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Technologies and Techniques Continue Relentless Advance

By Gregory C. Janis

As technology everywhere advances relentlessly and challenges almost daily our concept of small enough, fast enough, and good enough, innovations are constantly improving the tools of laboratory testing.

In the past decade, the performance of laboratory equipment has improved by orders of magnitude (as measured by lower limits of quantitation), while the instruments have become smaller, faster, and smarter. Instruments that once filled rooms are now benchtop; functional lower limits of quantitation have dropped to single pg/mL levels.

HPLC-MS/MS and UPLC

Over the past decade, high performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) has emerged as the workhorse of analytical, clinical, and forensic toxicology laboratories. In some arenas the technique has largely replaced both traditional HPLC and gas chromatography/mass spectrometry (GC/MS). Although HPLC and GC/MS will always have a role in an analytical laboratory, HPLC-MS/MS has become pivotally involved with most recent developments in the analytical, clinical, and forensic field. GC/MS innovation has certainly continued, but it is a significantly more mature technique, so the advancements appear at a less explosive rate. Both the relative infancy of LC/MS and the pharmaceutical industry’s nearly complete adoption of the technique have propelled its advancement.

Much press has been devoted to the latest incarnation of HPLC, ultra HPLC (UPLC). The technique utilizes HPLC columns with particle sizes of less than 2 µm in diameter. The decrease in particle size dramatically increases chromatographic efficiency. The cost of the efficiency gain is a significant in-

crease in column back pressure; UPLC pressures are routinely in excess of 600 bar (8700 psi). All major HPLC manufacturers now produce systems designed to withstand the pressures generated by UPLC columns, and most HPLC column manufacturers produce sub-2-µm column packing materials capable of withstanding pressures up to 1000 bar (14500 psi).

The efficiency gain translates to chromatographic peaks that are only a few seconds wide and allows some remarkable chromatographic separations not previously possible in HPLC. However, it is the speed of the technique that is primarily driving its adoption. The efficiency gains allow real-world analytical run times to be cut in half or more, decreasing turnaround times and theoretically doubling the capacity of the instrumentation.

Triple quadrupole MS

Triple quadrupole mass spectrometers, which are the most common type of mass spectrometer attached to an HPLC, have similarly evolved. The latest generation of triple quadrupole instruments use nonlinear flight paths that not only reduce background noise but also allow the instruments to maintain a footprint similar in size to that of a contemporary benchtop GC/MS. In addition, the speed of triple quadrupole mass spectrometers has dramatically increased from typical dwell times on the order of a few 100 milliseconds to less than 5 milliseconds. This speed allows the instruments to fully define the narrow peaks generated by a UPLC system; it also allows the mass spectrometer to rapidly cycle between many monitored transitions. With these in-

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Mistletoe Toxicity Appears to Be Low and Pose Little Danger

By Donald L. Frederick

As the holiday season, with all its decorations and seasonal music, rolls into the New Year, we pass through the “rite of the mistletoe.” Mistletoe is a big deal for many people, with entire websites dedicated to its lore and the latest news on the current mistletoe crop (1). The tradition of kissing under the mistletoe is probably several hundred years old, but was popularized in the United Kingdom during the 18th century.

Mistletoe is the common name for a group of partially parasitic plants in the order Santalales that grow affixed to the branches of trees or shrubs. In Europe and the United Kingdom, the main species is *Viscum album*. In the United States, there are many species in the genus *Phoradendron*, with *P. flavescens* the most common species sold commercially. American mistletoe is generally woody, with branches 10–80 centimeters long. The foliage is dichotomously branching, with opposite pairs of leaves that are fairly large (2–5 centimeters long) and green. The leaves are fully photosynthetic in some species, but minimally so in others. The plant draws its mineral and water needs from the host tree, as well as some of its energy needs. The fruit is a white or yellow berry containing several seeds embedded in the sticky, glutinous fruit pulp.

Toxicity

The toxicity of mistletoe has been known for centuries. In Nordic mythology, the famous death of Balder was caused by an arrow of mistletoe. The European species *V. album* has been extensively studied, with many of the toxins isolated and characterized. The toxic components are found on all parts of the plant, including stems and berries. One of the toxins is viscumin, a lectin that has been shown to be a type II ribosome-inactivating protein. Several research groups have isolated a series of these lectins and found some homology to other galactose-specific lectins such as ricin and abrin. The earliest European literature describes several cases of poisoning, but gives few details.

