# Historical evolution of chromatographic methods for the determination of endosulfan and its metabolites in water samples

https://doi.org/10.56238/sevened2024.018-049

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## ABSTRACT

Endosulfan is a highly toxic, broad-spectrum insecticide. Alpha-endosulfan, Betha-endosulfan, and their metabolites are on the Stockholm Convention on Persistent Organic Pollutants list. Endosulfan metabolites exhibit a wide range of chemical characteristics resulting in hard work for chemical analysts to specify all known degradation products of this insecticide in environmental matrices. This manuscript reviews the evolution of analytical methods related to the determination of endosulfan and its metabolites in environmental matrices. Specific metabolites, such as endosulfan alcohol, have very different physicochemical properties from the parent compound, so the use of a single satisfactory extraction method for endosulfan and its metabolites has not yet been achieved. Also, new endosulfan metabolites have recently been added to the list of their degradation products. The determination of these compounds in multi-pesticide analytical methods over the years was also discussed.

**Keywords:** Evolution of analytical methods, Organochlorine pesticides, Trace analysis, Two-dimensional gas chromatography, Water extraction.

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## INTRODUCTION

Endosulfan is a highly polluting and toxic pesticide, which has been used in many areas globally to control insects and mites and improve productivity. Concomitantly, endosulfan has also been associated with many cases of environmental pollution and various types of irreversible metabolic dysfunctions in living organisms both on soil and in water [1, 2]. The use of endosulfan has been banned or is strictly restricted in a number of countries. Its isomers and endosulfan sulfate were added to the Stockholm convention list of persistent organic pollutants to eventually complete elimination of endosulfan use [3].

The toxic effects of endosulfan and its metabolites to the environment added to its persistency, justifies the great concern of scientific community and steak holders for the monitoring of those compounds in different environmental matrices in the globe. The biggest challenges in the development of reliable analytical methods are the chemical variability of endosulfan metabolites and the extremely low concentration range of the degradation products. Some metabolites, such as endosulfan alcohol, have very different physicochemical properties from the parent compound so that the use of a single satisfactory extraction method for endosulfan and its metabolites has not yet been achieved [4-7]. In addition, recently new endosulfan metabolites were added to the list of their degradation products [8]. Endosulfan alcohol is a nontoxic metabolite to fish and other organisms. It can be further degraded to non-toxic endosulfan ether, endosulfan hydroxy ether, and endosulfan lactone [9].

Extraction methods are general focused on multi-residue determinations, using traditional clean-up methods, such as SPE, liquid-liquid partition extraction, [10] and matrix solid-phase dispersion extraction, [11] presenting low selectivity. It is essential to develop an effective method for the determination of endosulfan and its metabolite residues in environmental samples [12].

As a semi-volatile molecule, endosulfan is also a chlorinated and sulfur-containing compound. Those properties historically directed the analysts to the use of gas chromatography with selective detectors such as electron capture detector - ECD or flame photometric detector - FPD [13-15]. The use of mass spectrometric detectors and hyphenated techniques was also significantly employed such as GC-MS/MS [16-17] and comprehensive two-dimensional gas chromatography with time-of-flight mass spectrometry – GC×GC/TOFMS [18,19] improved the molecules confirmation for multi-residues determinations.

This review presents the evolution of analytical methods for the determination of endosulfan and its metabolites in the water matrix. It discusses extraction techniques and chromatographic methods limitations highlighting directions for further studies.

## ENDOSULFAN

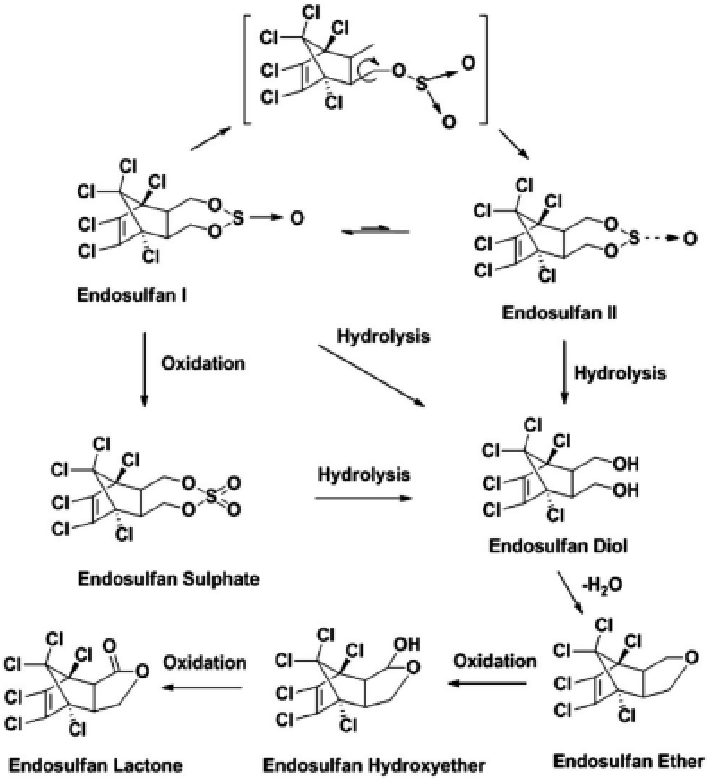
Endosulfan is a polychlorinated manufactured insecticide (CAS register number 115-29-7), first introduced in the 1950s [20]. It was widely used to control several insects on various agricultural products, such as grains, tea, fruits, vegetables, tobacco, and cotton. Endosulfan became a highly controversial agrichemical. Endosulfan has been considered an endocrine disruptor [21, 22]. It has also been attributed to adversely affecting human health in many ways, for example, by impacting human primary hepatocytes, inducing seizures, cancer development, reproductive system disorders, gastrointestinal diseases, and physiological disorders [2, 23]. Endosulfan has been identified as a cause of occupational poisoning in both developing and developed countries [24-25].

In the environment, soil or water, both endosulfan isomers are slowly degraded to endosulfan sulfate and then to other products such as chloride ions [26]. Many studies have demonstrated that endosulfan can provoke acute and chronic symptoms to fish, such as increase in mortality, no growth or reproduction, genotoxicity, and mutagenicity [1,27]. The eco-environmental behavior of endosulfan has raised great concerns because of the negative changes in biota [28-30]. As a result, the production and use of endosulfan has been discontinued in more than 60 countries, but it still in use for specific cultures in several nations, like China, India, Iran, Pakistan, Bangladesh and others [31-32].

For the chromatographic separation of endosulfan it is important to analyze its molecular structure. Endosulfan is actually a mixture of stereoisomers, called α and β. α-Endosulfan is more thermodynamically stable, while β-endosulfan is irreversibly converted to α form at room temperature [33].

The derivations of endosulfan as published by Reddy Mudiam et. al. [4] can be represented in figure 1.

