $EtHg^+$ | $NaBH_4$ | Fish | Microwave-assisted extraction | LC-CV-ICP-MS | $Hg^{2+}$: 0.06 ng mL$^{-1}$ MeHg$^+$: 0.05 ng mL$^{-1}$ EtHg$^+$: 0.09 ng mL$^{-1}$ | [33] |
| $Hg^{2+}$, $MeHg^+$, $EtHg^+$ | $NaBH_4$ | Water samples | | LC-CV-ICP-MS | $Hg^{2+}$: 0.11 ng mL$^{-1}$ MeHg$^+$: 0.03 ng mL$^{-1}$ EtHg$^+$: 0.04 ng mL$^{-1}$ | [36] |
| $Hg^{2+}$, $MeHg^+$ | $NaBH_4$ | Soil | Microwave-assisted extraction | LC-CV-ICP-MS | $Hg^{2+}$: 35 pg mL$^{-1}$ MeHg$^+$: 73 pg mL$^{-1}$ | [37] |
| $Hg^{2+}$, $MeHg^+$, $EtHg^+$ | $NaBH_4$ | Rice flour, wheat flour, and fish | Microwave-assisted extraction | LC-CV-ICP-MS | $Hg^{2+}$: 0.004 ng g$^{-1}$ MeHg$^+$: 0.003 ng g$^{-1}$ EtHg$^+$: 0.006 ng g$^{-1}$ | [38] |
| $Hg^{2+}$, $MeHg^+$ | $NaBH_4$ | Water and fish tissues | Ultrasound-assisted extraction | SPME-CV-ICP-MS | $Hg^{2+}$: 2.52 pg MeHg$^+$: 3.24 pg | [31] |
| $Hg^{2+}$, $MeHg^+$ | $SnCl_2$ | Urine | | LC-UV/nano-TiO$_2$ assisted CV-ICP-MS | $Hg^{2+}$: 0.1 ng mL$^{-1}$ MeHg$^+$: 0.03 ng mL$^{-1}$ | [29] |
| $Hg^{2+}$, Total Hg | $NaBH_4$ | Fish otoliths | Acid extraction | CV-ICP-MS | $Hg^{2+}$: 4.2 ng L$^{-1}$ Total: 6.4 ng L$^{-1}$ | [30] |
| Hg | $NaBH_4$ | Coal fly ash and sediment | Microwave assisted extraction using polypropylene tubes | FI-CV-ICP-MS | 0.9 ng g$^{-1}$ | [39] |
| Total Hg | $NaBH_4$ | Soil | Microwave induced combustion | CV-ICP-MS | 0.006 µg g$^{-1}$ | [40] |
| Total Hg | $SnCl_2$ | Humic-rich natural water | Oxidation with BrCl | CV-ICP-MS | 0.7 ng L$^{-1}$ | [32] |
| Cd | $NaBH_4$ | Seawater, bone ash, dogfish liver and mussel tissue | Microwave-assisted acid digestion | CV-ICP-MS | 5.2 ng L$^{-1}$ | [35] |
| Cd-metallothioneins (MTs) | $NaBH_4$ | Rabbit liver | Acid extraction | CE-CV-ICP-MS | Cd-MT$_1$: 193 ng mL$^{-1}$ Cd-MT$_2$: 223 ng mL$^{-1}$ | [34] |
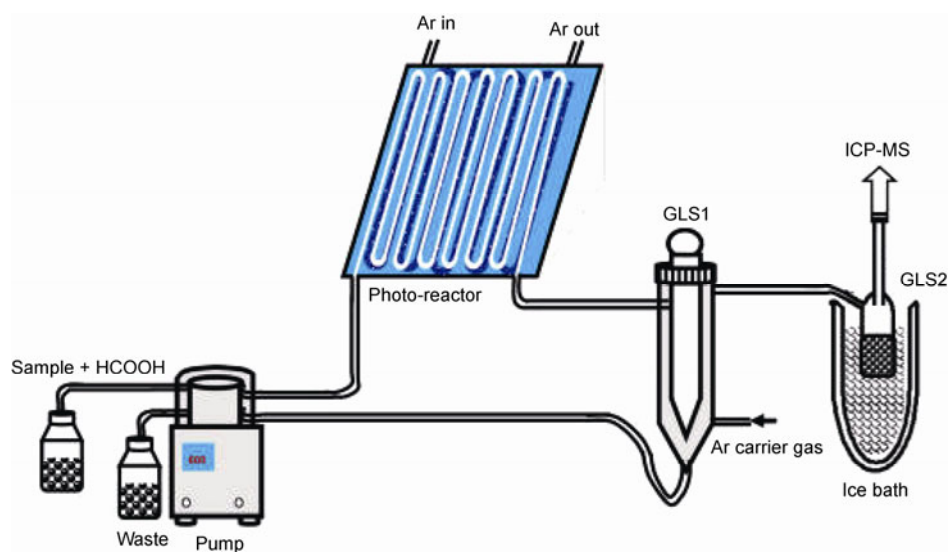


