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Introduction

"Food safety is a fundamental need for life, and ideally, humans would be trusted to follow the moral imperative set into laws designed to protect our ecosystem and produce safe food for consumption. However, human nature and past transgressions have demonstrated that testing is needed to verify good agricultural and food safety practices."

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Detailed knowledge of the chemical processes in plants, animals, and in our environment with air, water, and soil, about the safety of food and products, has been made possible only through the power of modern instrumental analysis. In an increasingly short time span, more and more data are being collected. The detection limits for organic substances are down in the attomole region, and counting individual molecules per unit time has already become a reality. In food safety and environmental analysis, we achieve measurements at the level of background contamination. However, samples subjected to chemical trace analysis carry high matrix. With the demand for decreasing detection limits by legal regulations, in the future effective sample preparation and separation procedures in association with highly selective detection techniques will be of critical importance for analysis. In addition, the number of substances requiring detection is increasing, and with the broadening possibilities for analysis, so is the number of samples. Even there is the concern of "the inadequacy of current regulations in effectively controlling food contact materials (FCM)" for food safety (Diaz-Galiano *et al.*, 2024). The increase in analytical sensitivity is exemplified with the persistent organic pollutants (POPs) in the case of the "dioxins" with 2,3,7,8-tetrachlorodibenzodioxin (TCDD), the most potent cancer-promoting and teratogenic congener of the polychlorinated dibenzodioxins (PCDDs), still continuously analyzed as contamination in food and feed (Table 1.1).

Capillary gas chromatography with mass spectrometry detection (GC-MS) is today the most important analytical method in organic chemical analysis for the determination of individual low molecular substances in complex mixtures. Mass spectrometry (MS) as the detection method gives the most meaningful data, arising from the direct determination of the substance molecule or of fragments. The

Handbook of GC-MS: Fundamentals and Applications, Fourth Edition. Hans-Joachim Hübschmann.

Table 1.1 Sensitivity progress in mass spectrometry.

Year	Instrumental technique	Limit of detection (pg)
1967	GC-FID (packed column)	500
1973	GC-MS (quadrupole, packed column)	300
1976	GC-MS-SIM (magnetic instrument, capillary column)	200
1977	GC-MS (magnetic sector instrument)	5
1983	GC-HRMS (double focusing magnetic sector MS)	0.15
1984	GC-MSD/SIM (quadrupole mass selective detector)	2
1986	GC-HRMS (double focusing magnetic sector MS)	0.025
1989	GC-HRMS (double focusing magnetic sector MS)	0.010
1990	GC-HRMS required for PCDD/Fs by the US EPA	Method 1613 Rev.A
1992	GC-HRMS (double focusing magnetic sector MS)	0.005
2006	GC×GC-HRMS (using comprehensive GC)	0.0003
2010	Cryogenic zone compression (*t*-CZC) GC-HRMS	0.0002
2011	*t*-CZC GC-HRMS reports low attogram levels in serum (Patterson, 2011; Patterson *et al*., 2011)	<0.0001
2014	GC-MS/MS EU approval for PCDD confirmation in food	EU No. 589/2014
2017	GC-Orbitrap reports U.S. EPA 1613 compliance	0.0001
2018	GC-MS/MS reports low femtogram sensitivity	0.0006
2018	APGC-MSMS reports attogram LODs in fly ash	0.0001

APGC, atmospheric pressure gas chromatography; t-CZC, time controlled cryogenic zone compression; FID, flame ionization detector; GC, gas chromatography; HRMS, high resolution mass spectrometry; LOD, limit of detection; MS, mass spectrometry; MS/MS triple quadrupole analyzer; MSD, mass selective detector; SIM, selected ion monitoring; and US EPA, United States Environmental Protection Agency.

results of MS are therefore used as a reference for other indirect detection processes and finally for confirmation of the facts. The complete integration of MS and gas chromatography (GC) into a single GC-MS system has shown itself to be synergistic in every respect.