Fig. 1 – Derivations of the endosulfan



Source: Reddy Mudiam et. al. [4]

The first chromatographic studies with endosulfan found in the literature dating from 1958[34], where Neiswander studied the mass transfer of the endosulfan from the soil to the air, mainly in the ether form. Since then, endosulfan has been found in various environmental compartments, including air, soil, vegetation, and water [35]. Endosulfan often enters the environment at the locations where it was directly applied. Endosulfan is one of the most commonly detected pesticides in surface water in the USA and is one of the most abundant organochlorine pesticides in the air [36]. Endosulfan is less persistent than other organochlorine pesticides in the environment, but the half-lives of the toxic components of endosulfan (α-endosulfan, β-endosulfan, and endosulfan sulfate) being between nine months and 6 years [37,38].

## EXTRACTION METHODS APPLIED TO ENDOSULFAN AND ORGANOCHLORINE PESTICIDES

Many methods or variations of methods are used to extract pesticides from non-liquid samples for residue analyses. Soxhlet extraction has been widely used since the 1960s for the analysis of air (fiberglass filters), soil, and sediment containing chlorinated pesticides. Nash et.al.[39] compared the extraction efficiency of chlorinated hydrocarbon insecticides from soils using three methods: agitation, soxhlet, and column extraction. Column extraction was faster than soxhlet or shake and did not require heat as soxhlet extraction. However, column extraction was less efficient than soxhlet extraction for DDT residues. Hesselberg and Johnson [40], obtained 96 to 100 percent recovery of organochlorine insecticides in fish samples, advocating the use of extraction columns.

Mixing of solid samples with organic solvents followed by filtration and combination of reagents in several stages, such as sulfate and sodium chloride, was very common in the 1970s. The solid-liquid extraction described by some authors, speeded up the mixing with a blender and subsequent filtration in a Büchner funnel. The filtrate was transferred to a separatory funnel and mixed with other reagents, homogenized and then concentrated in a Kuderna-Danish concentrator or rotary evaporator [41-43].

In the 1980s, solid phase extraction (SPE) of organic components from water solution, octadecyl ($C_{18}$) bonded porous silica started to become the most popular. Schneider, Bourne & Boparai [44] and Jimenez, Atallah & Bade [45] used to determine chlorinated pesticides and PCBs with recovery between 73 to 100.7%.

In the same decade, microwave irradiation started to be introduced (sonication extraction) to the extraction of various types of compounds from soil, seeds, foods and feeds as a novel sample preparation method for solid samples. In comparison with the traditional soxhlet technique, microwave extraction was presented as more effective regarding the yield of the extraction and the protection of the compounds to be analyzed. The method was suitable for the rapid extraction of large sample series [46,47], but not yet used for pesticide extraction. Schäfer and Baumann [48] used supercritical fluid extraction in the determination of pesticides obtaining between 90 and 100% recovery. However, soxhlet extraction and mixing of solid samples with organic solvents still with its permanent use in research.

In the next decade, sonication extraction became a classical extraction method such as soxhlet extraction in environmental laboratories. Other extraction techniques are still under development and discussion by the researchers. Snyder et. al. [49] used supercritical fluid extraction for soil samples, achieving average recoveries of 91.16% compared to soxhlet (89.16%) and sonic probe extraction (91.66%) of organochlorine pesticides statistically evaluated at the level of 95% confidence. Lopez et. al. [50] compared microwave-assisted extraction (MAE), Soxhlet, sonication, and supercritical fluid extraction (SFE) for sediment and soil samples with recoveries of 94 compounds. Soxhlet and MAE had recoveries greater than 80% for 50 and 51 compounds while sonification 63. Only SFE had 37 compounds above the mentioned recovery. The main advantages of MAE are shorter extraction time (typically 10 min for extraction and 40 min for cooling, centrifugation, and concentration) and less use of solvent.

Heemken et. al. [51] used accelerated solvent extraction (ASE) for determination of organic micropollutants in marine particulate matter in comparison to SFE, soxhlet, sonication, and methanolic saponification extractions. Using SFE, the average recoveries ranged from 96 to 105%

while for ASE the recoveries were in the range of 97-108% compared to the others methods, with the majority of the compounds within the confidence limits. The use of the SPE technique was not only in water samples. Redondo et. al. [52] applied SPE for soil samples, using sonication with water and acetone obtained between 56 to 100% recovery.

For water samples, the most used method was SPE using $C_{18}$ cartridges. Solid phase micro-extraction in the 90s became popular among several researchers for both air, water, juice, fruit, and vegetable samples [53-55]. The new micro-extraction method was developed by Arthur and Pawliszyn [56].

Magdic, S., and Pawliszyn [53] have outlined the successful development of a method based on the SPME technique for the analysis of organochlorinated pesticides from aqueous samples. The fiber selected for the analysis of the organochlorines was a fused-silica rod 1 cm long, coated with 100 µm of polydimethylsiloxane (PDMS). The method is precise, reproducible, and linear over a wide range. The detection limits obtained for the SPME method using either ECD or MS are comparable, if not better than those required by US EPA methods 508, and 625 respectively.

Entering the 21st century, a novel extraction technique for aqueous samples namely stir-bar sorptive (SBSE) was introduced in 1999 by Baltussen et. al. [57]. Bicchi et. al. [58] analyzed in pear pulp (a heterogeneous matrix) by extraction on polydimethylsiloxane stir bar (SBSE) followed by recovery through thermal desorption (TD). Pesticide recoveries at different levels were quite homogeneous and all above 70%, with the exception of chlorthalonil whose average recovery was 32.1%.

To analyze pesticide residues in solid samples, a rapid and inexpensive approach was reported by Anastassiades et. al. [59], coming back to the solvent extraction procedures of the 70s. The authors named this method QuEChERS which stands for *Quick*, *Easy*, *Cheap*, *Effective*, *Rugged,* and *Safe*. Lehotay et. al. [60] conducted the method for the determination of 229 pesticides fortified at 10–100 ng $g^{-1}$ in lettuce and orange matrixes. Recoveries for all but 11 of the analytes in at least one of the matrixes were between 70–120% (90–110% for 206 pesticides), and repeatabilities typically <10% were achieved for a wide range of fortified pesticides. Despite the trend towards fast and less wasteful methods, the oldest methods are still used in research and routine laboratories.