**Figure 2**    (Color online) Schematic of online UV-PVG-ICP-MS system. Reprinted with permission from Ref. [53], Copyright (2008) American Chemical Society.

interferences from transition metals.

Taking advantages of PVG, Sturgeon et al. [54] established an integrated spray chamber/UV photolysis unit to enhance sample introduction efficiency of ICP-MS. In their spray-chamber/UV photolysis unit setup, a 6 W mercury pen lamp was inserted in the cyclonic spray chamber to efficiently generate volatile species of analytes. Enhancement factors of 2- to 40-fold were obtained for Ag, As, Se, Sb, Hg, I, Bi, Pb and Sn. This modified system has been successfully applied to the determination of iodine in sediments and biological materials. Recently, a versatile thin-film reactor in order to achieve better performance of PVG was developed by the same group [55]. The device utilized a vertical central quartz rod which was inside a concentric

quartz tube served both as a generator and a gas liquid separator. The outside of concentric quartz tube was surrounded by a 20 W low pressure mercury discharge lamp. Sample solution was pumped onto the rod to form a thin liquid film and carrier gas was passed through the concentric quartz tube to transport the photo-generated volatile species to the detector. This new system provided several advantages over the conventional reactor such as more efficient UV penetration and photo-generation of volatile species, and greatly improved the gas-liquid separation due to the large surface-to-volume ratio. However, its application with use of ICP-MS for trace metal determination needs to be explored further.

Recently, the use of nanosemiconductor material such as $TiO_2$ has demonstrated to be beneficial for photocatalytic conversion of element species into volatile species [56]. Sun et al. [57] developed an UV/nano-$TiO_2$ vapor generation device inserted between a chromatographic column and an ICP-MS for the speciation of inorganic selenium species. Both Se(IV) and Se(VI) can be efficiently converted on-line into volatile Se species in this pohtocatalysis reduction device, avoiding the problem of inefficient hybridization of Se(VI) in HG for the direct derivatization of both Se species. Later, Zheng et al. [43] proposed a temperature- and nano-$TiO_2$-enchanced photo-CVG system for Se(VI) and Se(IV) determination. At low temperature, Se(IV) can be selectively reduced and determined. The use of boiling water bath with nano-$TiO_2$ catalyst facilitated the generation of $H_2Se$ from Se(VI), so that both Se(IV) and Se(VI) were photochemcially converted to selenium volatile species. In 2012, Wang and co-workers [58] further developed nano-semiconductor-based PVG efficient sample introduction techniques for atomic spectrometric detector using nano Ag-$TiO_2$ and nano $ZrO_2$. In addition to Se(IV), the nano-semiconductor-based PVG system allowed direct VG of Se(VI) and organic Se species such as selenomethione (SeMet) and selenocystin as result of high $e^-$ density from nano-Ag-$TiO_2$ and the high negative potential conduction band $e^-$ of $ZrO_2$, respectively. The detection limits of Se(IV), Se(VI), selenocystine and selenomethionine obtained were 10, 14, 18, and 8 pg $mL^{-1}$ for UV-Ag-$TiO_2$-HCOOH and 6, 7, 10, and 5 pg $mL^{-1}$ for UV/$ZrO_2$-HCOOH with ICP-MS detection, respectively. This novel technique was applied to determine total Se in a selenium enriched yeast sample and used as interfaces between HPLC and AFS or ICP-MS for selenium speciation.