A review of the cases of mistletoe ingestions involving American species indicates that their toxicity is limited. In 1986, 14 cases were reviewed (2), and in 1996, another 92 cases were summarized (3). In the following year, 1754 exposures recorded by the American Association of Poison Control Centers were published in the *American Journal of Emer-*

gency Medicine (4). Pediatric exposures accounted for 92% of the exposures, with more than 94% listed as accidental. The authors found no reported differences in outcomes between the treated and untreated groups. Only about 5% of the exposures resulted in symptoms, with the most common being mild gastrointestinal effects. No fatalities were reported in any exposures to *Phoradendron*.

Mistletoe extracts and teas have been used for many years for a variety of ailments. Recently, extracts have been used as complementary and alternative medicines in various cancers (5–7). Over the past 15 years much basic and clinical research has been conducted on the use of *V. album* extracts in cancer therapy (8). The studies have found improvement in the quality of life, but the data on prolonged survival are conflicting. Clinical trial data regarding the toxicity and pharmacokinetics of mistletoe components with known in vitro or preclinical activity are lacking.

Thus, this holiday season, if you kiss under mistletoe, the danger posed by the mistletoe is probably much less than your risk of exposure to the H1N1 virus.

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Carbon Monoxide Can Kill At Any Season of the Year

By Michael A. Wagner

At the change from daylight to standard time, health and fire departments campaign to remind us to replace the batteries in the smoke detectors and carbon monoxide detectors throughout our homes. To prepare for cold weather, we are winterizing our homes by adding insulation, replacing weather stripping around the doors, and perhaps sealing leaky windows with plastic covering. These techniques are important to maintain comfort and fuel efficiency, but sealing a house tightly can place a home at risk for carbon monoxide (CO) accumulation if we fail to conduct other winterizing precautions, such as checking the furnace for poor air circulation and poor filtration, and checking for leaks in the heating and cooling system. In addition, other faulty heating equipment (space heaters, water heaters, and stoves) that use carbonaceous fuel sources (wood, coal, kerosene, and propane) can be sources of carbon monoxide gas build-up. Attached garages even pose the potential danger of exposure to automobile fumes.

These are the classic winter carbon monoxide sources that place one at risk of exposure if they are not properly managed, but there are sources of carbon monoxide poisoning in other seasons as well. These include exposure to carbon monoxide while

boating, including water skiing or even teak surfing (being dragged behind the boat while hanging onto a platform).

Sign and symptoms

Carbon monoxide is often referred to as a silent killer because it is a colorless, tasteless, and odorless gas. Sources of carbon monoxide can vary widely, but it is commonly formed from incomplete combustion processes or from exposure to organic chemicals. Unintentional carbon monoxide exposure leads to about 500 deaths and about 15,000 visits to the emergency room annually.

Carbon monoxide binds to the heme group in hemoglobin with an affinity exceeding that of oxygen by 200 to 250 times. Thus, carbon monoxide prevents oxygen transport and exchange and leads to oxidative stress and ischemic injury. Carbon monoxide forms not only carboxyhemoglobin but also binds to myoglobin and other compounds containing heme-moieties. These complexes have negative effects on cellular energy metabolism.

The symptoms of carbon monoxide poisoning include headache, nausea and vomiting, and central nervous system depression. When a patient presents with altered mental state or coma combined with acidosis, the differential diagnosis should consider carbon monoxide inhalation as a possible cause (Table 1). Other combustion products that could be involved in the exposure include cyanide and hydrogen sulfide. Highly profused organs are affected the most,

Table 1. Physiological Effects of Carbon Monoxide Exposure (1, 2)