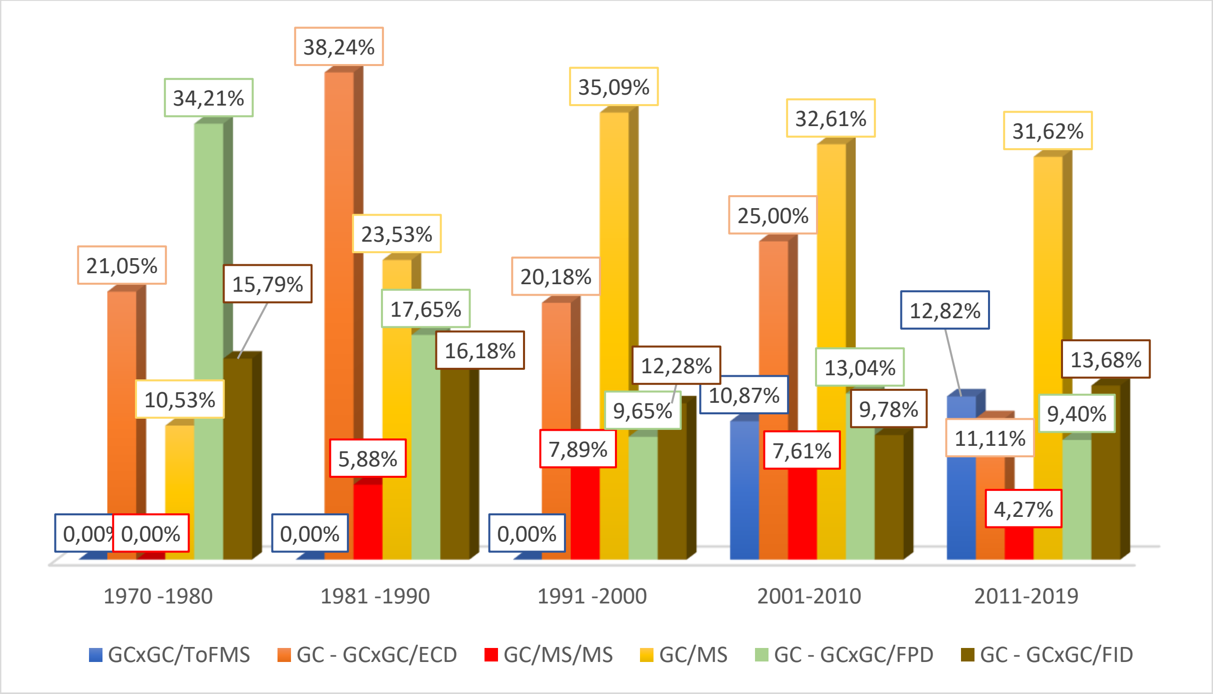
## HISTORICAL EVOLUTION OF ANALYTICAL METHODS FOR ORGANOCHLORINE PESTICIDE DETERMINATION IN ENVIRONMENTAL MATRICES

The evolution of analytical methods applied to endosulfan determination came along with the evolution of chromatography. After paper chromatography, a very simple and highly sensitive detector was developed in 1955 by Scott [61] and based on the combustion of organic compounds present in the column effluents in a hydrogen flame in an atmospheric environment and on the measurement of the temperature variation of the flame during combustion. From this detector, two new detectors were created in 1958. The FID flame ionization detector, widely used in the 1970s, and the argon ionization detector. The argon ionization detector is a creation of Lovelock [62], who was the first to show that a normal beta ionization detector, when used with argon as a carrier gas, creates metastable argon atoms that collide with the vapor molecules and transfers their excitation energy. However, the modifications of the original argon detector, the so-called electron capture detector (ECD), proved to be very important in selective analysis. FPD and ECD were popularized in the 60´s, but still important today [63].

In 1961, the flame photometric detector (FPD), was first used in gas chromatography for the visual detection of chlorine-containing substances. In 1964, Huyten and Rijnders [64] constructed a FPD with a photomultiplier for the determination of halogens. Juvet and Durbin present a more detailed characterization of the operation and performance of the flame photometric detector as applied to certain metal chlorides, metal chelates, organic compounds, and phosphorus and sulfur-containing pesticides [65]. In 1965, electron capture gas chromatography was applied to chlorinated insecticides in milk. With an improved cleanup method, it was possible to quantify DDT, DDE, lindane, dieldrin, heptachlor, heptachlor epoxide, and endrin [66]. In 1966, using the same cleanup procedure, endosulfan required 800 and 1,000 ml for the elution of its two isomers with 85% recovery [67].

More than 500 authors were considered in the survey of techniques used to determine pesticides in environmental matrices only, such as soil, sediment, air, water, and biota. The literature presents a transition of the tendency for application of different analytical techniques over the decades, since 1970, as presented in Figure 2. In the 70s, the best available technology in analytical labs to deal with endosulfan environmental analysis was still GC-FPD. The flame photometric detector (FPD), lost space for GC-ECD, GC-MS over the decades. While GC-ECD was the most applied technique in the 90s due to its selectivity and lower detection limits, this tendency was overcome by the development of more sensitive mass spectrometry detectors, and the higher selectivity associated with MS/MS platforms, applied with GC.

Fig. 2 – Analytical techniques employed for organochlorine pesticides in environmental matrices



Mass spectrometry (MS) has an additional advantage because it is not only for quantification but also for the identification of pesticides in complex samples [68]. Suspicious screening processes tailored for gas chromatography coupled with high-resolution mass spectrometry (GC-HRMS) have been used to identify novel compounds of concern [69-70].

The ability of the MS detector to perform tandem mass spectrometry (MS-MS) promotes pesticide analysis at low picogram levels, even in the presence of interference, significantly reducing background noise [71]. However, along with the increase in the number of organic contaminants in the environment, measurement is traditionally complex and tedious and, more importantly, more expensive, as standard chemicals are expensive and may be a cause of declining use. The popularity of high-resolution mass spectrometry (HRMS) instruments has importantly grown mainly due to the availability of time-of-flight (TOF) and Orbitrap systems at affordable costs. The major advantage of these mass spectrometers is the possibility of acquiring full-scan spectra at high resolution, whereas Triple Quadrupole Mass Spectrometer (TQMS) techniques only register selected or multiple reaction monitoring (SRM or MRM) data defined by the user before the analysis [72].

Currently, GC×GC/TOFMS is widely used to investigate the presence of a large number of contaminants in samples due to their complementary characteristics to determine from nonpolar/ volatile to polar/nonvolatile compounds. Reasonable sensitivity to full spectrum acquisition and accurate mass data provided by TOFMS allow for a noticeable increase in the number of compounds to be investigated, with the possibility of subsequent search for additional compounds in a retrospective analysis without the need for further sample injections [73]. Its growing use in pesticide samples was started in the year 2000.

Over the decades, new technologies and enhancements, have left the right side of techniques that are now less used today. The quantification of pesticides and their major metabolites has been performed in multi residue analytical methods, along with other pesticides.

## GAS CHROMATOGRAPH ELECTRON CAPTURE DETECTOR GC-ECD

Since the 60's, gas chromatography has been considered one of the most frequently used methods in the analysis of pesticide chemicals in environmental samples [15, 74-77]. The ECD detector is probably the most sensitive and selective of the traditional GC detectors available and is widely used in the detection and analysis of high electron affinity compounds [78].

ECD detector has long been recognized as the detector of choice for trace analysis of halogenated organic compounds such as organochlorine pesticides, herbicides, and halogenated hydrocarbons in a range of samples. It uses a radioactive beta (electron) emitter to ionize some of the carrier gas and produce a standing current between a biased pair of electrodes. Containing electronegative functional groups, such as halogens, phosphorus, and nitro groups, some organic molecules have electrons captured by the detector which reduce the current measured between the electrodes. ECDs have been used successfully for the detection of various compounds, including hazardous substances [79-81].

In 1969, Chau [74] had identified in a 10 g sample plant material, 0.03 ppm or more of the parent insecticide endosulfan in a time run of 20 min using GC-ECD. The column was a 1 + 1 mixture of 4 % DC-11 and 6% QF-1 on 60-80 mesh acid-washed Chromosorb W in a 31.75 mm id × 12.7 cm glass column. In the following two decades, chromatographs analyzed organochlorine and phosphorous pesticides through non-polar packed GC columns such as OV-1, SE-30, QF-1, OV-17, and CP-5, with a majority of 80-120 mesh. The number of analytes was limited to less than 15 compounds and the analysis time was relatively long [43, 82-87].

