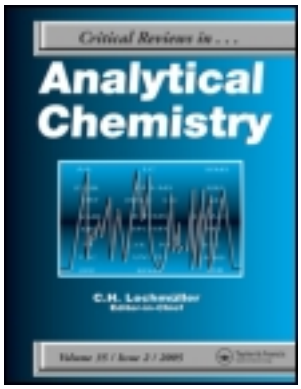

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Methods for the Determination of Platinum Group Elements in Environmental and Biological Materials: A Review

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Methods for the Determination of Platinum Group Elements in Environmental and Biological Materials: A Review

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Automobile catalysts are major anthropogenic sources of ultra-traces of platinum group elements (PGEs) in the environment. Nanoparticles of platinum, palladium, and rhodium, the active components of autocatalysts, are being spread into the environment during vehicle operation. Bioaccumulation of the metals can lead to their elevated levels in living organisms. The evaluation of the health risk from PGEs requires the investigation of a large variety of environmental and biological materials for their content. Plants, airborne particulate matters, soils, and sediments are most often examined for such purposes. The introduction of platinum and ruthenium complexes as anticancer agents into chemotherapy has stimulated growing interest in their determination in clinical materials (physiological fluids and tissues). Identification and determination of drug species formed under physiological conditions are fundamental for recognition of the mechanism of their biological activity. Analytical procedures applicable to the determination of PGEs in various environmental and clinical samples are reviewed in this article.
Supplemental materials are available for this article. Go to the publisher's online edition of **Critical Reviews in Analytical Chemistry** ***to view the free supplemental file.***

Keywords Platinum group elements, environmental samples, clinical analysis, metallomics, sample preparation, instrumental techniques, speciation analysis

INTRODUCTION

Interest in the examination of a large variety of environmental and biological materials for the content of platinum group elements (PGEs) emerged in the last decades of the twentieth century as a consequence of two events: (1) the introduction (1975 (USA), 1976 (Japan), and 1986 (Europe)) of the metals as the components of automobile catalysts for cleaning exhaust gases and (2) the introduction (1978) of cisplatin into worldwide chemotherapy as an effective anticancer agent. These applications were found to be anthropogenic sources of ultra-traces of PGEs in the environment due to thermal and mechanical abrasion of the catalysts during vehicle operation (Zereini and Alt, 2000, 2006; Ravindra et al., 2004; Moldovan, 2007; Dubiella-Jackowska et al., 2009) and a release of pharmaceuticals used from urban and hospital effluents (Kümmerer et al., 1999). Ultra-trace amounts of PGEs can also occur in the environment as a result of their wide industrial (chemical, electrical, glass, and jewellery) applications (Johnson Matthey, 2010). The amounts of the metals emitted from autocatalysts substantially exceed those released from the other sources. In 2001 the annual Pt-emission from automobile catalytic converters into the environment was estimated as 0.5–1.4 ton year^{-1} (Barbante et al., 2001). The correlation of mutual metal ratios in various environmental compartments and some convertor units used in the 1990s was observed (Ravindra et al., 2004). Currently, such identification may be difficult owing to different types of autocatalysts, with various mutual PGE ratios, used.

The assessment of the toxicity of environmental PGEs for living organisms has become important owing to earlier knowledge of the sensitizing and allergenic effects of the metals on employees exposed to them during catalyst production and recycling (Ravindra et al., 2004; Gebel, 2000; Merget and Rosner, 2001; Melber et al., 2002; Kielhorn et al. 2002). Occupational asthma and dermatitis were observed under chronic exposure to soluble platinum compounds, in particular to some halogenated salts. Allergic contact dermatitis from palladium and mutagenic and carcinogenic potential of rhodium halogenated compounds were also reported. Extremely low (ng g^{-1}, pg g^{-1}, and fg g^{-1}) concentrations of PGEs occurring in the environment do not exhibit direct hazard to living organisms. The metals are emitted

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from the catalysts predominantly in metallic, biologically inert forms. Some amounts of easily soluble metal oxides and chlorides, being the products of the interaction of the metals with air oxygen under high temperature in engines and with fuel additives, provide more mobile metal fractions. Soluble fractions of PGEs in the exhaust gases were found to be less than 10% of the total amount emitted from fresh catalysts with a tendency to increase, in particular for Pd and Rh, with catalyst aging (Ravindra et al., 2004; Merget and Rosner, 2001; Palacios et al., 2000; Moldovan et al., 2002). Transformation of metallic forms of the elements into soluble forms under the action of various agents occurring in the environment can result in the generation of biologically available species (Ek et al., 2004). The soluble platinum in airborne and tunnel dusts examined varied between 30% and 43% and 2.5% and 6.9% of its total amount, respectively (Alt et al., 1993). Bioavailability of the metals can lead to their bioaccumulation in various environmental compartments. Reliable evaluation of the content of the metals in various materials, as well as transformation routes into bioavailable species, became essential for risk assessment. Plants, airborne particulate matters, soils, and sediments are most often examined for the content of PGEs due to confirmed tendency for their bioaccumulation.

An uptake of the metals by plants is of special interest because it creates one of the main links between environmental deposition of the metals, their bioavailability, and the possibility of their entering the food chain. Roadside grass and vegetation samples are often examined for the assessment of the bioavailability of automotive-emitted PGEs. Substantially higher content of the metals in roadside grass than in that from rural areas was confirmed. Tree bark from areas exposed to traffic is also utilized as a biotest reflecting PGE emission. The accumulation tendency of the metals is also examined by growing plants under laboratory conditions with a realistic metal supplier, e.g., by cultivation on soil spiked with road dust or exposed to soluble metal compounds, e.g., $[Pt(NH_3)_4](NO_3)_2$.

Platinum metals are emitted from vehicle catalysts mostly (Pt $>$ 95%, Pd $>$ 85%, and Rh $>$ 90%) as nanocrystaline particles attached to the Al_2O_3 support (Colombo et al., 2008a). Once dispersed in the atmosphere they can be deposited on solid air-suspended matter, transported for long distances, and gradually removed by wet and dry deposition as road dust, in aquatic environments, and on plants, soils, and sediments. The occurrence of fine dispersed particles, in particular, easily bioavailable nanometer particles, generates problems with their inhalation and entering the respiratory tract (lung, trachea). There are reports of 16% and up to 30% retention of platinum in the lungs of rats after 1 and 90 days, respectively, due to inhalation of model aluminium oxide particles ($\leq$5 μm. loaded with platinum particles $\geq$4 nm) (Artelt et al., 1998). High percentages of bioavailable metals, up to 88% (Colombo et al., 2008a) and 15.7–16.7% Pt and 63.6–67.5% Rh (Colombo et al., 2008a), from road dusts were observed using extraction tests simulating physiological conditions in the human digestive tract and lung fluids, respectively. Nanoparticles of PGEs deposited on plants and vegetables can be a direct source of the metals for the food chain.

Significantly elevated PGE contents in road-near soils and sediments were reported shortly after the introduction of autocatalysts, from 46 μg kg^{-1} Pt, 7 μg kg^{-1} Rh, and 6 μg kg^{-1} Pd (in 1994) up to about 4 times higher (with maximum values of 330 μg kg^{-1} Pt and 45 μg kg^{-1} Rh) (in 1996) concentrations in the upper soil profile (0–2 cm depth) (Schäfer et al., 1999), from 3.0 ng g^{-1} (in 1984) to 8.9 ng g^{-1} (in 1991) Pt in road sediments (Wei and Morrison, 1994b), and 6–16 times larger in 1992–2002 (20 $\pm$ 6 ng g^{-1}) than prior to the introduction of the catalysts (1.4–2.1 ng g^{-1}) in sediments from an urban lake (Rauch et al., 2004). Several hundred elevated levels of the metals in soils along roadsides were reported in 1999 as compared with their geochemical background in uncontaminated soil ($<$1 μg kg^{-1} Pt, $<$0.5 μg kg^{-1} Pd, and $<$0.2 μg kg^{-1} Rh in typical soils of southwest Germany) (Zereini et al., 2000; Schäfer amd Puchelt, 1998). Metal concentrations in soils decrease with increasing distance from the edges of roadways and with sampling depths. Measurable quantities of the metals usually occur down to 20 cm of the upper layer of soil. Sediments with high clay content and exchangeable cation concentrations exhibit relatively high affinity for the metals (Sako et al., 2009). In 2007 the enrichment ratios of PGEs in road sediments exceeded 400 (64 ng g^{-1} Rh, 105 ng g^{-1} Pd, and 506 ng g^{-1} Pt, determined) (Sutherland et al., 2007). Transformation of PGEs from autocatalyst-emitted particles into soluble bioavailable species under the action of redox and complexation agents occurring in soils and sediments can significantly affect their mobilization in the environment.