# 4   Electrochemical hydride generation systems

Electrochemical hydride generation system (ECG) benefits from cost/labor effective. However, few studies were focused on its analytical applications with ICP detection. There is only one publication in this research field since 2002. The limited ECG forming elements as well as the poor stability of the cathode may account for its slow development. In 2003, Bings et al. [59] developed a low volume electrolysis cell for the determination of six hydride forming elements by ICP-TOF-MS. Through investigation, it was found that the optimum electrolysis current was 0.7 A and the optimum argon carrier gas flow rate was 0.91 L $min^{-1}$. The compromised operation parameters of the electrolysis were 1.4 and 3 mL $min^{-1}$ for the anolyte and catholyte flow rates, respectively. Under the optimum conditions, the absolute detection limits were in a range of 10–160 pg for As, Bi, Ge, Hg, and Sb, and 1.1 ng for Se with use of 200 μL sample solution.

# 5   Alkylation

Alkylation is mainly used to convert ionic and organometallic compounds to volatile or thermally stable species by means of aqueous derivatization reagents. With increasing interest in trace metal speciation, considerable efforts have been devoted to this area. Alkylation has become a common practice in analytical chemistry, especially in GC-based atomic techniques. Derivatization of organometallic compounds by alkylation has greatly extended its applications in GC-related atomic spectrometry techniques for elemental speciation. The most commonly used alkylating reagents are $NaBEt_4$, $NaBPr_4$ and $NaBPh_4$, which can be selected depending on the volatility of analyte. $NaBEt_4$ is the most widely used for the derivatization of organometallic species, but it suffers a major disadvantage of inability to distinguish EtHg and inorganic Hg (similarly, the problem of inorganic Pb and $Et_4Pb$). $NaBPh_4$ and $NaBPr_4$ are good alternatives for those metal species speciation. Alternatively, chloroformate [60] and cyanogen bromide [61] have been used as devertization reagents for the determination of seleno amino acids. Moreover, synthesized $BrMgEt_4B$ was used for in situ ethylation of organolead, organotin and organo-mercury to replace the commercially available high cost alkylborates [62]. Recently, Yan et al. [63] reported to use butyl magnesium bromide as a derivatization reagent to avoid the loss of species specific information of analytes and employed synthesized $Pr_3PbCl$ as an alternative internal standard to improve the analytical precision and accuracy for the simultaneous determination of different Pb and Hg species.

After derivatization, preconcentration/extraction by purge and trap extraction, solid phase micro extraction (SPME) [64], headspace SPME [65] or solvent extraction [61,66] can be performed to enhance the analytical sensitivity. Liquid phase micro-extraction (LPME) has also found its application in derivatization/extraction procedure. Head space single drop micro-extraction (HS-SDME) combined with GC-ICP-MS detection was proposed for the analysis of butyltin compounds after derivatization with $NaBEt_4$ and $NaBH_4$ [60]. Derivatization with $NaBEt_4$ has proved to be

more sensitive and robust than that with NaBH$_4$, leading to better LODs for butyltin compounds. Later, hollow fiber LPME-GC-ICP-MS method was developed and successfully applied for the separation and determination of seleno amino acids in biological samples [67].

Sample preparation is a key step for the accurate determination of element species in different sample matrices. Microwave assisted leaching [65] and alkaline dissolution methods [67] are two commonly used techniques, because of their high extraction efficiencies and high sample throughput. Rodrigues et al. [68] established a fast sample preparation procedure for the determination of mercury species in blood samples using closed-vessel microwave assisted extraction with TMAH. The sample preparation procedure can be finished in 10 minutes. In addition, enzymatic hydrolysis, a gentle digestion procedure, was reported for the determination of MeHg$^+$ and EtHg$^+$ in foods with GC-ICP-MS [69].