In the 1980s, the migration from packed column chromatography to capillary columns with similar stationary phases was observed. Known as high resolution capillary columns, they can be useful in applications that require high analysis speed. Schneider, Bourne & Boparai, Seymour et. al., Bidleman et. al., Buchert, Class & Ballschmiter, and Jimenez, Atallah & Bade used capillaries columns between 30 and 60 m long with diameter from 0.1 to 0.32 mm and thickness film 0.1 to 0.25 μm [44-45, 88-90].

In addition, a small volume electron capture detector cell has been described by Wells [91], that is compatible with columns of internal diameters as small as 100 microns. The unique method of transporting the sample through the active region of the cell allows the use of hydrogen as a carrier gas without sample loss by adsorption on surfaces activated by the hydrogen. The combination of short, narrow columns and hydrogen carrier gas allows reduced analysis times.

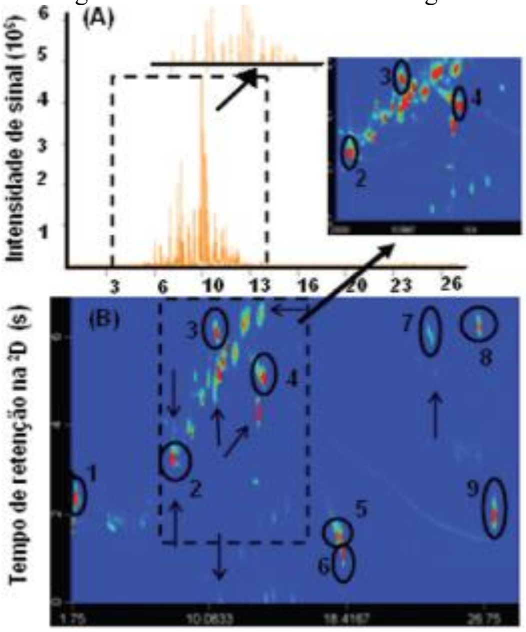
In the 90s, pesticides research such as Jiménez et. al., Hajslová et. al., Albanis et. al. already present multiresidual analyzes of pesticides [53, 92-94]. The analysis time is usually more than 40 min, and can be shorter or much longer. Long chromatographic columns (e.g. 60 m x 0.25 mm I.D. and 0.25 μm film thickness) are preferably used, however, columns with other dimensions can be found. The stationary phase found is often non-polar DB-5 (5% phenyl, 95% methylpolysiloxane) and HP-1 (100% methylpolysiloxane), as well as HP-50 mid-polarity (50% phenyl, 50% methylpolysiloxane).

In addition, the new ECD was designed to address inherent deficiencies in classical electron capture detectors (ECD), especially with respect to sensitivity, linearity, dynamic range, and ruggedness. The improved performance of Micro-ECD met all CLP criteria for the analysis of OCP over a period of 6 months. System validation was performed throughout this period for a wide variety of samples and analyses of different EPA methods. Micro-ECDs showed improved sensitivity, greater dynamic and linear operating ranges, more stable response, required minimal maintenance, and showed rapid recovery after switching between methods [95]. The micro-electron capture detector (μECD) has a much smaller inner volume than classical ECDs and is an excellent detector for quantitative analysis and screening of polyhalogenated organics by GC×GC [79, 96]. Also, according to von Mühlen et. al., μECD shows a variable sample rate from 5 to 50 Hz, suitable for rapid chromatography and minimizing the chance for contamination in the anode.

In the first decade of the 20th century, most of method development using GC-ECD was focused on reduction of analysis time, in order to improve the sample throughput. Oviedo et.al., Domotorová et. al., Vagi et. al., Khummueng et.al., and Kim et. al. obtained the separation of 9 to 17 compounds in 15 to 25 min run [97-101]. Borga et. al. injected aliquots of organochlorine extract into two identical GC-ECDs equipped with capillary columns of different polarity [102]. The detection limit of compounds ranged from 0.002 to 0.365 ng $g^{-1}$ of wet weight. The compound-dependent detection limit decreased to 0.003 to 0.078 ng $g^{-1}$ wet weight, equipped the GC with a Ni-micro-ECD.

The combination of comprehensive two-dimensional gas chromatography with the μ-ECD detector expanded the compound scan and reinforced the improvement. Khummueng et. al. and Korytár et. al. used GC×GC to analyze more than 40 pesticide analytes [100, 103]. According to Silva et. al. the analysis of sediments by GC×GC in relation to the 1D-GC allows the separation of the 8 pesticides with less probability of interference from constituents of the matrix [104]. The greater potential of the GC×GC technique was evident for the separation and quantification of organochlorine compounds. Regarding the analysis time, the two methodologies are practically equivalent, with 27.9 min for 1D-GC and 29.4 min for GC×GC (figure 3).

Fig. 3 - Sediment extract chromatogram

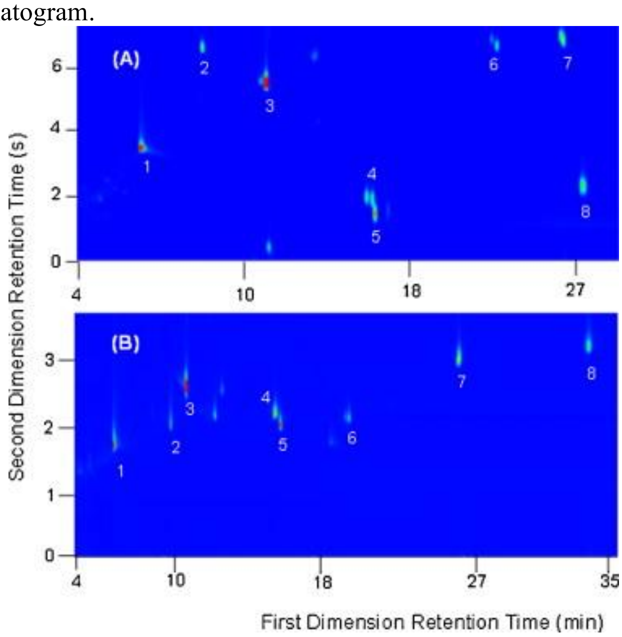


Source: Silva et. al. [104]

The detection limits found by Silva et. al. also were 0.60 to 2.31 µg L$^{-1}$ to 1D-GC and 0.08 to 1.07 µg L$^{-1}$ in GC×GC to sediment sample showing performance improvement.

As an early development stage of GC×GC, the authors used to evaluate different column configurations and stationary phases for different applications (figure 4). Researchers used column stationary phases such as 5% methyl silicone in the first dimension combined with (DB-5, non-polar), polyethylene glycol (polar) in the second dimension, 6 - 14% cyanopropyl-phenyl -methyl polysiloxane (example DB-1701, low/mid-polarity) and DB-17 (similar to HP 608 - mid polarity). The diameter of the column and the film varied considerably in each survey and in some surveys, they already work with columns shorter than 30 m [105].

Fig. 4 - GC × GC-μECD color plots for a 100 μg $L^{-1}$ solution of the pesticides. (A) DB-5/DB-17ms column set, (B) HP-50+/DB-1ms column set chromatogram.