Analytical results for the content of the metals in physiological fluids (blood, urine, lung fluids) and tissues (kidney, liver, lungs) are the basis for toxicological assessment of human exposure to environmental PGEs. Confirmed elevated physiological levels of the metals in the organisms exposed to them clearly indicate their bioavailability. The examination of biological fluids, tissues, and cells (defined in the work as clinical materials) for the content and speciation of two PGEs, platinum and ruthenium is fundamental for monitoring the mechanism of action of both metal complexes used as anticancer agents. In 1978 cisplatin was introduced into chemotherapy and has become one of the most successful drugs for treatment of lung, ovarian, bladder, head, and neck cancers (Keppler, 1993; Wong and Giandomenico, 1999; Galanski et al., 2005; Timerbaev et al., 2006b; Arnesano and Natile, 2008). The problems of severe side effects such as neurotoxicity, nephrotoxicity, ototoxicity, nausea, and vomiting and development of drug resistance during treatment have stimulated great efforts to search for metal-containing cytotoxic compounds of better antitumor characteristics and safety profiles that are able to overcome limitations in applications of cisplatin. Research aiming at developing compounds of a wider spectrum of activity and reduced toxicity and cell

resistance has resulted in about 35 second-generation platinum compounds entering clinical trials. Some of them, carboplatin and oxaliplatin, are worldwide approved and are in routine clinical practice today; lobaplatin, nedaplatin, and heptaplatin were approved in China, Japan, and South Korea, respectively. A comprehensive review of platinum complexes in clinical use and evaluation by 2005 is available (Galanski et al., 2005). Among the other transition metal–containing compounds synthesized and tested for anticancer activity, some ruthenium(III) and ruthenium(II) complexes appeared most promising with improved, as compared with platinum compounds, therapeutic activity against tumors with developed resistance to cisplatin. Numerous ruthenium-based complexes have been extensively investigated in terms of their pharmacokinetic properties (Keppler, 1993; Timerbaev et al., 2006b; Allessio et al., 2004; Kostova, 2006; Ang and Dyson, 2006; Reisner et al., 2008; Levina et al., 2009). Knowledge of the metabolism of Pt- and Ru-based anticancer agents, mechanism of their cytotoxic activity, biotransformation processes, interactions with bioligands (peptides, DNA), hydrolysis and redox reactions under physiological conditions, bioavailability, and toxicity has become a fundamental requirement for chemotherapy. The problems have attracted great attention of scientists from many fields of interest, among them chemist analysts. Analytical results of the content and speciation of metal-based drugs in clinical materials are a key to the explanation of their biological activity.

The determination of ultra-traces of PGEs in a large variety of environmental materials, as well as the investigation of the metabolism of metal-containing drugs, is a challenge for chemist analysts. Extremely low analyte concentrations in complex environmental samples, often below detection limits (DLs) of available instrumental techniques, and numerous interfering effects from matrix elements require the application of appropriate preparation steps ensuring quantitative transformation of the metals into soluble species, separation from interfering elements, and preconcentration up to the level detectable by the technique used. Generally, higher concentrations of the metals occurring in clinical materials and lower interference from biological matrices make the determination of the total amounts of the metals less complicated. However, the explanation of the drug mechanism action requires the characterization of various drug species formed under physiological conditions and their biotransformation products. This generates more complex analytical problems requiring a great emphasis on isolation of particular forms, ensuring their stability and detection of the metal-containing species. Hybrid techniques comprising effective separation and sensitive detection have potential to resolve problems in speciation analysis of clinical materials.

A brief overview of analytical procedures developed for the determination of PGEs in environmental and clinical materials is presented in this article.

SAMPLE PREPARATION STEPS IN ANALYSIS OF ENVIRONMENTAL AND CLINICAL MATERIALS

Sample preparation can substantially affect the reliability of the results in the analysis of PGE samples. Sampling procedure is particularly important in the analysis of complex environmental materials. Heterogeneity of such materials generates problems with obtaining representative samples. Larger samples and their careful homogenization are recommended to minimize the effects of nonhomogeneous distribution of PGEs. Description of the area of sampling, including roadside distance, average traffic, and even weather conditions that can affect the content of the metals in the examined samples is needed. Storage and digestion procedures require protection from contamination from container materials and reagents used. Devices routinely used in hospital and clinical laboratories (disposable stainless steel needles, blood collection tubes, serum separation tubes, plastic pipettes, and plastic vials) for sampling and storage of blood and serum can contribute to contamination risk (Rodushkin and Ödman, 2001). Digestion procedures can generate problems with the blanks, which can substantially affect the possibility of detection by instrumental techniques. Minimizing the blanks by the application of a limited number of analytical steps and the amount of the reagents used is important. Quantitative transformation of the metals into soluble forms suitable for separation and detection procedures generally requires more complex digestion steps in the analysis of environmental samples than with clinical materials.

Losses of the analytes owing to sorption onto container walls require special attention. Noble metals, in particular at low concentrations, exhibit strong tendency to hydrolysis and precipitation under weakly acidic and neutral conditions. Acidification of the examined solutions can prevent the complexes from hydrolysis and can minimize the sorption. Kinetics of sorption may depend on the kind of vessel material used. Quartz vessels are recommended for reducing sorption of the analytes during sample digestion and storage (Alt et al., 1998). Vapor cleaning with boiling mineral acids can be used for decontamination of quartz vessels. Multiple cleaning steps with various acids under high pressure conditions may be necessary for decontamination of the vessels previously used for the examination of samples of relatively higher metal concentrations. Vapor-cleaned (HCl and H_2O_2) quartz flasks were found the most suitable for storage of platinum standards (1–5 μg L^{-1} w 1 mol L^{-1} H_2SO_4) (Hoppstock et al., 1989). However, quartz vessels cannot be compatible with the vacuum concentration system (Haus et al., 2009). Teflon vessels could be an alternative, but losses of platinum over time can occur. Quantitative (80–100%) recoveries for Pt from animal tissues were reported only in the initial phase of experiments. After the seventh experiment, Pt recoveries were unpredictable and Pt loss increased (20–90%) with every new digestion.

Environmental Samples

Representativeness of the examined sample and quantitative transformation of PGEs into soluble complexes substantially limit the reliability of the results in the analysis of environmental materials. Extremely low concentrations of the metals, often below detection limits of the available instrumental techniques, and large excess of interfering elements can require additional separation and preconcentration steps.

Plant tissues are digested in mixtures of mineral acids prior to determination of the total PGE contents. Mixtures of HNO_3 and HCl; HNO_3, HCl, and $HClO_4$; HNO_3, HCl, and HF; and HNO_3, HCl, and H_2SO_4, under high pressure microwave-assisted conditions, are applied. The introduction of HF can be advantageous in the case of incomplete sample digestion. Preliminary surface cleaning by washing with tap and distilled water or blowing with an airstream, drying, and cutting into smaller parts is applied prior to the digestion step. Careful sample cleaning is necessary for removing dust and other solid particles from the plant surface. The samples are dried under air or elevated temperature until constant weight is reached, and they are homogenized prior to digestion. The kind of material of the mill used requires attention. The use of a mill made of zirconium dioxide, usually containing high amounts of HfO_2, can provide a serious contamination source for Pt determination by the inductively coupled plasma-mass spectrometry (ICP-MS) technique. Agate, Teflon, or tungsten carbide mills can be used instead.

Airborne particles are usually sampled with medium PM-10 (24–30 m^3/day), high-volume (1700–1800 m^3/day) collectors and multistage (1350 m^3/day) impactors (Palacios et al., 2000; Rauch et al., 2001; Gómez et al., 2002). Road dust can be sampled by sweeping from the chosen surface using a hand brush or a vacuum cleaner; the dust is then oven dried to remove volatile components, sieved to separate into different fractions of particle size, and homogenized. Monitoring of the level of autocatalyst emission of PGEs is also carried out by the evaluation of their accumulation on tree bark exposed to traffic (Becker et al., 2000; Ma et al., 2001). Solid particles emitted from automobiles with exhaust fumes can be trapped in a paper filter attached to the end of a car exhaust pipe (Goncalves et al., 2008).

The complexity of airborne matter and road dust matrices and high concentrations of interfering elements cause difficulties in quantification of ultra-traces of PGEs. A kind of digestion procedure applied directly affects the recovery of the metals from such matrices as well as the amount of interfering elements in the obtained solutions. A mixture of aqua regia and HF under high pressure microwave-assisted conditions is recommended for digestion of airborne particles and dust samples (Gómez et al., 2000, 2003; Zischka et al., 2002; Kanitsar et al., 2003). The introduction of small amounts of $HClO_4$ into the digestion mixture can enhance the decomposition of organic matter. Good recoveries for Pt and Rh from dust samples were reported under treatment with HNO_3, HCl, and HF (Niemelä et al., 2005). Subsequent application of aqua regia/HF/$HClO_4$/aqua regia was suggested as useful for digestion of airborne particulate matter collected on quartz-fiber filters prior to determination of Pt (Mukai et al., 1990).

Soil samples taken from different distances from the edges of roadways and different sampling depths are examined for estimation of the distribution of PGEs. The samples are dried, sieved, and milled to obtain the required fractions prior to the digestion steps. Fire assay (FA) and mineral acid treatment proved to be the most efficient digestion procedures in the analysis of soil and sediment samples for PGE contents (Balcerzak, 2002). Fire assay digestion and preconcentration is a very attractive method due to the possibility of the examination of large (up to 50–100 g) samples, which helps with the elimination of the problem of heterogeneity of the examined materials, and a collection of the metals into a relatively small bead of the collector used (Schäfer et al., 1999; Rauch et al., 2004; Zereini et al., 2000; Heinrich et al., 1996; Farago et al., 1998; Hutchinson et al., 2000; De Vos et al., 2002). Nickel sulfide is the most effective FA collector for quantitative recovery of PGEs from soil and sediment samples. Large amounts of chemicals required for the FA procedure may provide high procedural blanks and problems with direct detection of the analytes in the obtained solutions by instrumental techniques. Treatment with mixtures of mineral acids: aqua regia, aqua regia and HF, HCl + HNO_3 and HNO_3 + $HClO_4$, HCl + HNO_3 and HF, HF + $HClO_4$ and HNO_3 + HCl, is widely applied for the decomposition of soil and sediment samples prior to determination of PGEs. Total digestion of samples with the use of HF is recommended for quantitative recovery of the metals. It can, however, result in higher amounts of matrix elements, e.g., 224 $\mu g\ g^{-1}$ Zr, than in the case of the use only aqua regia (17.5 $\mu g\ g^{-1}$ Zr), transformed into the obtained solution from soil samples (Simpson et al., 2001).