CO in atmosphere (ppm)	Time	COHb in blood (%)	Signs and symptoms
10	—	2	No appreciable effects
70	—	10	No appreciable effects except shortness of breath on vigorous exertion; dilation of cutaneous blood vessels
120	—	20	Shortness of breath on moderate exertion; occasional headache
220	2 – 3 h	30	Headache; irritability; easily fatigued; disturbed judgment; dizziness; dimness of vision
350 – 520	1 – 2 h	40 – 50	Headache; confusion; collapse; fainting on exertion
800 – 1200	25 min – 45 min	60 – 70	Unconsciousness; intermittent convulsion; respiratory failure; death if exposure is long and continued
1600 – 1950	10 – 20 min	80	Rapidly fatal
3200	5 – 10 min		Fatal
6400	1 – 2 min		Fatal
12,800	1 – 3 min		Fatal

and in postmortem examinations a characteristic cherry red color can be remarkable.

Case report: home exposure

A 53-year-old father and his 16-year-old son lived in a New Hampshire farmhouse. On a day in late May, the father arrived at work at 6:00 a.m., but felt ill and left after 20 minutes. He called the son's school at 8:30 a.m. to say that the son was ill and would not attend that day. The father and son were seen two days later at a local store. They did not answer several telephone calls in the following days and did not show up for a dinner invitation by relatives. The property caretaker went to investigate and found two decomposing bodies upstairs. The father had more advanced decomposition than the son. Postmortem autopsy revealed the classic cherry red discoloration of the skin, appendages, and organs.

The local fire department measured carbon monoxide levels at 12 ppm downstairs, at 54 ppm in the son's bedroom, at 217 ppm in the father's bedroom, and at 540 ppm in the basement. Inspection of the premises the following morning revealed that the chimney pipe was corroded and dislodged from the propane furnace. Carbon monoxide had been venting directly into the house. These dangerous gas levels highlight the need for care givers, investigators, and first responders to consider their own safety before entering such a building (Table 2). They should take precautions such as air monitoring of the scene and noninvasive blood monitoring of personnel (3).

Case reports: exposure from house boats

A houseboat's generator compartment sits directly under the rear deck and is exhausted out the

Table 2. Workplace standards for CO exposure

American Conference of Governmental Industrial Hygienists

Time-weighted average for 8-hour shift (TWA): 25 ppm
Short-term exposure limit: 400 ppm

National Institute for Occupational Safety and Health

TWA: 35 ppm
Immediately dangerous to life and health: 400 ppm

Occupational Safety and Health Administration

TWA: 50 ppm
Permissible exposure limit: 200 ppm

boat's rear, directly underneath the swim platform. Carbon monoxide concentrations as high as 85,000 ppm have been measured at the exhaust point, and many fatalities have been reported (4).

A 57-year-old male exposed for just minutes while diving to free an anchor had a carboxyhemoglobin (COHb) level of 22%. A 64-year-old male exposed for less than 20 minutes while cleaning the scum line had a COHb level of 62%. A 12-year-old exposed for 30 minutes to deck fumes had a COHb level of 54%. An investigation of the scene related to this last case revealed open air CO concentrations at the stern of 7000 to 10,000 ppm. Ten feet away, the CO concentration was 200 ppm.

Case reports: exposure from boat engines

Boats with propulsion engines can also expose people to dangerous levels of carbon monoxide (Figure 1). Propulsion engines can produce as much as 60,000 to 80,000 ppm of CO. The exhaust port is at the rear of the boat, and carbon monoxide becomes more concentrated the closer one is to the ex-