Source: Silva et. al. [105]

The DB-5/DB-17ms column provided better analytical results compared to HP-50+/DB-1ms as analysis time was shorter (29.4 min and 35.7 min, respectively) and the resolution was better for permethrin isomers (6) (Rs = 0.72 versus Rs = 0.36) Resolution between propiconazole (4) and trifloxystrobin (5) was 0.6 for both column sets. Potential of the application of GC×GC-μECD was demonstrated for better separation between analyte and matrix interference, minimizing the possibility of coelutions.

The evolution of GC-ECD method development and application in the last 18 years is presented in Table 1. The application of GC×GC-ECD for pesticide analysis in the second decade of the 20th century was directed to the diversification of the type of samples, with small variations between column configurations and analysis time [106, 107]. The analysis time continues on average between 30 and 50 min not using fast methods to soil, sediment and sludge, raw food, water, wastewater, atmosphere, biota, fish, aqueous samples, and honey bees [31, 106-114]. Another important information is the analysis of several matrices simultaneously [114-118].

Table 1: GC-ECD methodologies for water researched after 2000

| **Author** | **Extraction** | **GC-ECD** | **Column** | **Analysis time** | **LOD ηg.L$^{-1}$** | **LOQ ηg.L$^{-1}$** |
|---|---|---|---|---|---|---|
| López-Blanco et. al. [119] | SDME<br>Endosulfan | A Fisons 8000 series | MDN-5S<br>30mx0.25mmx0.25μm | 32 min. | 10 | 20 |
| Shen et. al. [120] | LMF-DMMLE<br>Endosulfan | Agilent gas chromatograph 7890A series | HP-5<br>30mx0.32mmx0.25μm | 37 min. | 3.2 - 4.1 | - |
| Behfar et. al. [121] | Glass column packed with Florisil and $Na_2SO_4$<br>Endosulfan | Agilent 6890N (HP) gas chromatograph | DB-5<br>30mx0.25mmx0.25μm | 29 min. | 8 – 8.8. | - |
| Karadeniz & Yenisoy-Karakas [122] | SPE<br>Endosulfan | Hewlett Packard (HP) 6890 N series gas chromatography | HP-5MS<br>30mx0.25mmx0.25μm | 32.8 min | 0.06 – 0.3 | 0.2 - 1 |
| Carmo et. al. [109] | SPME<br>6 organochlorine pesticides | A Shimadzu GC-14B gas chromatograph | HP-5<br>30mx0.32mmx0.25μm | 43 min. | 0.44 - 0.64 | 1.65 - 2.12 |

It is possible to observe in Table 1 the change in the applied extraction techniques. There is also an improvement in detection limits over the years with more efficient extractions as well as more sensitive detectors. The use of non-polar columns such as 5 % phenyl 95 % methylpolysiloxane has remained constant.

## GAS CHROMATOGRAPH MASS SPECTROMETRY GC-MS

Several investigators have reported the use of mass spectrometry in the study of individual pesticides [123,124] and for the identification of pesticides in mixtures since the 60s [125]. MS detectors have had their application increased since the 1970s for the analysis of chlorinated pesticides in environmental matrices using GC-MS quadrupole.

In 1974, Baughman [126] performed analyses of 2,3,7,8-tetrachlorodibenze-p-dioxin (TCDD) with methodology with detection limit between 0.02 and 0.15 ρg.mL$^{-1}$ with response calibrated with standard solution monitoring the molecular ions of TCDD m/e 320 and 322. As part of a broad study to determine whether 2,3,7,8-tetrachlorodibenzo-E-dioxin (TCDD) is accumulating in the environment due to approved uses of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) based herbicides, Shadoff et. al. [127] collected samples of fish, water, mud and human milk from areas in Arkansas and Texas where 2,4,5-T herbicides are used and were analyzed for TCDD. TCDD was not detected by a GC-MS in any sample, with an average detection limit less than 0.01 ρg.mL$^{-1}$.

PCBs and chlorinated naphthalenes have been separated by silicic acid column chromatography prior to analysis by gas chromatography. However, the use of a gas chromatograph - mass spectrometer enables the qualitative and quantitative analysis of these compounds without prior column chromatography or complete separation on a gas chromatographic column [128]. GC-MS techniques have been a major instrumental advance in identifying traces of xenobiotic chemicals in biological tissues, but work has been needed to improve the sensitivity of instrumentation and enrichment of the trace chemicals [129]. Most applications in this decade were directed to qualitative analysis.

In the 1980s, quantification of organochlorine pesticides was performed with an electron capture positive and negative detector and other detectors, while MS was used in qualitative confirmation methods [130-134]. The signal acquisition rate of the first mass spectrometers was very low, but with very high detection limits. This limited the application of MS for quantification.

However, researchers like Hargesheimer [135], used selected ion monitoring mass spectrometry (SIM) by chemical methane ionization (CI) to identify and conclusively distinguish 19 organochlorine pesticides from polychlorinated biphenyls (PCBs) in levels of parts per trillion a part per billion in extracts from environmental water samples with minimal sample cleanliness. The detection limit for pesticides and PCBs by CI- SIM screening was 5 and 100 ρg.ml$^{-1}$, respectively. CI-SIM can be used as an alternative method for the analysis of biological or environmental samples containing interferences that complicate the detection of PCBs and chlorinated pesticides.

In the 90s, this improvement of MS allowed the development of pesticide quantification methods directly with GC-MS. Huskes and Levsen, Aguilar et. al., and Silva et. al. [136-138] identified and quantified pesticides in selected ion monitoring mode using masses and their peak area ratio to characterize a compound, while Benfenati et. al. [139] for example, used the electron impact ionization (EI) mode. Advantages of EI ionization is a low influence of molecular structure on response and a large number of characteristic fragments [140]. Most of the published studies in this decade on residue analysis by GC-MS reported the use of single quadrupole instruments and EI ionization [141-142]. The columns used in the GC follow the same pattern as those used in ECD with small variations in column dimensions and sorbent thickness.

After that decade, researchers have used capillary columns used nonpolar with measures of 30mx0.25mmx0.25um, varying very little for other dimensions and stationary phases. The analysis methods have been improving the analysis time concerning the number of compounds analyzed, however they are greater than 20 min [59, 143-145].

It was also the beginning of two-dimensional gas chromatography applications for pesticides. The theoretical peak capacity of GC×GC has been determined as being an order of magnitude higher than conventional GC methods [146] and has been effectively used for the simultaneous analysis of multiple classes of chemicals in complex environmental matrices: snow samples, soil, sediments, and biota [147-149].

Since 2005, mass spectrometry has been increasingly used in the environmental sciences with the objective of investigating the presence of organic pollutants. A clear trend has been observed, from the very popular GC-MS with a single quadrupole mass analyzer, to tandem mass spectrometry

(MS/MS). The ability of the MS detector to perform tandem mass spectrometry (MS/MS) promotes pesticide analysis at low picogram levels, even in the presence of interference, significantly reducing background noise [71].