High sample throughput analysis is always desired and has become a main research direction in analytical chemistry. ICP-MS is well known for its capability in simultaneous multi-elemental determination. The combination of ICP-MS with chromatographic techniques (especially with GC separation) has been explored to achieve high throughput elemental speciation. Coupling of multicapillary GC (MCGC)-ICP-TOF-MS with SPME, a simple, rapid and accurate method was developed for the simultaneous speciation of 10 organometallic compounds of mercury (including inorganic mercury), tin and lead [70]. Using MCGC separation, a total chromatographic run time was reduced below 200 s. In addition, different SPME fibers were compared for extraction efficiencies, a 65 mm polydimethylsiloxane/divinylbenzene fiber was found to offer the best overall extraction efficiency. Detection limits below 1 pg g$^{-1}$ levels were obtained for organic Pb and Sn. A slightly higher detection limits were obtained for methylmercury (MeHg, 1.3 pg g$^{-1}$) and inorganic mercury (Hg, 2.0 pg g$^{-1}$).

As an essential component of GC-ICP-MS system, the interface is vital to have effective coupling of GC to ICP-MS in order to prevent condensation of the analyte of interest. Typically, a heated transfer line is required to maintain the temperature required for transferring analyte from GC to ICP, whereas all cold spots along the line need to be eliminated. Wuilloud et al. [71] and Bouyssiere et al. [72] presented comprehensive reviews on the developments of GC-ICP-MS, especially focused on comparison of different GC-ICP-MS interface designs. Popp et al. [73] described a commercial interface of GC-ICP-MS in their review article. Currently, several commercial transfer lines are available for the coupling of GC to ICP-MS. In addition to commercial transfer lines, Yan et al. [63] recently designed an alternative thermodiffusion interface using a copper tube for GC-ICP-MS. The copper tube was connected to the column oven and used the thermodiffusion effect to have same temperature as that in the oven, and wrapped by an asbestos attemperator tube (see Figure 3). The Ar gas used was preheated and introduced to make up the nebulizer gas at an angle of 45°, eliminating any possible condensation of analyte in the interface.

Furthermore, one of the most important advances of alkylation-based GC-ICP-MS system is the application of isotopic dilution analysis (IDA) in GC-ICP-MS for the accurate determination of element species, which will be discussed in Section 7 "Isotope dilution".

## 6    Other chemical vapor generation systems

Volatile metal-chelate generation has experienced extensive developments in trace metal measurements since the late 1950's to the early 1980's. Several reagents including dithiocarbamate, dithiophosphates, acetylacetonates, trifluoroacetylacetonates (TFA) and hexafluoroacetylacetonate were studied and used to generate metal chelates for their determination by ICP-MS/ICP-OES, or for metal speciation using GC. In 2005, Yang et al. [74] successfully utilized SPME for the extraction of Cr after reduction with SO$_2$-sautrated water and subsequent derivatization with TFA for the determination of total Cr in water by ID GC-SF-ICP-MS. The combination of chelate generation and SPME-GC-SF-ICP-MS detection can effectively eliminate spectroscopic interferences and lead to accurate results. For As, Ge, Sb, Se and Sn determination, halide generation is an alternative to HG. Sturgeon and co-workers [75] compared chloride- and hydride-generation for the quantitation of Ge by HG SPME-ICP-TOF-MS detection. In addition to high selectivity, chloride generation provided two fold enhancement of sensitivity compared to HG.

dos Santos et al. [76] found that Hg$^{2+}$ can be automatically reduced to mercury vapor at high pH solution without any reducing reagent. Inspired by this finding, Wu et al. [77] proposed a method for mercury speciation in biological sample by ICP-MS, based on reduction of inorganic mercury in TMAH solution, a typical tissue solubilizer. This approach allowed the inorganic mercury in biological samples to be selectively determined. For the detection of total mercury, microwave-assisted oxidation with H$_2$O$_2$ was carried out, followed by the TMAH reduction and ICP-MS determination. As a result, only one calibration curve using inorganic mercury aqueous standards was needed for both procedures. However, the mechanism of reduction mercury in alkaline solution is not well understood and needs to be further investigated.