Separation of platinum metals from interfering matrix elements and their preconcentration up to the quantification limit (QL) of the instrumental technique used are generally necessary when examining soil and sediment samples. Chromatographic techniques and reductive coprecipitation with tellurium are most often applied in separation and preconcentration procedures. In the analysis of soil samples the precipitation with Te can, however, result in low recoveries of the metals, e.g., 55–87% Pt (Tresl et al., 2000). The application of ion exchange (both cation and anion) chromatography in the analysis of complex environmental materials has beeen examined. The use of anionic resins is strongly limited owing to difficulties with quantitative elution of PGEs exhibiting strong affinity to the resins (Hodge et al., 1986; Müller and Heumann, 2000). The 11–22% and 19–35% recoveries of Pt and Pd, respectively were reported with conc. HNO_3 applied as an eluent (Müller and Heumann, 2000). The use of only fresh resins was suggested due to strong memory effects of PGEs. Elution with conc. HNO_3 at 83°C can provide better recovery of the metals (>95% Pt) (Hodge et al., 1986). Hydrofluoric acid used for sample digestion may cause problems with separation of some interfering matrix elements by ion chromatography, e.g., Hf, which forms anionic fluoride

complex behaving similarly to PGE complexes during the separation step. Sorbents with various chelating agents (e.g., dithizone, 2,2′-dipyridyl, dietyloditiocarbamate, and thiourea derivatives) can be more effective for separation and preconcentration of PGEs from soil samples (Chwastowska et al., 2004; Ljubomirova and Djingova, 2008). The 98% and 95% recoveries of Pt and Pd, respectively, from soil samples were reported by the use of dithizone sorbent (Chwastowska et al., 2004). Thiourea and conc. HNO_3 were used for elution of both metals. Two-dimensional chromatography (AG 50W-X8 and C18 immobilized with *N,N*-diethyl-*N*′-benzoylthiourea) was applied for on-line separation and preconcentration of Pd from soil and dust samples (Rudolph et al., 2006). The enrichment factors of 41.7 (Bosch Ojeda et al., 2003) and 14 (Gonzalez Garcia et al., 2003) for Pt in soil samples were achieved with the use of 1,5-*bis*(di-2-pyridyl)methylene thiocarbohydrazide immobilized on silica gel and anion-exchange column, respectively.

General overviews of methods for sample preparation (digestion, separation, and preconcentration) in the analysis of various materials for PGEs are available (Balcerzak, 2000, 2002; Akatsuka and McLaren, 2000; Prasada Rao and Daniel, 2003; Godlewska-Żyłkiewicz, 2004; Mokhodoeva et al., 2007).

Clinical Samples

The isolation, identification, and determination of species formed under physiological conditions as the results of biotransformation processes are essential for pharmacokinetic characterization of metal-containing drugs. Species stability during sampling, storage, and analysis of clinical materials requires particular attention. Stability of the complexes used is also important for calibration procedures. Solutions containing more than 0.3% sodium chloride were recommended to ensure stability of cisplatin. Dilute cisplatin solutions in 0.9% NaCl at 37°C used for calibration were stable for six to seven days (Barefoot and Van Loon, 1996). Stability of platinum complexes rapidly (50% in 24 hours) decreases under exposure to fluorescent light. Storage conditions of samples (blood, plasma, ultrafiltrate, urine) can directly affect the stability of species formed after drug administration. Chloride concentration and pH influence kinetics of cisplatin hydrolysis. Monohydrated complex is considered an active biological form of cisplatin (Barefoot, 2001). The half-lives of cisplatin and its monohydrated complex at concentrations of 50 μmol were estimated as 1.43 hours and 9.36 hours (in blood) and 0.88 hours and 0.05 hours (in plasma), respectively, at a temperature of 37°C and pH 7.4 (Andersson and Ehrsson, 1995). Higher (three weeks) stability of both species was observed at lower (−70°C) temperature. Stabilities of cisplatin in plasma ultrafiltrate for five days (Kinoshita et al., 1990) and carboplatin for eight months (Van Warmerdam et al., 1995) stored at −20°C were reported. Treatment of plasma samples with acetonitrile and a citrate buffer enhances the stability of cisplatin. Carboplatin is more stable in glucose medium (Barefoot and Van Loon, 1996; Yang et al., 2002). Blood samples should be centrifuged immediately after sampling and analyzed as soon as possible to prevent losses of the analytes. Eventual storage prior to analysis requires temperatures <0°C. Ultrafiltrate samples should be analyzed directly after preparation. If direct analysis is not possible, storage of the samples at temperatures <−10°C is recommended. Urine samples should be stored at −20°C, however; recent results from the investigation of intact oxaliplatin in patient urine samples have shown that accurate quantification of the intact drug required storage at −80°C and rapid measurement after thawing (Koellensperger and Hann, 2010).

The determination of PGEs in clinical samples usually requires dilution in order to decrease the concentration of dissolved salts or digestion of organic matrix. Large quantities of solids can cause problems with detection, e.g., by blocking the sampler and skimmer in the ICP-MS technique. Proteins at high concentrations can act similarly. The dilution of physiological fluid samples prior to determination of the metals was carried out with: water, diluted HCl, diluted HNO_3 or a mixture of EDTA and Triton X-100 (Pt and Ru, ICP-MS technique) (Brouwers et al., 2008); 0.15 M NaCl and 0.2 M HCl (Van Warmerdam et al., 1995; Brouwers et al., 2005); water (Einhäuser et al., 1996; Deforce et al., 1998); water with 0.2% Triton X-100 (Kloft et al., 1999); plasma/0.2 mol L^{-1} HCl (Tibben et al., 2002); 0.1% Triton X-100 and 0.2% HNO_3 (Meerum Terwogt et al., 2000), 10% HCl (urine); and 5% Triton X-100 (plasma) (Vouillamoz-Lorenz et al., 2001) (Pt, ET-AAS technique). The choice of the dilution medium depends on the kind of matrix and the instrumental technique employed. Preservation from precipitation of peptides during dilution with acids requires attention. Loss of sensitivity upon dilution can be problematic. Digestion of organic matrix with mineral acids is generally a better approach. Samples of blood and plasma can be digested under treatment with conc. HNO_3 (Morrison et al., 2000), aqua regia, or a mixture of conc. HNO_3 and $HClO_4$ (Nygren et al., 1990). Mixtures of HNO_3 and H_2O_2 and HNO_3, H_2O_2, and aqua regia were used for digestion of blood and urine samples (Begerow et al., 1997a, b; Hann et al., 2003). Ultraviolet photolysis allows complete digestion of the examined samples with smaller amounts of the reagents, which results in minimizing the blanks (Begerow et al., 1997a, b). Urine samples can be digested only in the presence of H_2O_2 (Begerow et al., 1997b). Digestion by treatment with mineral acids, mostly HNO_3, a mixture of HNO_3 and H_2O_2, or HNO_3 and HCl, can be applied in analysis of tissue samples (Milačič et al., 1997; Zimmermann et al., 2001). The suitability of the proteomics bottom-up approach for the study of Pt-containing proteins (cisplatin-insulin) based on tryptic digestion procedure was examined (Moreno-Gordaliza et al., 2010). Such procedures allow the identification of Pt-binding sites in the protein.

INSTRUMENTAL TECHNIQUES FOR DETECTION OF ULTRA-TRACES OF PGEs IN ENVIRONMENTAL AND BIOLOGICAL MATERIALS

Low concentrations of PGEs in environmental and biological materials, and complexity of the examined samples, require

detection techniques of high sensitivity and selectivity for their determination. Inductively coupled plasma-mass spectrometry (ICP-MS), adsorptive voltammetry (AV), electrothermal atomic absorption spectrometry (ET-AAS), and neutron activation analysis (NAA) are most often used for such purposes (Balcerzak, 1997; Barefoot and Van Loon, 1999; Rao and Reddi, 2000; Perry et al., 1995). Numerous interfering effects from matrix elements, in particular when examining complex environmental samples of extremely low PGE concentrations, may limit direct application of particular techniques. Separation and preconcentration steps often precede the final detection of the metals. Hyphenated techniques, most often ESI-MS, HPLC-MS, HPLC-ICP-MS, CE-MS and CE-ICP-MS, are applied in speciation analysis of PGEs in biological and environmental materials.

Inductively Coupled Plasma-Mass Spectrometry

Inductively coupled plasma-mass spectrometry has found wide applications in the analysis of PGE samples, but not without limitations. The fundamental problem concerns serious interfering effects from matrix elements and polyatomic species generated under plasma conditions on the signals of platinum metals (Gómez et al., 2000; Perry et al., 1995; Bencs et al., 2003). The ICP-MS signals of Pt can be seriously affected by hafnium oxide (HfO^+) generated in plasma. The HfO^+ signals overlap the signals of all platinum isotopes (^{190}Pt (0.013%), ^{192}Pt (0.78%), ^{194}Pt (32.9%), ^{195}Pt (33.8%), ^{196}Pt (25.3%), and ^{198}Pt (7.19%)). The main interference of Pd signals comes from polyatomic species of copper ($ArCu^+$), yttrium (YO^+), strontium (SrO^+), and zirconium (ZrO^+). Polyatomic species of copper ($ArCu^+$) and rubidium (RbO^+) and signals of Pb^{2+} provide the most important interference for rhodium. The extent of interfering effects directly depends on the concentration of matrix elements. This means that the problem of interference is crucial in the analysis of environmental samples (dusts, soils, and sediments) due to a larger occurrence of the interfering elements.