It was Fred W. McLaffert who pioneered the technique of coupling a gas chromatograph with a mass spectrometer with Roland Gohlke at Dow Chemical Co., developing a GC-Time-of-Flight (TOF)-MS instrument "capable of rapidly characterizing organic chemical mixtures boiling below 350 °C" (Gohlke 1959). Still at the beginning of the 1980s, MS was considered to be expensive, complicated, and time-consuming or personnel-intensive. At the beginning of the 1990s, MS became more widely recognized and furthermore an indispensable detection method for GC. There is now hardly a GC laboratory which is not equipped with a GC-MS system. The simple construction, clear function, and an operating procedure, which has become easy because of modern computer systems, have resulted in

the fact that GC-MS is widely used alongside traditional spectroscopic methods. The universal detection technique, together with high selectivity and very high sensitivity, has made GC-MS indispensable for a broad spectrum of applications. With recent developments, even higher selectivity is provided by the structure selective MS/MS and the elemental formula providing accurate mass technologies for modern multi-residue methods with short sample preparation and clean-up steps. Benchtop GC-MS systems have completely replaced in many applications the stand-alone GC with selective detectors. GC-MS/MS has found its way to routine replacing many single quadrupole systems today, and accurate mass detection follows on its heels.

The control of the chromatographic separation process still contributes significantly to the exploitation of the analytical performance of the GC-MS system (or according to Koni Grob: "Chromatography takes place in the column!"). The analytical prediction capabilities of a GC-MS system are, however, dependent upon mastering the spectrometry. The evaluation and assessment of the data are leading to increasingly greater challenges with decreasing detection limits and the increasing number of compounds sought or found. As quantification is the main application in trace analysis today, the appropriate data processing requires additional measures for confirmation of results provided by mass spectrometric methods.

The high performance of GC lies in the separation of substance mixtures and providing the transient signals for data deconvolution. With the introduction of fused silica columns, GC has become the most important and powerful separation method of analyzing complex mixtures of products. GC-MS accommodates the current trend toward multi-methods or multi-component analyses (e.g. of pesticides, environmental contaminations, fragrances, drugs, and beyond) in an ideal way. Even isomeric compounds, which are present, for example, in essential oils, metabolic profiling, polychlorinated biphenyls (PCBs), or dioxins, are separated by GC, while in many cases their mass spectra are indistinguishable. The high efficiency as a routine process is achieved through the high speed of analysis and the short turnaround time and thus guarantees high productivity with a high sample throughput. Adaptation and optimization for different tasks only require a quick change of column. In many cases, however, and here, the analyst relies on the explanatory power of the mass spectrometer, one type of medium polar column can be used for different applications by adapting the sample injection technique and modifying the method parameters.

The area of application of GC and GC-MS is limited to substances that are volatile enough to be analyzed by GC. The further development of column technology in recent years has been very important for application to the analysis of high boiling compounds. Temperature-stable phases now allow elution temperatures of up to 500 °C for stable compounds. A pyrolizer in the form of a stand-alone sample injection system extends the area of application to involatile substances by separation and detection of thermal decomposition products. A typical example of current interest for GC-MS analysis of high boiling compounds is the determination of polyaromatic hydrocarbons, which has become a routine process using the most modern column material.

The coupling of GC with MS using fused silica capillary columns has played an important role in achieving the current high performance level in chemical analysis. In particular in the areas of environmental analysis, analysis of residues, and forensic science, the high information content of GC-MS analyses has brought chemical analysis into focus through, sometimes, sensational results. For example, it has been used for the determination of process contaminants in food and feed or the accumulation of persistent organic pollutants in the food chain. With the current state of knowledge, GC-MS is an important method for monitoring the introduction, the location and fate of man-made forever-chemicals in the environment, foodstuffs, chemical processes, and biochemical processes in the human body. GC-MS has also made its contribution in areas such as the atmospheric ozone depletion, the safeguarding of quality standards in foodstuffs production, in the study of the metabolism of pharmaceuticals or plant protection agents, or in the investigation of polychlorinated dioxins and furans produced in certain chemical even natural processes, to name but a few.

The technical realization of GC-MS coupling occupies a very special position in instrumental analysis. Fused silica columns are easy to handle, can be changed rapidly, and are available in many high quality forms. New microfluidic switching technologies extend the application without compromising performance for flow switching or parallel detection solutions. The optimized carrier gas streams show good compatibility with mass spectrometers, which is true today for both carrier gases, helium and hydrogen. Coupling can therefore take place easily by directly connecting the GC column to the ion source of the mass spectrometer.