## 7    Isotope dilution

Isotope dilution analysis (IDA) is a method for quantification by measuring the modified isotope ratio in the sample spiked with isotopically enriched spike. The application of
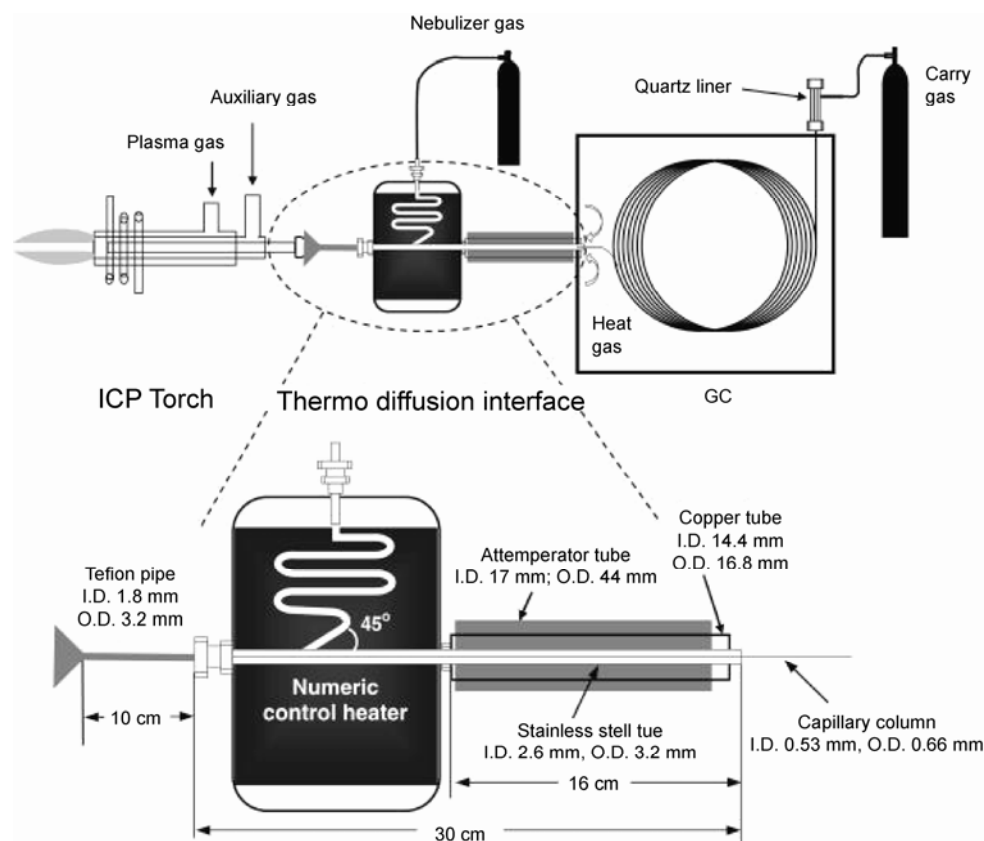
**Figure 3** Schematic diagram of the thermodiffusion interface (TDI). Reprinted with permission from Ref. [63], Copyright (2008) American Chemical Society.