Modifications in classical ICP-MS spectrometers used, the application of various sample introduction methods or chemical separation procedures, were extensively examined to overcome, or minimize, spectral interference in PGEs detection by the ICP-MS technique. Mathematical correction, the introduction of reaction/collision cells, and the use of double-focusing sector field mass spectrometers (SF-ICP-MS) are examples of instrumental improvements. The application of sector field mass spectrometers is very attractive. Sector field apparatus offers substantially better mass resolution ($m/\Delta m$ up to 11000) than quadrupole filters. The resolution required for the elimination of hafnium oxide–based interference in the detection of platinum (^{194}Pt/^{178}Hf/^{194}HfO) and (^{195}Pt/^{179}Hf/^{195}HfO) was evaluated as about 8000–10000 (Rauch et al., 2000). A detailed summary of the applications of SF-ICP-MS spectrometers in the analysis of PGE samples of geological origin, including environmental matrices, was published (Barefoot, 2004). The application of mathematical correction, involving quantifying of the interfering signal that overlaps the analyte signal and substracting it by mathematical equation, is limited by the intensity of the interference. In the case of platinum, mathematical correction provides accurate results for Pt for Hf/Pt ratios of up to 50 (Parent et al., 1997). The examination of the concentration of the interfering element and the evaluation of the efficiency of the formation of particular interfering species, e.g., $R_{HfO} = HfO^+/Hf^+$ for Pt determination, under the conditions used (nebulizer flow rate, the lens voltage, and rf power) are required prior to detection of the metals in a complex matrix. Mathematical correction is usually sufficient for the detection of Pt, Pd, and Rh in plant samples (Djingova et al., 2003a). Modifications in sample introduction techniques in order to obtain "dry" plasma conditions, under which the intensity of O- and OH-containing molecular ions are substantially reduced as compared with those obtained in wet plasma, can help with overcoming the interference occurring in the determination of PGEs in complex matrices. Electrothermal vaporization, thermospray nebulization, laser ablation, and membrane desolvation of sample aerosol are applied for such purposes. The application of dynamic reaction cells (DRCs) presents an interesting approach. The advantages of the use of the DRC-ICP-MS technique, using O_2 or NH_3 as a reaction gas, in the analysis of soil (Simpson et al., 2001) and dust samples (Kan and Tanner, 2004), respectively, for the content of Pt and Pd were demonstrated. Methods for the elimination of hafnium interference with the determination of platinum in environmental samples by the ICP-MS technique have recently been discussed in detail (Balcerzak, 2009). Chemical separation of PGEs from interfering elements provides the most reliable analytical procedures. Such procedures generally enable simultaneous preconcentration of the analytes prior to detection. Fire assay digestion and preconcentration method, ion exchange chromatography, and coprecipitation with tellurium often precede the detection of the metals by ICP-MS in complex environmental materials.

Lower effects from biological matrices on the signals of PGEs generally allow direct application of the ICP-MS technique to the detection. Sample dilution or digestion of the organic matrix may be sufficient for sample preparation. The introduction of a preconcentration step can result in better detection and quantification limits (Minakata et al., 2007).

Purity of the reagents and the vessels used require special attention in analysis of environmental and clinical materials for ultra-traces of PGEs. Memory effects can cause sources of serious errors in the obtained results.

Atomic Absorption Spectrometry

Atomic absorption spectrometry with electrothermal atomization is applicable for the determination of platinum metals in environmental and clinical samples. The technique employing flame atomizers does not cover the concentration ranges of interest, in particular when examining environmental materials. High matrix effects and small linear concentration ranges are disadvantages of the AAS technique. In the analysis of environmental materials the quality of the results is substantially affected by sample preparation steps. Separation

of PGEs from the interfering elements and preconcentration are generally required. The technique can often be directly applied to the detection of metals in clinical samples after chemotherapy treatment. Dilution of the examined samples prior to detection can be sufficient. In some cases digestion of tissues and physiological fluids would be advantageous.

Adsorptive Voltammetry

Adsorptive voltammetry (AV) is a very sensitive technique offering DLs adequate for the determination of traces of PGEs in environmental and biological materials (Locatelli, 2007b; Weber and Messerschmidt, 2005). The available detection limits allowed the assessment of physiological levels of Pt, $\leq$0.8–6.9 ng L^{-1} in blood and 0.5–15 ng L^{-1} in urine (Messerschmidt et al., 1992). The most popular voltammetric methods involve the formation and adsorptive accumulation of PGE complexes on the surface of a hanging mercury drop electrode. The voltammetric response of the complex used directly corresponds to its surface concentration. The determination of Pt is most often based on the measurement of catalytic reduction of protons by the Pt(II) complex with formazone (a condensation product of formaldehyde and hydrazine) accumulated on the surface of a mercury electrode. Palladium-dimethylglyoxime complex is mostly used for the determination of Pd. Mutual PGE interference limits the application of AV to procedures prevalently addressed to single metals (Locatelli, 2007b). Very close reduction peak potentials of particular metals in commonly used supporting electrolytes hinder the determination of neighboring elements owing to serious overlap of their signals. Attempts at simultaneous determination of ultra-traces of Pt and Rh in the presence of hydroxylamine (or acetone oxime) and formaldehyde (Huszał et al., 2005), or hexamethylene tetramine (Dalvi et al., 2008), in environmental materials were presented. Sequential determination of Pt, Pd, and Rh with hydroxylamine and formaldehyde was described (Locatelli, 2005). Adsorptive voltammetric methods for PGEs are extremely sensitive to organic matrices, in particular to surface-active agents. Destroying the organic matrix to limit carbon content to below 0.1% is required (Helmers and Mergel, 1998). Ashing in a muffle furnace and high pressure ashing (HPA) are the most often used digestion procedure for AV. Dry ashing is believed to be the most reliable for the destruction of matrices with high concentration of organic substances. Interference and blank value problems in the determination of Pt by AV were discussed (Hoppstock et al., 1989; León et al., 1997). A critical review of voltammetric methods developed for PGEs in environmental and biological materials has recently been published (Locatelli, 2007b).

Neutron Activation Analysis

High sensitivities (pg g^{-1} and sub-pg g^{-1} levels) available by neutron activation analysis (NAA) and a practical lack of blanks make the technique particularly suitable for the determination of ultra-traces of the elements in complex materials (Dybczyński, 2001). The determination of PGEs is accomplished by the production and detection of specific radionuclides of particular elements (Alfassi et al., 1998; Garuti et al., 2000; Chajduk-Maleszewska and Dybczyński, 2004; Valente et al., 1982). Radiogold daughter isotope, one of the products of thermal neutron activation of platinum (^{198}Pt (n,γ)^{199}Pt $\rightarrow$ ^{199}Au ($t_{1/2}$ = 3.15 d)), is used as a measure of platinum content. Palladium and rhodium are detected using the reactions ^{108}Pd(n,γ)^{109}Pd ($t_{1/2}$ = 13.4 hours) and ^{103}Rh(n,γ)^{104}Rh ($t_{1/2}$ = 42 seconds), respectively. Direct application of NAA in the analysis of complex environmental samples is restricted due to interfering effects from matrix elements, which are critical in the determination of very low analyte concentrations. Separation and preconcentration are often applied, either before or after the irradiation. Fire assay preconcentration, ion exchange chromatography, and coprecipitation with a suitable collector are most frequently used to separate PGEs from the interfering matrix. Recent application of the technique to the determination of Rh in filter paper for wiping tests of deposits in exhaust tips can be noted (Grass et al., 2007). Access to a radiation source to produce activated analyte nuclides and safety of analytical procedures used restrict the accessibility of NAA methods. The technique can, however, be very useful for checking the results obtained by different instrumental techniques.

METHODS OF DETERMINATION OF PLATINUM, PALLADIUM, AND RHODIUM IN ENVIRONMENTAL MATERIALS

Determination of Metals in Plants

The examination of plants for platinum content has been the subject of a majority of analytical works owing to its higher amounts in autocatalysts than palladium and rhodium. Growing interest in the determination of Pd has recently been observed due to an increasing trend to replace Pt by Pd in autocatalysts (Johnson Matthey, 2008; Fumagalli et al., 2010). Plants exhibit a higher tendency for bioaccumulation of Pd than for Pt and Rh. The evaluated transfer rates (concentration ratio plant/soil) of Pd in different plants were in the range of 0.05–0.5 and were comparable with that of zinc (Eckhardt et al., 2000). Similar values for Pt and Rh, 0.01–0.05, corresponded with those for Sb, Ni, and Cu. Transfer factors for Pt between soils and plants determined in agricultural experiments for two types of soils were 0.004 and 0.008 (dandelion was considered as most adequately reflecting the pollution) (Djingova et al., 2003b).

Adsorptive voltammetry and ICP-MS techniques are most often applied for the detection of PGEs in plant samples. The available DLs allow direct determination of the metals in solutions obtained after digestion of the examined samples without any further treatment. No significant interference in the determination of Pt by AV from other metal ions occurring in plants were reported (León et al., 1997). Platinum-formazone and dimethylglyoxime complexes are generally used for the detection of Pt and Pd, respectively (Hoppstock et al., 1989; Helmers and

Mergel, 1998; León et al., 1997; Locatelli et al., 2005; Desimoni et al., 2002, 2004). Platinum and rhodium in plant samples were determined with semicarbazide (Huszał et al., 2004) and hydroxylamine and acetone oxime (Huszał et al., 2005). Platinum in grass, leaves sampled from a nonpolluted area, and roots taken from an area of heavy road traffic was determined by a voltammetric method using a solid electrode of glassy carbon (Kołodziej et al., 2007).