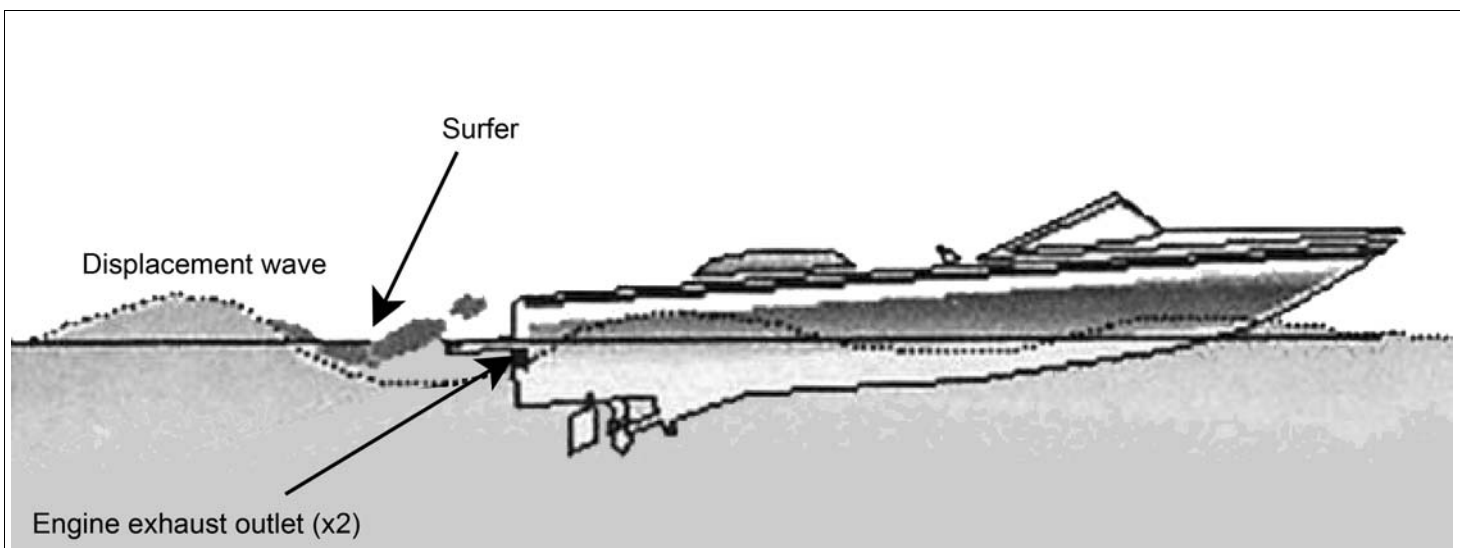


Figure 1. Teak surfing or dragging (Reprinted with permission from [3].)

haust port. The rear of the boat is the same area where passengers sit on deck and where swim platforms and teak boards are located. Carbon monoxide tends to follow the boat in times of travel and concentrate during idling periods, so one can be more at risk for exposure in the water or on deck than in a home.

Whether passengers are fishing, teaking/dragging, skiing, or just sitting near the rear of the boat socializing, they can be at significant risk, as illustrated by several reported fatalities (4). A 62-year-old who died sitting on a swim platform had a COHb level of 89%. After five minutes of teak surfing, an 18-year-old male sank and drowned. When his body was recovered two days later, his COHb level was found to be 57%. Two nine-year-old girls were playing near a boat generator's exhaust for 10 minutes. One girl was found unresponsive with an HbCO level of 15%. The other girl had drowned, with an HbCO level of 39%.

Not all boaters' headaches are from sun exposure, dehydration, or seasickness, and not all bodies found in the water are there solely because of drowning. In these cases, the potential role of carbon monoxide as a causative agent should be considered, especially in cases of apparent drowning.

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New Technologies

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struments, quantitative assays that measure tens or even hundreds of compounds in less than 10 minutes can be created.

The triple quadrupole mass spectrometer remains the most versatile quantitative mass spectrometer available. However, HPLC systems connected to other mass spectrometer designs are becoming more common. Quadrupole-linear ion traps (Q-traps), quadrupole-time of flight (Q-TOF), and Orbitrap mass spectrometers all have advantages over triple quadrupole instruments for some applications, but these instruments have not yet been widely exploited in the clinical and forensic area.

Overcoming ion suppression

LC-MS/MS gained prominence because of its selectivity and ability to measure compounds possessing at least limited water solubility in an underivatized state. The power of LC-MS/MS has allowed laboratories to greatly simplify their sample extraction and chromatographic procedures. However, experience has shown that sample processing and good chromatography are essential to a successful LC-MS/MS method because of the lingering specter of ion suppression.

Ion suppression is the phenomenon in which co-eluting matrix components alter the ionization efficiency of analytes of interest and affect the ability to detect and quantify the analytes. Although isotopic internal standards can minimize the impact of ion suppression in a quantitative bioanalytical assay, matrix effects can still have a significant negative impact on the ability of an assay to detect and quantify analytes at low levels.