More recently, high-resolution mass spectrometry (HRMS) has for years is coupled to HR magnetic sector instruments. The increasing interest in the use of HRMS in the environmental sciences is because of its suitability for both targeted and untargeted analysis, owing to its sensitivity in full-scan acquisition mode and high mass accuracy [150]. In addition, new combinations of mass spectrometers are tested and evaluated bringing improvements in the area of analysis as the hybrid quadrupole time of flight mass spectrometry (QqTOF-MS), effectively employed in the detection of photo-degraded or the hydrolyzed products of pesticides found in environmental waters [151] and orbitrap mass spectrometer recently development used as single-stage mass spectrometer in the form of orbitrap technology for the analysis of pesticides to ensure food safety [152].

Since 2010, in the articles studied, not many changes have been observed besides columns and increasingly sophisticated materials that make chromatography faster, and easier to handle, with greater conservation of components, savings in consumption, and better analytical detection. There is also an improvement in sensitivity combined with modern extraction techniques, reaching lower LOD values. On the other hand, Peterson et.al. [153] details the development and characterization of a GC-QLT-Orbitrap hybrid mass spectrometer with high resolution (up to 100,000 at m/z 400) and subpart mass accuracy per million GC-MS. A high-service cycle, innovative scanning type, nested scanning, was implemented to synchronize the Orbitrap acquisition rate and the gas chromatography time scale (up to 6.5 Hz at 7500 resolution), but it is not applied to pesticides analysis yet.

## GAS CHROMATOGRAPHY TANDEM MASS SPECTROMETRY GC-MS/MS

Tandem mass spectrometry (MS-MS) has gained rapid acceptance in the analytical community since its introduction in the 1970s [154]. Its acceptance has been due largely to its ability to provide sensitive and selective analysis of complex mixtures rapidly, often with minimal, if any, sample cleanup [155-158]. Due to the acceptance of MS/MS, research involving pesticides was carried out in 1986, Hummel & Yost [159] analyzed organophosphate and carbamate levels with LOD between 0.1 and 20 ηg.µl$^{-1}$ on to the 50 cm packed GC column and Simon et. al. [160] for quantification of tetrachlorodibenzo-p-dioxin in soils and sediments com detection limits above 1 ηg.g$^{-1}$ and 5% RSD.

McLafferty [161] concluded MS-MS does appear to offer a promising potential for obtaining analytical information from complex organic mixtures which are difficult to analyze by GC-MS. Trace quantitative analysis for specific compounds in complex mixtures, analogous to selected ion monitoring in GC-MS, is feasible. The utility of the technique lies in combining the specificity and sensitivity of MS/MS with retention time data and an increased time scale, which allows multiple experiments to be performed. Bonner [162] demonstrates direct mixture analysis is feasible in some cases, GC-MS/MS is extremely useful since retention time (isomer) information is retained and "multi-experiments". Most recently, Dai et. al. and Lozowicka et al. [163, 164] considered a limitation of this technique is the susceptibility to the matrix effects, which negatively affect quantification and qualification, mainly in the analysis of complex samples, even though, they considered GC-MS/MS as the most efficient strategy for the determination of pesticide residues in different matrices. There are a growing number of protocols relying on the application of these new techniques GC-MS/MS to improve the analysis of POPs in environmental matrices and to determine new emerging contaminant classes [165,166].

GC-ITMS allows the ion trap to isolate an ion of interest and then produce characteristic collision-induced dissociation (ICD) descending ions and can unambiguously distinguish the compound of interest from other compounds that have parent ions with the same mass / charge ratio. The ability to intercept an ion of interest for some time and then remove matrix ions makes it possible to analyze directly for specific compounds in complex matrices [167].

This decade produced several researches on the use of tandem GC in the quantification of pesticides. Analysis in water [168,169] fruits and vegetables [170], soil [171], and even endosulfan in human urine [172] were produced using ion-trap, quadrupole, and hybrid mass spectrometer.

Johnson et. al. [173], compared on Quadrupole Ion Trap (ITMS) and Triple Quadrupole. ITMS and TQMS produced child ions of similar abundances, with ITMS being more efficient in fragmentation, collection, mass selection, and transmission of child ions to the detector. The detection limits were set at approximately 5 ρg for both detectors. One of the most important advantages of the ion trap is the high efficiency with which MS/MS can be implemented. Comparison of MS/MS on the ITMS to MS/MS on the more conventional TQMS demonstrated that the ITMS has higher CID efficiencies (80-90%) with an overall MS/MS efficiency approximately 14 times higher than that of the TQMS. In addition, the quantitative studies showed that the ITMS was able to obtain complete daughter spectra on low picogram amounts of analyte, 100 times lower than the amounts required for comparable spectra on the triple quadrupole.

Other comparisons were made. Frenich et. al. [174] also compared the ITMS and TQMS detectors concluding that ITMS is the best option since the number of analytes and the instrumental analysis time is not a key factor in laboratory performance. The MS data obtained by each analyzer were very similar within the group of compounds studied, including endosulfan, although more spectral information (ion spectrum of the complete product) was provided by the IT analyzer.

The triple quadrupole instruments excel in the area of quantification and targeted compound analysis. The single reaction monitoring and MRM modes of operation of triple quadrupoles provide high-duty cycles, maximizing sampling efficiency [175]. Belarbi et. al. [176] performed multi-residue analyses of one hundred pesticides and contaminants comparing Triple Quadrupole and Q-Orbitrap. Results involving endosulfan sulfate show better quantification results for Q-Orbitrap with 0.1µg/kg despite the small difference.

Hybrid instruments such as tandem mass spectrometers that incorporate sector-type analyzers (magnetic and/or electrostatic analyzers) and quadrupoles have fallen out of use while the ion-trap and quadrupole models have become more popular [176]. Therefore, the use of a new hybrid quadrupole / linear ion trap, known as Q TRAP, offers unique benefits as an MS-MS detector for small and large molecule analysis. Combined methods such as atmospheric pressure gas chromatography quadrupole-time-of-flight mass spectrometry (APGC-QTOF-MS) shorten the analysis time compared to traditional GC–MS/MS and therefore have a great advantage for the rapid screening of organic contaminants. The screening detection limits (SDL) for this method were determined for endosulfan I (not determined), II (10 µg kg$^{-1}$) and endosulfan sulfate (50 µg kg$^{-1}$) [177].

The numerous methods available for pesticide analysis show the importance of this application and the fast pace of development in analytical chemistry. For endosulfan, the tandem GC method has achieved increasingly lower LODs in recent years using Triple Quadrupole and Q-Orbitrap detectors as shown in Tables 2 to 5.