The concentrations close to the available DLs (0.09 μg L^{-1} Pt, 0.12 μg L^{-1} Pd, 0.05 μg L^{-1} Rh) and 8.6 μg kg^{-1} Pt, 1.9 μg kg^{-1} Pd, and 1 μg kg^{-1} Rh were determined in plants (spinach, cress, phacelia, and stinging nettle) cultivated on the reference uncontaminated and contaminated soil (soil taken from the roadside of a highway), respectively, by the ICP-MS technique (Schäfer et al., 1998). Similar results for vegetables (onion, radish, potato, maize, and broad bean) grown under natural conditions (the concentration of Pt close to DL (2–5 ng L^{-1}) and only slightly higher amounts (0.02–0.6% bioaccumulation of Pt introduced into the soil) in the examined plants grown in soil treated with platinum containing tunnel dust were published (Lustig et al., 1997). Mosses are often used as biomonitors for environmental pollution owing to rainwater and dry deposition being their main nutrient sources (Djingova et al., 2003a; Niemelä et al., 2004, 2007).

The other instrumental techniques are relatively rarely employed for the detection of PGEs in plant samples, mainly due to worse DLs available. Introduction of a preconcentration step, e.g., electrochemical deposition on a pirolytically coated graphite tube (Beinrohr et al., 1993), preconcentration on anionic resin (Dowex1×8) immobilized with thiocarbohydrazide (Gonzalez Garcia et al., 2003) makes the determination of Pt in plants possible by ET-AAS. Rhodium recoveries of 99.9% and 101.1% were reported for ET-AAS preceded by preconcentration on chelating (1,5-*bis*(2-pyridyl)-3-sulphophenyl methylene thiocarbonohydrazide) resin immobilized on Dowex1×8 (Sanchez Rojas et al., 2004, 2009). NAA was adequate for the determination of background levels of Pt in plants (Valente et al., 1982).

Combination of effective separation methods with highly sensitive detectors is necessary for speciation of the metals in environmental samples (Weber et al., 2000). Gel chromatography combined with AV (Messerschidt et al. 1994), ICP-MS (Klueppel et al., 1998; Leśniewska et al., 2004) and capillary electrophoresis (CE) (Messerschmidt et al., 1995; Alt et al., 1998) were used for the identification and determination of Pt species in plants. Several species of Pt were identified in grass exposed to soluble Pt compound, $[Pt(NH_3)_4](NO_3)_2$ (Messerschmidt et al., 1994). More than 90% of platinum was bound to low molecular weight species (about 1 kDa), whereas less than 10% of Pt was bound to species with molecular weights from 19 up to > 1000 kDa. Only one Pt form (160–200 kD) was detected in the native grass extract (0.02 M ammonium acetate made up to pH 8.0 with TRIS used as extracting agent). There are reports of 90% and 10% of Pt present as inorganic and organic compounds, respectively, in grass samples (Jakubowski et al., 1998). Attempts to distinguish among the organic fractions of sulfur-containing amino acids or peptides used by plants for metal complexation by combination of size-exclusion chromatography and ICP-MS techniques were presented (Klueppel et al., 1998). The investigation of Pd binding to organic ligands in contaminated endive by gel permeation chromatography and X-ray fluorescence (XRF) revealed 23% of the total palladium bound to high molecular weight species (>10 kDa) (Alt et al., 2002). To date, available data on speciation of PGEs in plants are not sufficient.

Determination of PGEs in Airborne Particles and Road Dust

The determination of PGEs in airborne particles and road dust is a challenge owing to high complexity of the examined matrices, difficulties with complete digestion, and large excess of interfering elements. Matrix elements can occur in such materials at concentrations several orders of magnitude higher (ng m^{-3}, μg m^{-3} in the case of Cu and Pb) than PGEs (typically pg m^{-3} and ng g^{-1} in aerosol and dust samples, respectively) (Gómez et al., 2000; Zischka et al., 2002; Kanitsar et al., 2003). Background concentrations of 3 pg m^{-3} Pt and <0.2 pg m^{-3} Rh in airborne particulate matter (Germany) were reported (Zereini et al., 2001).

The ICP-MS technique has found the widest application in the determination of PGEs in airborne particles and road dusts. The majority of studies are focused on the determination of Pt. The determination of Pd and Rh, usually occurring at lower concentrations in such kinds of matrices, can generate more difficulties due to serious spectroscopic interference arising from more abundant matrix elements. The interference contribution to the determination of Rh in airborne samples was evaluated as 50–75% (Gómez et al., 2000). Reliable results for Pd and Rh mostly require matrix separation. Preliminary treatment of the samples with diluted HCl, e.g., 0.35 M (Simitchiev et al., 2008), can substantially remove some interfering elements from the examined samples in soluble forms without losses of PGEs. Mathematical correction (Gómez et al., 2000; Djingova et al., 2003a), "dry plasma" conditions obtained by modifications in sample introduction systems (Rauch et al., 2001; Kanitsar et al., 2003; Fragnière et al., 2005; Köllensperger et al., 2000; Vanhaecke et al., 2002; Petrucci et al., 2000), the use of dynamic reaction cell (Simpson et al., 2001; Kan and Tanner, 2004), and chemical separations (Gómez et al., 2003; Mukai et al., 1990; Müller and Heumann, 2000; Bruzzoniti et al., 2003) were employed to minimize or eliminate interference in PGEs detection. The isotope dilution method can be a key approach for quantification of metals. The influence of instrumental parameters such as nebulizer flow rates and plasma power on the detection of Pt, Pd, and Rh (DLs of 0.6, 3.3, and 0.9 ng L^{-1}, respectively) was investigated (Gómez et al., 2000). Platinum was detected after mathematical correction of HfO^+ interference up to 10% contribution. The interference with Rh determination was

minimized by lowering plasma power. The determination of Pd was hampered by the enormous contribution of YO^+ and $ArCu^+$ signals. Introducing electrothermal vaporization allowed direct determination of Pt and Rh in road dust and airborne particles by the ICP-MS technique without a chemical decomposition step (Vanhaecke et al., 2002). Direct analysis of solid samples can be accomplished by laser ablation (LA) ICP-MS. The technique allows the examination of surface distribution of the metals in airborne particles (Rauch et al., 2001, 2002; Boulyga and Heumann, 2005). Ultrasonic nebulization and membrane desolvation (USN-MDS) combined with sector field ICP-MS allowed significant reduction in the ratio HfO^+/Hf^+ and direct quantification of Pt in solutions obtained after digestion of aerosol samples by the isotope dilution technique (Kanitsar et al., 2003). The determination of palladium required preliminary chromatographic separation of interfering elements. Two major sources of interference in the detection of Rh, $^{40}Ar^{63}Cu^+$ and $^{206}Pb^{2+}$, were eliminated at m/Δm 7609 and 1234, respectively. Effective elimination of hafnium interference with the detection of Pt in road dust samples when using sector field ICP-MS and USN-MDS was earlier reported (Köllensperger et al., 2000). Interference with the determination of Pd and Rh, not eliminated by mass resolution, could be evaluated by standard addition of contaminant ions. Mathematical correction for Sr can be necessary for the detection of Pd. Careful consideration of the results for Pd and Rh in airborne particle matter and road dust, respectively, obtained by USN-MDS-ICP-MS was suggested owing to serious interference from the matrix (Petrucci et al., 2000).

Chemical separation may be a key solution for the detection of PGEs in complex materials. In the analysis of airborne particles and road dust the matrix elements were separated by, for example, on-line cation (Mukai et al., 1990) or anion (Müller and Heumann, 2000) exchange. The coprecipitation of PGEs with tellurium can result in the elimination of more than 95% of the interference (Gómez et al., 2003). Careful checking of the contribution of $ArCu^+$ and YO^+ to ^{105}Pd and Cd^+ to ^{106}Pd signal and eventual application of mathematical correction was suggested. A highly effective method for quantification of Pd in airborne particulate matter with Hg-coprecipitation of the metal and the use of He collision gas has recently been published (Alsenz et al., 2009). The use of Hg as a collector depletes the concentrations of interfering matrix constituents by at least one order of magnitude greater than Te coprecipitation. The use of He gas plasma can minimize interference, particularly that arising from $CuAr^+$, YO^+, and ZrO^+ during the detection of Pd.