Phospholipids have been identified as the likely perpetrators in most instances of bioanalytical ion suppression in blood and plasma samples. Solid-phase extraction vendors have responded with protein precipitation plates containing packing materials designed to remove or reduce phospholipids in the clarified sample. Samples are simply mixed with organic solvents and passed through the lipid depletion material.

Lipid-depletion columns or plates can remove enough phospholipids to render ion suppression minimal. However, a careful investigation must be performed to ensure that the lipid-removal procedure does not significantly impact the recovery of the analytes of interest. The techniques incorporating lipid-depletion columns are relatively simple to use, but are significantly more expensive and complex than sim-

ple protein precipitation methods (also known as dilute-and-shoot).

Sample preparation

Liquid-liquid extraction can eliminate most matrix effects, with the flexibility to ensure reasonable recovery of the analytes of interest. The technique's low cost, flexibility, and relative simplicity make it very appealing. However, it falls short in a high-throughput environment because of its high labor requirements and the difficulties of scaling the technique to accommodate large numbers of samples.

Both scale-up and automation are better accomplished using solid-phase extraction (SPE) columns or 96-well plate arrays containing SPE materials. Here again, lab supply vendors have attempted to address this need with the refinement of supported liquid extraction. The technique uses diatomaceous earth or a similar solid support packed into either individual SPE cartridges or well plates. The aqueous sample is loaded onto the column and allowed to disperse into an extremely thin film covering the surface of the support. The aqueous sample eventually becomes adsorbed onto the surface of the solid support. A water-immiscible, organic extraction solvent is then introduced into the column, and analytes are desorbed into the organic solvent. The high surface area of the solid support allows for a relatively fast (on the order of 10 minutes) and efficient partition extraction process. The column effluent is then dried and analyzed using the instrumental method of choice.

The technique is less costly and less complex than most SPE procedures, while maintaining ease of automation and scalability, especially when used in a 96-well plate format. Some caution must be exercised when evaluating supported liquid extraction materials because quality and consistency vary widely among manufacturers.

On-line sample preparation

The gold standard for both automation and cleanliness of sample preparation currently resides with on-line extraction technology, techniques that produce very clean samples prior to chromatographic analysis without significantly increasing the required labor beyond a simple dilute-and-shoot procedure. These methodologies essentially employ two HPLC systems that process a sample in sequence. The first HPLC system performs a sample clean-up step akin to SPE, eluting salts, proteins, and other potentially interfering compounds to waste while retaining the analytes of interest. The flow path is then switched and the analytes are eluted from the prep column onto the analytical column,

where the second HPLC system performs traditional LC prior to MS detection and analysis.

The technique produces very clean sample extracts free of most matrix effects. Precise control of the system components allows for elution of one component while the second LC component is in a re-equilibration or loading cycle. As a result, cycle times are generally limited only by the time elapsed while acquiring data from the final chromatographic analysis. Homemade systems or purpose-designed commercial systems are in place at a number of laboratories and are extensively used for their ability to rapidly and efficiently process large numbers of samples.

Novel mass-spectral methodologies

Some recently developed, exciting techniques, which are still being explored for clinical and toxicological testing, forgo the use of a chromatographic system prior to mass spectral analysis. The related techniques of desorption electrospray ionization (DESI) and direct analysis in real time (DART) introduce the sample directly into the source of the mass spectrometer at atmospheric pressure.

In DESI, the charged droplets of an electrospray stream are aimed at an analytical target or sample source. Ions are then generated from the surface of the target and drawn into the mass spectrometer. The resulting ionization spectra are similar to those generated by normal electrospray ionization, generating multiple-charged proteins and peptides and single-charged pseudomolecular ions (when small molecules are being analyzed).

The technique has proven to be well-suited for detecting drug or explosive residues left on the surface of paper, skin, and other solid or semi-solid materials (1). It also has gained acceptance as a tool for mass spectral imaging on tissue slices for detecting localized differences in levels of proteins, peptides, and small molecules (2). As intriguing as DESI is, issues remain as to its potential for electrospray ionization suppression and difficulties surrounding the appropriate use of internal standards when performing quantitative analysis.