The obvious challenges of GC and GC-MS lie where actual samples contain involatile components (matrix). In this case, the sample must be processed before the analysis appropriately, or suitable column-switching devices need to be considered for backflushing of high boiling matrix components. The clean-up is generally associated with the enrichment of trace components and the separation from incompatible matrix. In many methods, there is a trend toward integrating sample preparation and enrichment in a single instrument. Headspace and purge and trap techniques, thermodesorption, or the micro-SPE clean-up and solid phase microextraction (SPME) are coupled online with GC-MS and integrated into the data systems for seamless control.

Future developments will continue with green analytical chemistry in mind, miniaturized, highly productive with automated sample preparation for multi-compound trace analysis and quantitation of regulated target analytes. In addition, to comply with the aspects of food safety and product safety requirements, non-targeted analytical techniques for the identification of potentially hazardous contaminants will evolve applying combined full scan and accurate mass capabilities.

1.1 The Historical Development of the GC-MS Technique

The foundation work in both GC and MS, which led to the current realization, was published at the end of the 1950s. At the end of the 1970s and the beginning of the 1980s, a rapid increase in the use of GC-MS in all areas of organic analysis

began. The instrumental technique has now achieved a mature level for the once much-specialized operation to become an indispensable routine analysis method.

1910: The physicist J.J. Thompson developed the first mass spectrometer and proved for the first time the existence of isotopes (^{20}Ne and ^{22}Ne). He wrote in his book Rays of Positive Electricity and their Application to Chemical Analysis: "I have described at some length the application of positive rays to chemical analysis: one of the main reasons for writing this book was the hope that it might induce others, and especially chemists, to try this method of analysis. I feel sure that there are many problems in chemistry which could be solved with far greater ease by this than any other method." Cambridge 1913. In fact, Thompson developed the first isotope ratio mass spectrometer (IRMS).

1910: In the same year, Mikhail S. Tsvet, a Russian-Italian botanist, published his book in Warsaw on "Chromophores in the Plant and Animal World." With this, he may be considered to be the discoverer of chromatography.

1918: Arthur J. Dempster used electron impact ionization for the first time.

1920: Francis William Aston continued the work of Thompson with his own mass spectrometer equipped with a photoplate as detector. The results verified the existence of isotopes of stable elements (e.g. ^{35}Cl and ^{37}Cl) and confirmed the results of Thompson.

1929: Walter Bartky and Arthur J. Dempster developed the theory for a double-focusing mass spectrometer with electrostat and magnetic sector.

1934: Josef Mattauch and Richard F. K. Herzog published the calculations for an ion optics system with perfect focusing over the whole length of a photoplate.

1935: Arthur J. Dempster published the latest elements to be measured by MS, platinum (Pt), and iridium (Ir). Aston thus regarded MS to have come to the end of its development.

1936: Kenneth T. Bainbridge and Edward B. Jordan determined the mass of nuclides to six significant figures, the first accurate mass application.

1937: Lincoln G. Smith determined the ionization potential of methane (as the first organic molecule).

1938: A. Hustrulid published the first spectrum of benzene.

1941: Archer J.P. Martin and Richard L.M. Synge published a paper on the principle of gas-liquid chromatography (GLC).

1946: W.E. Stephens proposed a TOF mass spectrometer: *Velocitron*.

1947: The US National Bureau of Standards (NBS) began the collection of mass spectra as a result of the use of MS in the petroleum industry.

1948: John A. Hipple described the ion cyclotron principle, known as the Omegatron that now forms the basis of the current ion cyclotron resonance (ICR) instruments.

1950: Roland S. Gohlke published for the first time the coupling of a gas chromatograph (packed column) with a mass spectrometer (Bendix TOF).

1950: The Nobel Prize for chemistry was awarded to Martin and Synge for their work on GLC (1941).

1950: Fred W. McLafferty, Klaus Biemann, and John H. Beynon applied MS to organic substances (natural products) and transferred the principles of organic chemical reactions to the formation of mass spectra.