ET-AAS (Komárek et al., 1999; Tilch et al., 2000; Matusiewicz and Lesiński, 2002; Boch et al., 2002; Limbeck et al., 2003, 2004; Tokalioglu et al., 2004; Dimitrova et al., 2004; Leśniewska et al., 2005; Tsogas et al., 2008), AV (Alt et al., 1993; Helmers and Mergel, 1998; Hoppstock and Alt, 2000; Wei and Morrison, 1994a; Schierl and Fruhmann, 1996; Locatelli, 2007a), and NAA (Probst et al., 2001; Giaveri et al., 2001; Fariseo et al., 2005) are applicable to the determination of Pt, Pd, and Rh in airborne particles and road dust. Extremely low DLs, 0.5 pg m^{-3} (Schierl and Fruhmann, 1996) and 2 pg absolute (Alt et al., 1993), were reported for the determination of Pt in airborne particles by AV directly in solutions after sample digestion. A separation and preconcentration step is generally necessary when examining airborne particulates and dusts by ET-AAS. Platinum in aerosol samples was determined after adsorption of anionic Pt-$SnCl_3^-$ complexes on C18 micro-column preliminary loaded with *N,N*-diethyl-*N*′-benzoylthiourea (Limbeck et al., 2004). High preconcentration factors, 416 for Pt, 503 for Pd, and 423 for Rh, were achieved by electrodeposition of the metals on a graphite tube (Matusiewicz and Lesiński, 2002). Palladium in road dust was determined by AAS after preconcentration on C18 micro-column loaded with *N,N*-diethyl-*N*′-benzoylthiourea (Boch et al., 2002; Limbeck et al., 2003), the complex with dimethylglyoxime on silica gel (Tokalioglu et al., 2004), and $Pd(SCN)_4^{2-}$ complex in a knotted reactor (K^+18-crown-6 as a counter ion) (Dimitrova et al., 2004). On-line preconcentration of Pd on fullerene C60 loaded with dithiocarbamate (DDTC) was used in the analysis of road dust samples (Leśniewska et al., 2005). A considerable increase in analytical features of ET-AAS in the determination of Pt, Pd, and Rh in road dust samples (DL of 1.9 ng g^{-1} Pt, 0.45 ng g^{-1} Pd, and 0.6 ng g^{-1} Rh) was achieved by the appropriate combination of extraction conditions and atomization program (Tsogas et al., 2008). The effect of HCl, HNO_3, and HF on the effectiveness of the extraction of the metals using a microwave-assisted procedure was simultaneously examined.

Instrumental NAA allowed the determination of Pt without sample digestion (Probst et al., 2001). Preconcentration of Pt on anionic resins prior to neutron irradiation was applied for the determination of Pt in urban air particulate matter (Giaveri et al., 2001) and road dust (CW7 and CW8) (Fariseo et al., 2005).

The concentrations of PGEs in air particulate matter can differ depending on their size and sampling side (Zaray et al., 2004). Approximately twice the platinum was revealed in aerosols (d <2 μm) collected in Budapest than in those from Vienna. The coarse (d $= 2$–10 μm) fractions showed a contrasting picture, with five times higher Pt concentration in the samples collected in Vienna. Heterogeneous distribution of PGEs in airborne particles is characteristic (Rauch et al., 2001; Gómez et al., 2002).

It should be noted that the evaluated Pt amounts in airborne particles are still below allowed occupational settings (2 μg m^{-3}) (Gómez et al., 2002; Merget, 2000). However, rapid increase in traffic-related PGE emission into the environment generates the necessity of monitoring the content of the metals, including in airborne particles. Comparison of the content of metals in the investigated urban area in Germany in 1999 and in 2005 has shown substantial increase in Pt and Rh concentrations (Wichmann and Bahadir, 2001; Wichmann et al., 2007). In 2005 the contents of the metals revealed in air and airborne dust were:

159 pg m^{-3} and 1730 μg kg^{-1} Pt, 37.8 pg m^{-3} and 410 μg kg^{-1} Pd, and 10.0 pg m^{-3} and 111 μg kg^{-1} Rh, respectively.

Studies on the transformation of metals from particulate matter and dust into more soluble forms are needed. In case of road dust attempts to extract various Pt species from spike ($PtCl_6^{2-}$ complex used) samples using several extractants (HCl, methionine, EDTA, and thiourea) and detection by HPLC-ICP-MS were described (Nischwitz et al., 2004). Less than 60% of the spike was recovered. Low (<5%) extraction coefficient of total Pt from unspiked road dust samples confirmed the occurrence of Pt in such materials in an elemental form. The results obtained by the application of the sequential extraction procedure confirmed that up to 5% of Pt was in mobile form in street dust (Ljubomirova et al., 2008). For Pd and Rh such values were 70% and 14%, respectively.

Determination of PGEs in Soils and Sediments

Large concentrations of matrix elements in soil and sediment samples make the determination of traces of PGEs extremely difficult. In river sediments (ng g^{-1} levels of Pt, Pd, and Rh) the concentrations of the elements interfering with detection by the ICP-MS technique were evaluated as: 0.05–1 μg g^{-1} Hf, 10–500 μg g^{-1} Cu, 50–1000 μg g^{-1} Zn, 10–500 μg g^{-1} Pb, 1–100 μg g^{-1} Y, 5–50 μg g^{-1} Sr, 1–50 μg g^{-1} Rb, and 0.01–5 μg g^{-1} Cd (Rauch et al., 2000). Chemical separation steps are usually necessary in the analysis of soils and sediments. ICP-MS (Schäfer et al., 1999; Rauch et al., 2000, 2004; Farago et al., 1996, 1998; Hutchinson et al., 2000; De Vos et al., 2002; Simpson et al., 2001; Rudolph et al., 2006; Haus et al., 2007; Motelica-Heino et al., 2001; Moldovan et al., 2001; Beccaloni et al., 2005) and GFAAS (Zereini et al., 2000; Hodge et al., 1986; Chwastowska et al., 2004; Bosch Ojeda et al., 2003; Gonzalez Garcia et al., 2003; Patel et al., 2000; Enzweiler and Potts, 1995) have found the widest applications in the examination of soil and sediment samples for PGE content.

Sector-field ICP-MS instruments are preferable for the detection of PGEs in soils and sediments. They allowed direct detection of Pt, Pd, and Rh in lake sediments at background levels (0.6 $\pm$ 0.3 ng g^{-1} Pt, 3.0 $\pm$ 1.6 ng g^{-1} Pd, and 0.174 $\pm$ 0.019 ng g^{-1} Rh) after the NiS-FA digestion step (Rauch et al., 2004). Caution in considering results for Pd owing to difficulties in resolving interfering signals is recommended. Chemical separation of Pd from the matrix elements might be necessary. Between 2 and 14 times lower results for Pd in road dust were obtained after preliminary extractive separation of Pd with DDTC than with direct detection by Q-ICP-MS (Djingova et al., 2003a). Two-dimensional chromatography, cation exchange, and sorption onto C18 loaded with *N,N*-diethyl-*N′*-benzoylthiourea, combined with isotope dilution SF-ICP-MS, was applied for Pd determination in soil samples (Rudolph et al., 2006). Isotope dilution in connection with a chromatographic (anion exchange) separation allowed simultaneous determination of Pt and Pd in soil samples (Müller and Heumann, 2000). Errors in the results for Pd in the analysis of sediment samples, 80 ng g^{-1} when using LA-ICP-MS technique, instead of 68 ng g^{-1} after chemical digestion and SF-ICP-MS detection, could occur (Motelica-Heino et al., 2001). Dynamic reaction cells can substantially help with the elimination of some interference with ICP-MS detection of PGEs in soil samples, e.g., by conversion of matrix elements into higher oxides (e.g., $Zr^+ \rightarrow ZrO_{(1-4)}^+$ when using oxygen as a reacting gas (Simpson et al., 2001)).

ET-AAS allowed the determination of Pt, Pd, and Rh in soil samples taken along motorways after preconcentration by NiS-FA (Zereini et al., 2000), Pt and Pd after separation on dithizone sorbent (Chwastowska et al., 2004), Pd after separation and enrichment as Pd(II)-$SnCl_3^-$-*N*-butylacetamide (Patel et al., 2000), and Pt after preconcentration on silica gel loaded with 1,5-*bis*(di-2-pyridyl)methylene thiocarbohydrazide (Bosch Ojeda et al., 2003). Preconcentration on anionic column, Dowex AG-1, preceded the detection of Pt in marine sediments (Hodge et al., 1986). Direct detection of Pt, Pd, and Rh in soil samples after NiS-FA digestion by NAA was possible (Heinrich et al., 1996).

Detailed results for PGE contents in various environmental materials obtained by the discussed techniques are given in Table 1 (please see the supplementary table file on the journal's website).

METHODS OF DETERMINATION OF PLATINUM AND RUTHENIUM IN CLINICAL SAMPLES

Platinum in Clinical Materials

Knowledge about platinum-containing species formed upon interaction of drugs with biomolecules plays a fundamental role in understanding the mechanism of drug action. Enormous efforts have been undertaken to recognize the transport of drugs into cancer cells, activation and accumulation of Pt-complexes used, binding to nucleic acids, and DNA damage. The identification of biotransformation products of drugs in vivo conditions, stability of bio(macro)complexes formed, distribution, bioaccumulation of the drugs in various parts of the organism, and toxicological effects has become a basic requirement for their proper clinical applications and is the subject of numerous analytical studies. Recent overviews of various Pt-drug-biomolecule interactions considering different sample matrices (blood, urine, cell cytosol, DNA) could be mentioned here (Goodisman et al., 2006; Todd and Lippard, 2009; Esteban-Fernández et al., 2010; Crider et al., 2010; Groessl et al., 2010a).