DART is similar to DESI from a procedural perspective, but ions are generated without the use of a liquid solvent. A gas stream is passed through a high electric potential, creating a glow discharge and resulting in the formation of charged particles and excited-state molecules (metastables). Charged particles are electronically filtered out, and the spray of metastables is directed at the sample target, where they interact with and ionize molecules on the surface of the sample. Ejected ions are then drawn into the mass spectrometer.

The DART source mainly produces $[M + H]^+$ or $[M - H]^-$ pseudomolecular ions, which are best analyzed with information-rich, high-resolution mass spectrometers or tandem mass spectrometers.

DART has been successfully used for analyzing liquid biological samples for drugs and toxins (3). A sampling probe (as simple as a pipette tip or glass rod) is momentarily placed into the liquid sample. The probe is then inserted into the DART source. Generated ions are detected and quantified in the mass spectrometer. The technique has also been successfully used as a quick and simple method for detecting counterfeit pharmaceuticals, allowing mass spectral analysis without sample preparation. This technique is promising, but its functional sensitivity may need enhancement before it will gain widespread acceptance.

Alternative matrices and sample types

As MS-based techniques become increasingly sensitive, the natural progression is to promote smaller and smaller sample volumes. A few laboratories are taking advantage of the reduced sample volume requirements by employing dried blood spots (DBS) for drug and toxin monitoring. Although the practice is widely used in testing for inborn errors of metabolism in neonates, there is increased interest in the use of DBS for drug quantitation. DBS testing has been investigated for use in pain management and compliance drug testing, therapeutic drug monitoring, and drug development and clinical trials applications.

Although this sampling method appears to hold promise for therapeutic drug monitoring, technical and interpretive issues remain. The small sample volume of a DBS (<10 μ L) requires extremely sensitive methodologies to accurately quantify low-level drugs of interest. The impact of nonhomogeneous specimens is also a concern.

The most significant hurdle facing the acceptance of DBS testing lies in the interpretation of the results generated using a nonstandard sample type. Ideally, a new sample type should result in the generation of new, sample-specific reference ranges, but practical limitations inhibit the generation and compilation of this large body of work. Instead, attempts are being made to correlate DBS results to the values generated in plasma or serum by applying a normalization factor, although a correlation of this type may not be possible for all drugs.

To date, a wide variety of tests have been successfully performed on dried blood spots. To name only a few, the list includes pharmacokinetic testing for preclinical and clinical drug development, and monitoring assays for drugs of abuse, lead, vitamin

A, vitamin D, antiepileptic drugs, and immunosuppressants (4, 5). Currently, most DBS analyses rely on LC-MS/MS analytical techniques, but DESI and DART appear naturally suited for DBS analyses.

Recent technological advances have made it possible to investigate alternate sample types (such as DBS) for therapeutic drug monitoring and forensic testing. Although these new and refined techniques allow clinical and forensic laboratories to generate better data faster and with less labor, the field will continue to apply technological advancements creatively to allow analytical testing in ways not previously possible.

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New Principles of Forensic Toxicology Edition Published

The third edition of the classic, best-selling textbook, *Principles of Forensic Toxicology*, includes new chapters on non-narcotic analgesics and antihistamines, as well as a number of updated chapters covering mass spectrometry, cocaine, cannabis, neuroleptics, opioids, inhalants, and much more.

Since the publication of the first edition in 1999, the book has been used extensively for teaching students taking a one-semester course in forensic toxicology and has found its way to the reference shelf of a great many laboratorians.

The first section provides an introduction to postmortem forensic toxicology, human performance forensic toxicology, forensic drug testing, and pharmacokinetics and pharmacodynamics.

The second section is devoted to analytical principles, including both theory and applications. Meth-

odologies covered include specimen preparation, spectrophotometry, chromatography, immunoassay, mass spectrometry, and methods validation.

The third section covers commonly encountered analytes, including alcohol, benzodiazepines, GHB, miscellaneous central nervous system depressants, opioids, cocaine, cannabis, amphetamines/sympathomimetic amines, hallucinogens, anticonvulsants, antiarrhythmics, antidepressants, antihistamines, neuroleptics, non-narcotic analgesics, carbon monoxide, cyanide, inhalants, and metals.

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