1952: Erika Cremer and co-workers presented an experimental gas chromatograph to the ACHEMA in Frankfurt; parallel work was carried out by Jaroslav Janák in Czechoslovakia.

1952: Archer J.P. Martin and A.T. James published the first applications of GLC.

1953: Walter H. Johnson and Alfred O.C. Nier published an ion optic with a 90° electric and 60° magnetic sector, which, because of the outstanding focusing properties, was to become the basis for many high resolution, organic mass spectrometers (Nier/Johnson analyzer).

1954: Wolfgang Paul published his fundamental work on the quadrupole analyzer.

1955: W.C. Wiley and I.H. McLaren developed a prototype of the present TOF mass spectrometer.

1955: Denis H. Desty presented the first GC of the present construction type with a syringe injector and thermal conductivity detector. The first commercial instruments were supplied by Burrell Corp., Perkin Elmer, and Podbielniak Corp.

1956: A German patent was granted for the QUISTOR (quadrupole ion storage device) together with the quadrupole mass spectrometer.

1958: Wolfgang Paul published about his research on the quadrupole mass filter as
– a filter for individual ions
– a scanning device for the production of mass spectra
– a filter for the exclusion of individual ions.

1958: Ken Shoulders manufactured the first 12 quadrupole mass spectrometers at Stanford Research Institute, California.

1958: Marcel J.E. Golay reported for the first time on the use of open tubular columns for GC.

1958: James Lovelock developed the argon ionization detector as a forerunner of the electron capture detector (ECD, J. Lovelock and S.R. Lipsky, 1960).

1962: Ulf von Zahn designed the first hyperbolic quadrupole mass filter.

1964: The first commercial quadrupole mass spectrometers were developed as residual gas analyzers (Quad 200 RGAs) by Robert Finnigan and P.M. Uthe at EAI (Electronic Associates Inc., Paolo Alto, California).

1966: Milan S.B. Munson and Frank H. Field published the principle of chemical ionization (CI).

1968: The first commercial quadrupole GC-MS system for organic analysis was supplied by Finnigan Instruments Corporation to the Stanford Medical School Genetics Department.

1978: Raymond D. Dandenau and E.H. Zerenner introduced the technique of fused silica capillary columns.

1978: Richard A. Yost and Chris G. Enke introduced the triple-quadrupole technique.

1982: Robert Finnigan obtained the first patents on ion trap technology for the mode of selective mass instability and presented the ion trap detector as the first universal MS detector with a PC data system (IBM XT).

1989: Prof. Wolfgang Paul, Bonn University, Germany, received the Nobel Prize for physics for work on ion traps, together with Prof. Hans G. Dehmelt, University of Washington, Seattle, and Prof. Norman F. Ramsay, Harvard University, USA.

2000: Alexander Makarov published a completely new mass analyzer concept called *Orbitrap* suitable for accurate mass measurements of low ion beams.

2005: Introduction of a new type of hybrid Orbitrap mass spectrometer by Thermo Electron Corporation, Bremen, Germany, for MS/MS; very high mass resolution and accurate mass measurement on the chromatographic time scale.

2009: Amelia Peterson *et al.*, University Wisconsin, Prof. Josh Coon group, first published the results on the implementation of an EI/CI interface on a hybrid Orbitrap system for ultra-high resolution GC-MS using a GC-Quadrupole-Orbitrap configuration for full scan, selected ion monitoring (SIM), MS/MS, and selected reaction monitoring (SRM) at the American Society of Mass Spectrometry (ASMS) conference.

2011: Agilent Technologies Inc., Santa Clara, CA, USA, introduces Gas Chromatography - Quadrupole Time-of-Flight (GC-QTOF) systems for the high sensitivity detection and analysis of unknown molecules in complex mixtures.

2015: Introduction of the first high resolution accurate mass GC-MS system using Orbitrap technology by Thermo Fisher Scientific, Austin, TX, USA, covering routine GC-MS applications.

2020: Newly introduced Orbitrap GC-MS technology provides 240 000 mass resolution power at m/z 200 and sub ppm mass accuracy.

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