The distribution of drugs in organisms is generally investigated by determination of the total Pt content in physiological fluids and tissues by direct instrumental techniques for elemental analysis. The identification of species of interest requires analytical techniques of superior separation ability and minor impact on their stability. Liquid chromatography and capillary electrophoresis combined with sensitive detectors are most widely used for identification and quantification of metal-biomolecule adducts (Timerbaev et al., 2006a, b; Barefoot and Van Loon,

1996; Yang et al., 2002; Hartinger et al., 2003a; Hartinger and Keppler, 2007; Timerbaev and Keppler, 2007). Mass spectrometry is the most promising detection technique both for elemental (ICP-MS) and molecular (ESI-MS, MALDI-MS) studies (Brouwers et al., 2008). Ion trap electrospray ionization-mass spectrometry (ESI-MS) allowed the identification of four adducts of oxaliplatin with DNA nucleobases (Kerr et al., 2008). A particular suitability of multiple-stage tandem mass spectrometry (MS^n) for structural studies was demonstrated. A preferential binding of oxaliplatin to guanine and adenine in the presence of all four nucleobases was pointed out. Laser ablation ICP-MS allows the examination of the distribution of Pt in tissue samples (Zoriy et al., 2007). Owing to a wide concentration range covered, the ICP-MS technique is applicable to the examination of unexposed organisms as well as those with elevated metal contents, e.g., clinically treated or environmentally exposed. The technique has proved to be the most suitable for the evaluation of physiological levels of Pt in unexposed people, 0.3–1.3 ng L^{-1} in blood (DL of 0.3 ng L^{-1}) (Begerow et al., 1997a), 0.48–7.7 ng L^{-1} in urine (DL of 0.24 ng L^{-1}) (Begerow et al., 1997b), and <DL–0.778 ng g^{-1} in lung, 0.031–1.42 ng g^{-1} in liver, and 0.051–0.422 ng g^{-1} in kidney tissues (DL of 20 pg g^{-1}, 20 pg g^{-1}, and 34 pg g^{-1} of dry mass, respectively) (Rudolph et al., 2005). A detection limit of 26 pg g^{-1} Pt in samples of isolated DNA and exosome fractions from human ovarian and melanoma cancer cell lines was reported (Björn et al., 2007). In tumor tissues the levels of the drug adducts could be relatively higher than in normal tissues, e.g., by a factor of four to five (Hoebers et al., 2006).

Studies on the interaction of Pt complexes with DNA nucleobases (Hann et al., 2001; Iijima et al., 2004; Garcia Sar et al., 2006, 2009), blood and urine proteins (Groessl et al., 2010a; Bell et al., 2006; Ip et al., 2008; Esteban-Fernández et al., 2008; Smith et al., 2002; Oe et al., 2003), hemoglobin (Mandal et al., 2006), and methionine and cysteine (Stefánka et al., 2004) can serve as examples of the applications of liquid chromatography (LC) combined with mass spectrometry. The advantages of HPLC-ICP-MS (extended linear range and superior sensitivity (DL of 0.1 ng mL^{-1} Pt)) over HPLC-MS-MS (DL of 5 ng mL^{-1} Pt) for quantitative determination of the Pt-drug ZD0473 and its related biologically active aqua compounds in biofluids were demonstrated (Smith et al., 2003). The use of dimethylformamide as organic modifier of the mobile phase allowed substantial improvement (36 times) in sensitivity (DL of 0.2 ng mL^{-1}) of the LC-ICP-MS technique in the determination of cisplatin and its monohydrolyzed metabolite in in vitro–grown T289 human malignant melanoma cells (Nygren et al., 2008). Clear evidence of the stability of adducts of cisplatin with blood proteins (transferrin, albumin, and immunoglobulin G) identified by HPLC-ICP-MS and electrospray ionization quadrupole time of flight (ESI-Q-TOF) techniques after tryptic digestion was given (Esteban-Fernández et al., 2008). Different interactions of transferrin and albumin with cisplatin, resulting in the binding of one or four cisplatin molecules, respectively, were revealed. The superiority of LC-ICP-QMS over LC-ESI-TOFMS in terms of sensitivity (by a factor of 100) and uncertainty (5.7% and 23%, respectively) for quantification of carboplatin in urine was demonstrated (Koellensperger et al., 2008). The comparison of different ionization techniques, matrix-assisted laser desorption/ionization (MALDI) and nanoelectrospray (nESI-Q-TOFMS and nESI-ion trap(IT)-MS), showed the advantage of higher sensitivity of nESI-IT-MS over TOF instruments in the examination of the interaction of Pt-drugs with proteins (Hartinger et al., 2007). MALDI-MS was found a useful method for the analysis of metal binding to low molecular proteins. The use of a dynamic reaction cell (DRC) with oxygen as a reaction gas makes the HPLC-ICP-MS technique suitable for the investigation of the reaction of cisplatin with methionine (Stefánka et al., 2004). The adducts formed could be characterized by the determination of Pt:S stoichiometry. The use of oxygen allows eliminating the $^{16}O^{16}O^+$ interference in the detection of sulfur owing to the reaction: $S^+ + O_2 \rightarrow SO^+ + O$. Detection limits of 0.31, 0.25, 3.83, 1.07, 0.56, 0.82, and 2.38 μg L^{-1} for cisplatin, hydrated ions (*cis*-$[PtCl(NH_3)_2(H_2O)]^+$, and (*cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$) and the four identified Pt-adducts with methionine, respectively, were reported.

Capillary electrophoresis combined with specific elemental (ICP-MS) and structural (ESI-MS) detectors is particularly suitable for anticancer metallodrug research due to the possibility examining the reactions under similar to physiological (aqueous media, pH, temperature) conditions. Separation and identification of Pt adducts with DNA nucleotides (Hartinger et al., 2003b; Warnke et al., 2001; Schluga et al., 2005), interactions of cisplatin with oligonucleotides (gel electrophoresis coupled to ICP-MS and MALDI-TOFMS) (Brüchert et al., 2008), binding studies between cisplatin and human serum proteins (Timerbaev et al., 2004), and the determination of intact cisplatin and its hydrolytic metabolites in human serum (Huang et al., 2006) are examples of the application of CE techniques. The first coupling of microemulsion electrokinetic chromatography (MEEKC) with the ICP-MS technique for the separation of Pt(II) and Pt(IV) anticancer drugs and drug candidates has recently been described (Bytzek et al., 2010). The kind of CE-ICP-MS interface can affect the results for the determination of drugs in biological matrices (Moller et al., 2009). An excellent review of the applications of the ICP-MS technique in the analysis of Pt- and Ru-containing anticancer agents focused on the determination of total metal concentrations and the speciation of metal compounds in biological fluids, DNA, and protein adducts is available (Brouwers et al., 2008).

Graphite furnace AAS is also applicable to the determination of the total Pt content in tissues, blood, plasma, plasma ultrafiltrate, and urine (Tibben et al., 2002; Meerum Terwogt et al., 2000; Vouillamoz-Lorenz et al., 2001; Milačič et al., 1997; Brouwers et al., 2005). The technique was found suitable for the determination of Pt in solutions with a very high content of proteins (Einhäuser et al., 1996) and in the complexes with DNA separated by CE (Deforce et al., 1998), as well as for the

investigation of the interaction of Pt-drugs (cisplatin, oxaliplatin, and carboplatin) with DNA, Cd/Zn thionein, and glutathione (Goodisman et al., 2006). It was used for the examination of a profile of the decomposition products of carboplatin stored for 5 to 78 months (Schnurr et al., 2002). The available DL (70 ng L^{-1} Pt) did not allow the determination of a physiological level of Pt in urine samples of unexposed people, even using preliminary liquid-liquid extraction preconcentration (Begerow et al., 1997c).

Adsorptive voltammetry offers the possibility of the determination of low amounts (pg and ng L^{-1}) of Pt in clinical samples. About 20 times better DL than for sector field ICP-MS was reported in the analysis of fish liver and mussel soft tissue (Zimmermann et al., 2001). The technique was found suitable for the examination of long-term, even over 10 years, platinum excretion in patients treated with the drugs (Schierl et al., 1995; Gelevert et al., 2001) and physiological levels of Pt in blood and plasma (Messerschmidt et al., 1992). About 40 times higher than the background level of urinary Pt was revealed eight years after cisplatin therapy (Schierl et al., 1995).

Radiochemical and instrumental NAA were used for quantification of Pt in various tissue samples (DL of 1–2 ng g^{-1}) (Trebert Haeberlin et al., 1987; Esposito et al., 1987; Rietz et al., 2001). Enriched Pt in tumor tissues by a factor of 1.8–3.8 has been shown (Trebert Haeberlin et al., 1987).

Ruthenium in Clinical Samples

Among numerous ruthenium compounds examined as potential antitumor agents the complexes of imidazolium(Im) and indazolium(In): [HIm][*trans*-[$RuCl_4(Im)_2$] (KP418), [HIn][*trans*-$RuCl_4(In)_2$] (KP1019), [HIm][*trans*-$RuCl_4$(DMSO)Im] (NAMI-A), and Na[*trans*-$RuCl_4(In)_2$] (KP1339)] were found to be the most promising cytostatic agents and selected for clinical development (Keppler, 1993; Timerbaev et al., 2006b; Allessio et al., 2004; Kostova, 2006; Ang and Dyson, 2006; Reisner et al., 2008; Levina et al., 2009; Küng et al., 2001). These complexes are the objects of great attention owing to confirmed activity against cisplatin-resistant tumors and relatively smaller side effects. The KP1019 and NAMI-A compounds have successfully finished phase I clinical studies.

Analytical studies on Ru-based drugs are mainly focused on the examination of transport mechanism into cancer cells with plasma proteins (albumin and transferrin) and reactions occurring in the cells (hydrolysis, redox reactions, and binding towards DNA and other target molecules). Hydrated drug species, being a result of loosing chloride ligands, are supposed to be more active towards binding to biomolecules (Bouma et al., 2003; Cebrian-Losantos et al., 2008). Activation of the drug by reduction of Ru(III) to Ru(II), resulting in the labilization of chloro ligands and better accessibility for ligand exchange reaction, is proposed as the mode of action of the compounds used (Hartinger and Keppler, 2007). The explanation of the interaction of active compounds with DNA is fundamental for understanding their biological activity. Analytical techniques of high potential for separation and detection of various drug species formed under physiological conditions, free drugs, and proteins are necessary for such studies. Similar to the examination of Pt-drug biological interactions, hyphenated techniques, mainly LC and CE combined with sensitive detectors, are useful for the examination of the kinetics of the formation of the adducts with biomolecules and their stability and identifying drug binding sites. Instruments employing MS are beneficial owing to better sensitivity and selectivity and the possibility of distinguishing between the intact drugs and their transformation products.