isotope dilution in CVG-ICP-MS techniques provides high accuracy and precision determination of trace/ultra-trace elements. Once isotopic equilibrium between the analyte and the spike is achieved, IDA can account for any subsequent analyte loss during sample preparation/preconentration and determination [78,79]. Initially, enriched isotope was used as an ideal internal standard for the determination of elements like Cd [80], Te [81] and Tl [82] after vapor generation by ICP-MS. In 2002, Long et al. [83] proposed an ID-CV-ICP-MS based method for high accuracy determination of mercury in coals. Using compromised vapor generation conditions for different elements, simultaneous determination of several vapor forming elements were realized by HG/CV-ID-ICP-MS [78]. Recently, Yang and co-workers [53] first reported a PVG-ID-ICP-MS system for the determination of a few elements. The analytical performance for the determination of Ni, Se and Fe using this approach was investigated in detail. Compared to the pneumatic sample introduction, significant enhancements in sensitivities ranging from 27- to 355-fold were realized, and the isobaric interferences for these elements were minimized. To further improve the precision of CVG ID-ICP-MS measurement, Yang et al. [84] employed ICP-TOF-MS and ICP-SF-MS for obtaining isotope ratios instead of typical ICP-QMS, and compared both instruments for mercury determination. It was found that the use of ICP-TOF-MS de-

tection offered higher precision and better accuracy for the quantization of mercury in water samples.

Apart from measurements of total elements, the application of ID in elemental speciation plays an important role in CVG-ICP-MS. Two different spiking modes, including species-specific (SS) and species-unspecific spiking (SU) are frequently employed. SSID analysis requires the isotopically labeled spike to be in a same form as to the analyte in sample matrix. Thus, SSIDA is regarded as a primary method for highly accurate and precise speciation analysis. The latter is exclusively limited to the correction of errors during the detection. Since the vapor generation efficiency greatly depends on element species, studies are seldom focused on SUIDA-based CVG-ICP-MS for speciation. Significant improvements in GC-ICP-MS techniques have been represented by the implementation of SSIDA. Yang et al. [85] took advantage of SSIDA in combination with SPME-GC-ICP-MS for the determination of tributyltin (TBT) in sediment with improved precision. An 18-fold improvement in the precision of TBT concentration measured by ID was observed, clearly demonstrated its superiority in providing more accurate and precise results as compared to the standard addition calibration. Since the degradation or interconversion of analyte species during the sample preparation cannot be worked out by single spike SSIDA, multiple spike SSIDA approach was developed. Alonso and co-workers

[86] described a methodology for the determination of butyltin compounds based on a triple spikes SSID. Mathematical equations were derived to correct all possible degradation/interconversion of analytes during sample pre-treatment. Accurate determination of MBT, DBT and TBT concentrations and six degradation/interconversion factors were obtained with this approach. Similarly, a triple spike IDA method was successfully applied for the monitoring of degradation and solubilisation of butyltin compounds during *in vitro* gastrointestinal digestion [87]. Despite the advantages offered by the multiple spike isotope dilution analysis (MSIDA), the mathematical complicity has limited its acceptance for element speciation. Nevertheless, MISDA is regarded as a powerful approach for the evaluation of sample preparation methods and offers great advantage in establishing robust sample preparation techniques. Major applications for ID-CVG-ICP-MS techniques in the literatures are outlined in Table 3.

## 8 Summary and future trend

In recent years, many efforts have been devoted in the development of high sensitivity and accuracy CVG-ICP-MS based techniques for trace/ultratrace element determination and elemental speciation. Evidently, HG and alkylation are the most frequently used CVG methods in CVG-ICP-MS applications. Cold vapor generation has played a very important part for mercury determination and speciation. The development of PVG has offered a new avenue for the determination of many transition and noble metals. The application of IDA in GVG-ICP-MS system has permitted the determination of trace/ultratrace elements and elemental speciation with high accuracy and precision. In addition, IDA eliminates the effects of possible analyte loss during sample preparation/preconcentration and thus making CVG more versatile.