Table 2:Methodologies for GC-MS with water until 2000.

| **Author** | **Extraction** | **GC-MS** | **Column** | **Analysis time** | **LOD ηg.L$^{-1}$** | **Mass Ranger** |
|---|---|---|---|---|---|---|
| Pablo-Espadas et. al. [169] | SPE<br>14 pesticides<br>(Endosulfan) | Saturn 2000 Ion trap MS<br>GC-MS | DB-5 MS<br>30mx0.25mmx0.25µm | 40 min. | 2.4 – 81.5 | 85 – 450 m/z |
| Natangelo et. al. [168] | SPME<br>4 chloroacetanilides | GC HP 5890 – MS HP 5871<br>Quadrupole | PTA-5<br>30mx0.25mmx0.50µm | 14 min | 2 -30 | 88 – 179 m/z |
| Howard et. al. [178] | SPE<br>5 organochlorines<br>(Endosulfan) | GC HP 5890 – MS HP 5972<br>Quadrupole | DB 1701<br>15mx0.25mmx0.25µm | 16 min. | 200 – 1000 | 165 – 354 m/z |
| Huskes and Levsen [136] | SPE<br>10 compounds<br>Triazine and other. | GC (5890) – Magnetic sector<br>MS VG 70-SQ<br>GC-MS | DB-5625<br>Not Dimension | 24 min. | 3 - 30 | 40 - 440 m/z |
| Patsias & Papadopoulou-Mourkidou [179] | SPE<br>96 compounds<br>(Endosulfan) | Varian 3300 Tracker/Magnum ion trap MS | DB-5 MS<br>30mx0.25mmx0.25µm | 54 min | 10 - 50 | 50 – 450 m/z |

NI - Not informed

Table 3: Methodologies for GC-MS with water after 2000.

| **Author** | **Extraction** | **GC-MS** | **Column** | **Analysis time** | **LOD $\eta g.L^{-1}$** | **Mass Ranger** |
|---|---|---|---|---|---|---|
| Valenzuela et al. [180] | LPME<br>29 pesticides<br>(Endosulfan) | GC (7890) – MS Quad (5975) | DB 5MS<br>30mx0.25mmx0.25µm | 25 min | 17 – 784 | 45 - 500 m/z |
| Climent et. al. [181] | SPE<br>16 pesticides | GC (7890) – MS Triple Axi (5975C) | ZB 5MS<br>30mx0.25mmx0.25µm | 24 min | 11 – 30 | N.I. |
| Bulgurcuoglu et. al. [182] | DLLME<br>16 Compounds | GC (6890) – MS Quad | HP 5MS<br>30mx0.25mmx0.25µm | 7 min | 300 - 3000 | 35 – 700 m/z |
| Bonansea et. al. [183] | SPE<br>8 pesticides<br>(Endosulfan) | GC Varian 2200<br>MS ion trap | VF - 5<br>30mx0.25mmx0.25µm | 25 min. | 0.07 – 3.5 | 100 – 500 m/z |
| Hladik et. al. [184] | SPE<br>60 pesticides | GC Varian Saturn 2000 – MS Ion trap. | DB 5MS<br>30mx0.25mmx0.25µm | 61 min | 1 – 12 | N.I. |

NI - Not informed

Table 4: Methodologies for GC-MS/MS with water until 2000.

| **Author** | **Extraction** | **GC-MS/MS** | **Column** | **Analysis time** | **LOD $\eta g.L^{-1}$** | **Mass Ranger** |
|---|---|---|---|---|---|---|
| Pablo-Espadas et. al. [169] | SPE<br>14 Organochlorines<br>(Endosulfan) | Saturn 2000 MS Ion trap<br>GC-MS/MS | DB-5 MS<br>30mx0.25mmx0.25µm | 40 min | 0.4 – 22.5 | 85/450 m/z |
| Natangelo et. al. [168] | SPME<br>4 chloroacetanilides | Varian 3800 GC Ion trap<br>MS/MS<br>GC-MS/MS | HP-5 MS<br>30mx0.25mmx0.25µm | 26 min. | 2 - 15 | 88 – 223 m/z |
| Verma et. al. [185] | SPE<br>11 pesticides | GC (Varian) - MS/MS (Varian Saturn III ion trap)<br>GC-MS/MS | HP-5 MS<br>30mx0.25mmx0.25µm | 20 min | 0.3 - 2 | 50 – 400 m/z |
| Steen et. al. [186] | SPE<br>Irgarol 1051 | GC (Varian) - MS/MS (Varian Saturn III ion trap)<br>GC-MS/MS | DB-5 MS-ITD<br>30mx0.25mmx0.25µm | 41 min | 0.1 | 50 - 450 m/z |
| Steen et. al. [187] | SPE<br>5 pesticides | GC (Varian) - MS/MS (Varian Saturn III ion trap)<br>GC-MS/MS | BPX-5<br>25mx0.22mmx0.25µm | 49 min. | 0.20 - 0.50 | N.I. |

NI - Not informed

Table 5: Methodologies for GC-MS/MS with water after 2000.

| **Author** | **Extraction** | **GC-MS/MS** | **Column** | **Analysis time** | **LOD ηg.L$^{-1}$** | **Mass Ranger** |
|---|---|---|---|---|---|---|
| Canli et. al. [188] | SBSE<br>117 endocrine disruptors<br>(Endosulfan) | GC (7890B) – MS/MS (7000D)<br>Triple quad | HP-5ms<br>30mx0.25mmx0.25µm | 21 min. | 0.04 - 15 | N.I. |
| Cárdenas-Soracá et. al. [189] | UASE<br>SPME<br>18 Organochlorines<br>(Endosulfan) | GC (7890A) – MS/MS (7000)<br>Triple quad | HP-5ms<br>30mx0.25mmx0.25µm | 36 min. | 0.01 - 0.27 | 101 – 263 m/z |
| He & Aga [190] | SPE<br>52 Compounds<br>(Endosulfan) | GC (Thermo Trace) – TSQ Quantum MS<br>GC-MS/MS | DB-5HT<br>30mx0.25mmx0.25µm | 29 min | 0.8 - 9 | 128 – 362 m/z |
| Wang et. al. [191] | SPE<br>6 Organochlorines | GC (7890A) – MS/MS (7000B)<br>Triple quad | HP-5ms<br>30mx0.25mmx0.25µm | 17 min. | 0.04 - 0.35 | 50 - 400 m/z |
| Derouiche et. al. [192] | SPME<br>15 Organochlorines | Saturn 3 Ion Trap | DB-5MS<br>30mx0.25mmx0.25µm | 70 min | 0.4 - 26 | 50 – 650 m/z |

NI - Not informed

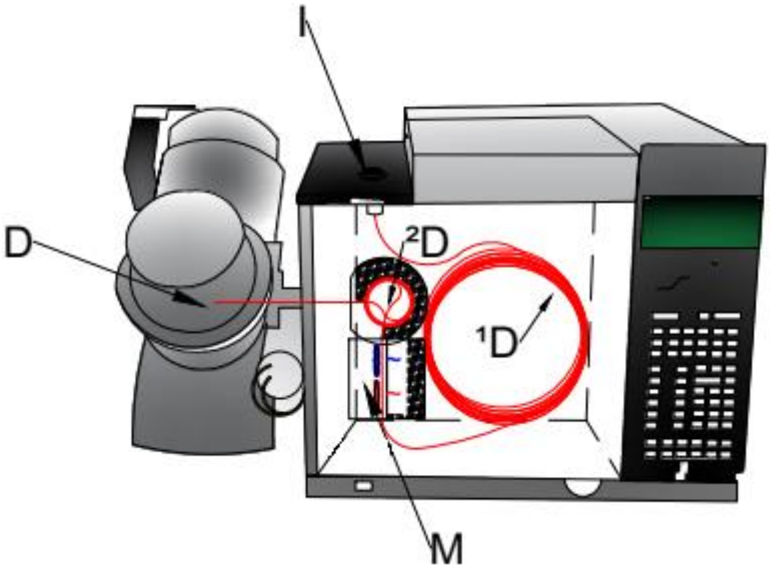
According to the tables, the LOD observed in GC-MS and GC-MS/MS differs between the authors. It is interesting to note that the LOD for GC-MS is on average higher than the MS/MS, but comparable to GC-ECD, presented on table 1.