Transport mechanism of the drugs into cancer cells with plasma proteins has been extensively examined. Studies aiming at the revision of earlier results obtained with the use of spectrophotometric detectors by elemental ICP-MS and molecular ESI-MS techniques have been carried out. The ESI-MS technique is particularly useful for such studies (Pongratz et al., 2004). The dominating role of transferrin cycle in drugs transport was established. The synergistic role of bicarbonate anions in effective binding of Ru-based complexes with transferrin can be emphasized. Much faster binding of the complex to transferrin than to albumin was estimated (Timerbaev et al., 2005; Połeć-Pawlak et al., 2006). The corresponding rate constants were determined as 39.5×10^{-4} s^{-1} and 3.3×10^{-4} s^{-1}, respectively (CE-UV) (Timerbaev et al., 2005) and 28.7×10^{-4} s^{-1} and 10.6×10^{-4} s^{-1}, respectively (CE-ICP-MS) (Połeć-Pawlak et al., 2006). It can be noted that the given rate constants were obtained in the absence of bicarbonate ions which were earlier (Kratz et al., 1994; Pangratz et al., 2004) considered necessary for binding of the KP1019 complex by transferrin. Less than 2% of KP1019 was expected to bind to transferrin in human plasma on the basis of the results obtained by two-dimensional size exclusion/anion exchange chromatography coupled to ICP-MS (Sulyok et al., 2005). The dominating role of albumin in binding KP1019 (80–90%) was earlier reported when using HPLC-UV-VIS (Kratz et al., 1994). The nature of the interaction of two complexes, KP418 and KP1019, with human serum albumin and transferrin has also been studied by electron paramagnetic resonance (EPR) (Cetinbas et al., 2010). Strong affinity of NAMI-A to human serum albumin was also confirmed by electrochemical measurements (Ravera et al., 2004). Large protein complexes/aggregates above 700 kDa as initial major binding partners (KP1019 and KP1339) in cytosol, followed by ruthenium redistribution to the soluble protein weight fraction below 40 kDa, were identified by tandem size exclusion chromatography (SEC-SEC) in combination with ICP-MS (Heffeter et al., 2010). Difficulties with detection of the Ru-transfferin adducts in the samples of plasma from patients treated with the drugs generate problems with improving the detection power of the available instrumental techniques.

The examination of the kind and the rate of the interaction of active drug species with DNA is particularly valuable for the explanation of the mode of anticancer action. The advantages of high-performance CE over HPLC (both with diode-array detectors) for studying the interaction between tumor-inhibiting

Ru(III) complexes and nucleotides was demonstrated (Küng et al., 2001). A preference for coordination with guanosine and adenosine monophosphates was established. ESI-ICP-MS is particularly helpful in the examination of adducts formed by Ru active species and nucleotides (Casini et al., 2009; Groessl et al., 2010b). The interaction of Ru- and Pt-based drugs with different double-stranded oligonucleotides by ESI-MS has shown that the extent of adduct formation decreased in the order: cisplatin > oxaliplatin > NAMI-A > RAPTA-T > carboplatin > KP1019 (Groessl et al., 2010b). RAPTA-T [$Ru(\eta^6\text{-}C_6H_5Me)(PTA)Cl_2$] belongs to the other promising antimetastatic ruthenium (Ru(II)-arene complex bearing 1,3,5-triaza-7-phosphaadamantate (PTA) ligands) compounds of confirmed better reactivity and selectivity than platinum (cisplatin, transplatin) complexes in protein binding (Egger et al., 2010).

Direct (only after the dilution of the samples) application of the ICP-MS technique allows the detection of total Ru content in clinical materials. Quantification of 30 ng L^{-1} of ruthenium in plasma ultrafiltrate and urine, and 75 ng L^{-1} of ruthenium in human plasma (150 μL of matrix) by ICP-MS was reported (Brouwers et al., 2007). ET-AAS can also be used for such analysis (DL of 0.85 μmol L^{-1} (plasma and urine) and 0.17 μmol L^{-1} (plasma ultrafiltrate) were reported) (Crul et al., 2001).

It should be emphasized that the number of Ru-complexes investigated for antitumor activity is still increasing. The nature of their biological activity has not been fully recognized.

QUALITY CONTROL IN ANALYSIS OF ENVIRONMENTAL AND BIOLOGICAL MATERIALS FOR THE CONTENT OF PGEs

Reliability of results is the main concern in the analysis of environmental and biological materials for ultra-traces of PGEs. The complexity of the examined samples, difficulties with quantitative digestion, and elimination of numerous interfering effects with the detection of the metals by instrumental techniques make the accuracy assessment of the results of great importance. Each step of the analytical procedure used, from sampling to detection, can provide severe sources of errors. High heterogeneous distribution of PGEs and low concentrations being determined, in particular in environmental samples, require special attention during sampling and sample handling. Losses of the analytes or contamination during sample preparation steps can occur. The choice of the appropriate analytical procedure is a key factor affecting the quality of the results.

The examination of certified reference materials (CRMs), interlaboratory studies, comparison of the results obtained by different analytical procedures, and recovery studies are generally used for the evaluation of the quality of results. The use of CRMs in the analysis of PGE samples is considerably restricted owing to the limited number of materials available. BCR-723 road dust, containing 81.3 ± 2.5 μg kg^{-1} Pt, 6.1 ± 1.9 μg kg^{-1} Pd, and 12.8 ± 1.3 μg kg^{-1} Rh, is currently the only environmental certified reference material for PGEs, available since 2001 (Zischka et al., 2002; Sutherland, 2007). It is widely used for the evaluation of the quality of the results in the analysis of dust, particulate airborne matter, soil, and sediment samples. Numerous CRMs existing for geological materials containing PGEs at μg g^{-1} concentrations, e.g., SARM-7 (3.740 ± 0.045 μg g^{-1} Pt, 1.530 ± 0.032 μg g^{-1} Pd, and 0.240 ± 0.013 μg g^{-1} Rh), do not cover the concentration levels of the metals in environmental materials (ng g^{-1} and pg g^{-1}). A lack of reference materials for biological and environmental matrices other than road dust origin is a problem. Calibration procedures, such as standard addition, or isotope dilution when using the ICP-MS technique, are recommended when the nature of the matrix is unknown or cannot be easily matched with the standards. Standard addition is often used in the analysis of biological samples. Standards simulating biological matrix, e.g., plasma, ultrafiltrate, or lung fluids, are recommended instead of pure solutions. Comparison of the results obtained by different analytical techniques or interlaboratory studies is strongly suggested.

Significant problems are encountered in speciation analysis of PGEs in environmental and biological materials. Conditions for stability of various analyte forms and their identification are required. The combination of different analytical techniques, e.g., HPLC-ICP-MS and HPLC-MS/MS (Smith et al., 2003), ESI-MS and MALDI-MS (Hartinger et al., 2007), MEKC, NMR, and MS (Schluga et al., 2005), AAS, ESI-MS, and CD spectroscopy (Pongratz et al., 2004), SEC-IC-ICP-MS and LC-ESI-MS (Sulyok et al., 2005), and SEC-ICP-MS and ESI-MS (Esteban-Fernández et al., 2007), for confirmation of the results in speciation analysis is advantageous.

CONCLUSIONS

The determination of ultra-traces of PGEs in environmental and clinical materials is a challenge to analysts. Extremely low concentrations being determined and serious interference from matrix components substantially limit the possibility of direct applications of the available instrumental techniques to the detection of the metals in environmental samples. An adequate knowledge of biological activity of Pt- and Ru-based complexes used in chemotherapy requires the identification and the detection of various drug species formed under physiological conditions. Ensuring stability of particular species formed, distinguishing between free drugs and various drug transformation products, as well as sufficient detection limits, are fundamental requirements for analytical procedure applied.

Mass spectrometry combined with element (ICP-MS) and molecular (ESI-MS, MALDI-MS) specific detectors is the most attractive instrumental technique for the examination of various environmental and clinical materials. The appropriate use of the technique requires recognition of the kind and the amount of interfering effects and a choice of methods for their elimination. This is particularly important in the analysis of environmental samples, which can contain a large excess of matrix elements contributing to the analyte signals. Various sample introduction techniques provide possibilities of improving the selectivity of PGE detection by the ICP-MS

technique. Chemical separation of interfering elements is usually required in the analysis of more complex materials, e.g., soils and sediments. Careful consideration of the results, in particular for Pd and Rh, due to difficulties with the elimination of spectral interference, is recommended. Mass spectrometry combined with a suitable ionization source is particularly useful as the detector for separation techniques, HPLC and CE, widely used in speciation analysis. Interest in speciation analysis for characterizing naturally occurring processes resulting in the formation of species of higher bioavailability, bioaccumulation, and biological activity is still growing. Improving the detection power of coupled techniques to be able to examine biologically active species in vivo conditions is a challenge.

Electrothermal-AAS, AV, and NAA are other instrumental techniques applied in the analysis of environmental and biological samples for PGE contents. Voltammetric techniques offer extremely low DLs. Their direct applications are, however, limited to relatively simple and easily digested biological matrices. High interfering effects and accessibility may restrict the practical use of ET-AAS and NAA techniques, respectively.

The quality of the results requires special attention. The representativeness of the examined sample, the kind of digestion procedure used, and methods of the elimination of interference affect the quality of the results obtained by all instrumental techniques. The evaluation of the results by the use of different analytical procedures or interlaboratory studies is strongly suggested, in particular in view of the limited number of CRMs of adequate matrix and PGE concentration ranges.

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