    It is hoped that the mechanism study of CVG will

**Table 3** Applications of ID-CVG-ICP-MS system for element determination and speciation

| Analytes | Sample preparation | Sample matrix | Preconcentration | CVG | Method | Limit of detection | Ref. |
|---|---|---|---|---|---|---|---|
| Total Hg | Closed digestion in a carius tube | Coal | | CV | ID-ICP-MS | 40 pg g$^{-1}$ | [83] |
| Tributyltin | Microwave assisted extraction | Sediment | HS-SPME | Ethylation | SSID-GC-ICP-MS | 0.09 ng g$^{-1}$ | [85] |
| Butyltin compounds | Solvent extraction | Sediment | | Ethylation | SSID-GC-ICP-MS | NA$^{a)}$ | [88] |
| Hg$^{2+}$ | | Bottled water | | CV | ID-ICP-MS | 0.1 ng L$^{-1}$ | [89] |
| MMeHg | Alkaline dissolution | Fish tissue | HP-SPME | Propoxylation | SSID-GC-ICP-MS | 2.1 ng g$^{-1}$ | [90] |
| MBT, DBT, TBT | Microwave assisted extraction | Mussel Tissue | Solvent extraction | Ethylation | MID-GC-ICP-MS | NA$^{a)}$ | [91] |
| Hg$^{2+}$, MeHg$^+$ | Alkaline dissolution | Fish tissue and zooplankton | Solvent extraction | Ehtylation | SSID-GC-ICP-MS | Hg$^{2+}$: 2.8 ng g$^{-1}$ MeHg$^+$: 4.6 ng g$^{-1}$ | [92] |
| Me$_3$Pb$^+$ | Alkaline dissolution | Biological reference materials and sediment | | Ehtylation | SSID-GC-ICP-MS | 0.09 ng g$^{-1}$ | [93] |
| Tutyltin | Microwave-assisted extraction | Sediment | Solvent extraction | Ehtylation | SSID-GC-ICP-MS | NA | [94] |
| Cd, Hg, Pb, Se | Slurry sampling | Sediment | ETV trapping | HG/CV | ID-ICP-MS | Cd: 0.15 μg g$^{-1}$ Hg: 0.09 μg g$^{-1}$ Pb: 6.0 μg g$^{-1}$ Se: 0.03 μg g$^{-1}$ | [95] |
| Total Hg | | Water samples | Gold trapping | CV | ID-ICP-TOF-MS | Direct CV: 0.024 pg g$^{-1}$ Trapping: 0.15 pg g$^{-1}$ | [84] |
| As | Slurry sampling | Vegetable oils | | HG/CV | ID-ICP-MS | As: 0.01 ng g$^{-1}$ | [96] |
| Cd, Hg | | | | | | Cd: 0.04 ng g$^{-1}$ Hg: 0.04 ng g$^{-1}$ | |
| Hg$^{2+}$, MeHg$^+$ | Alkaline dissolution with TMAH | Marine samples | | CV | ID-ICP-MS | 0.018 ng g$^{-1}$ | [97] |
| As, Cd, Hg | Slurry sampling | Cereals | | HG/CV | ID-ICP-MS | As: 0.1 ng g$^{-1}$ Cd: 0.16 ng g$^{-1}$ Hg: 0.07 ng g$^{-1}$ | [79] |
| Se, Te | Acid digestion | Geological samples | | HG | ID-ICP-MS | Se: 0.01 ng g$^{-1}$ Te: 0.003 ng g$^{-1}$ | [98] |
| Ni, Fe, Se | Microwave-assisted digestion | Fish tissue | | PVG | ID-ICP-MS | Ni: 0.18 ng g$^{-1}$ Fe: 1.0 ng g$^{-1}$ Se: 1.7 ng g$^{-1}$ | [53] |

a) Did not report in the paper.

improve our understanding to achieve better CVG efficiencies and the stability of generated volatile species. PVG and other new energy assisted CVG techniques, such as plasma-induced CVG [99], microwave-CVG [100] and ultrasound-CVG [101], in combination with ICP-MS detection are promising areas for further exploration. Instead of using single sample introduction, simultaneous introduction of analytes with integrated units of HG and PN or PVG/PN opens doors for multi-element determination. The design of versatile and multi-functional units, integrating advantages of different CVG systems, will advance applications of CVG-ICP-MS in the future.

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