In the 20th century, research has found more use of quadrupole-type mass spectrometers for GC-MS and ion traps for tandem mass spectrometers. Natangelo et. al. [168] and Pablo-Espadas et. al. [169] compared the two mass spectrometers obtaining superior analytical response in MS/MS. For GC-MS, the ion trap mass spectrometer is not commonly used to analyze pesticides in water, but it obtained low detection limits as much as the quadrupole type in the 21st century.

## TWO-DIMENSIONAL GAS CHROMATOGRAPHY TIME-OF-FLIGHT MASS SPECTROMETRY GC×GC/TOFMS

Comprehensive two-dimensional gas chromatography (GC×GC) is a technique characterized by the sequential combination of two columns, typically one of the conventional dimensions, and another one shorter (capable of generating fast-GC analysis), such that all samples pass through a modulator. In the most widely employed modulator system (based on cryogenic methods), modulation between the two columns provides compression of the chromatographic band eluting from the first column and fast introduction of the compressed band into the second column. This second step must be considered in light of the need to achieve a very fast separation in the second column. The modulator performs the function of collecting (focussing) the solute at the end of 1D and rapidly introducing it to the 2D column (figure 5). The detector therefore only records these very fast, narrow, modulated peaks [79,193, 194].

Fig. 5 - Schematic diagram of the GC×GC instrument, showing use of a short, fast elution second dimension column which produces very narrow peaks at the detector. I, injector; M, modulator; D, detector. 1D = first dimension column, 2D = second dimension column.



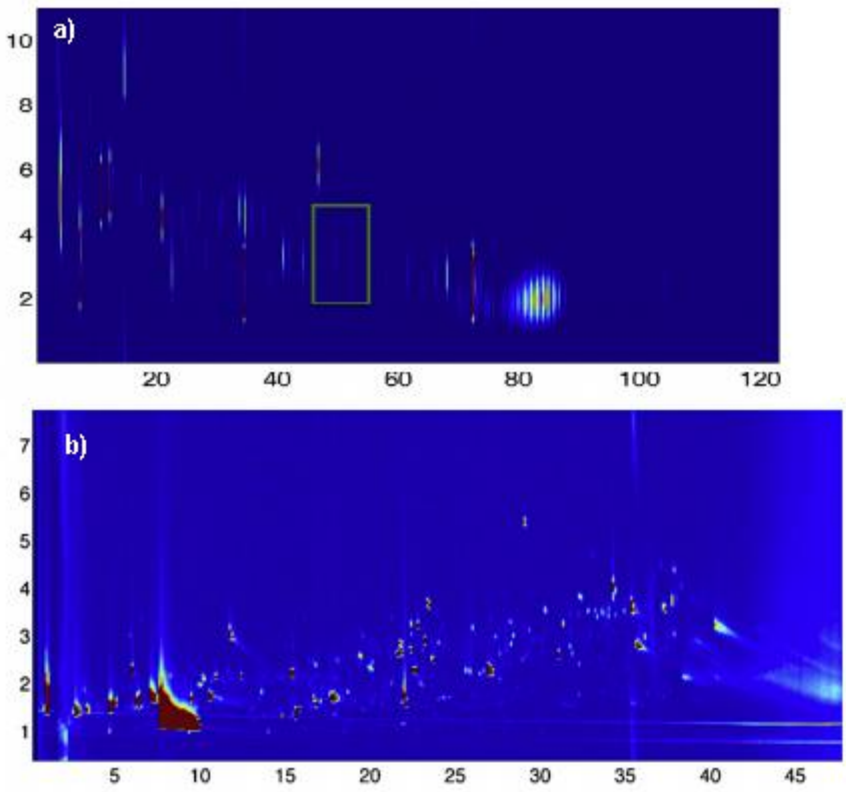
Comprehensive two-dimensional gas chromatography (GC×GC) has gained wide implementation in the analysis of complex environmental samples since pioneered nearly 30 years ago [195]. Many authors, such as Winnike et. al. [196] noted that even though the most abundant metabolites in the samples were detected on both the GC-MS and GC×GC-MS platforms, the GC×GC-MS platform detected a considerable number of chromatographic peaks that were not detected in GC-MS, resulting in the identification of a higher number of metabolites.

As the chromatographic peaks generated in the GC×GC system are narrower than the ones generated in a conventional GC, quadrupole mass spectrometers are limited in providing a sufficient data acquisition rate to obtain a Gaussian narrow peak, especially for trace analysis. The most consolidated detector at this moment for GC×GC trace analysis is the TOFMS, while ECD was also applied for organochlorine compounds, including endosulfan. Muscalu et. al. [197] developed an accredited routine method for the analysis of polychlorinated biphenyls, organochlorine pesticides, chlorobenzenes, and screening of other halogenated organics in soil, sediment, and sludge by GCxGC-µECD. This method became part of the Canada Protocol for Analytical Methods. Khummueng et. al. [100] use dual detection (NPD/ECD) in comprehensive two-dimensional gas chromatography for the multiclass analysis of pesticides from the same family.

Samanipour et. al. [198] performed an analyte quantification evaluating methods for baseline correction, peak design, and matrix effect elimination for real samples containing organochlorine pesticides. The chlorinated hydrocarbon standards and the lake water extract were analyzed by a GC×GC coupled to an electron capture and negative chemical ionization (ENCI) time of flight mass spectrometry. The separation was carried out on a 30 m length, 0.25 mm inner diameter (i.d.), 0.25

µm film thickness RXI-1MS column as the first dimension, and a 1 m length, 0.1 mm i.d., 0.1 µm film thickness BPX-50 as column as the second dimension (figure 6).

Fig. 6 - Trace level chlorinated hydrocarbon target analytes in the lake water extract. a) GCxGC-µECD. b) GC×GC/TOFMS



Source: Samanipour et. al. [198].

The first commercially successful time-of-flight mass spectrometer was based on a design reported by Wiley and McLaren [199]. Improvements have been made in mass resolution and high-speed data acquisition systems have been developed which enable the recording of all ions in each time-of-flight cycle [200]. The main limitation for the application of TOFMS at that time was the computational speed needed for the data acquisition. Nowadays, some equipment can register as much as 500 full mass spectra/min acquisition rate. This acquisition speed is not always used, especially due to the memory needed to save the big data generated [201]. However the literature presents the benefits of using acquisition rates such as 200 spectra/min to achieve a better deconvolution of mass spectra in complex samples.

Studies involving pesticide determination in environmental matrices using GC×GC/TOFMS have grown since 2002, revealing the potentiality of the technique. For a pesticide analysis, interferences with the same mass, but different molecular formulas, are commonly present, especially in complex matrices. In cases where multiple isomers of a pesticide are present in the sample, the resolution of the mass spectrometry unit often fails to differentiate these compounds. So, mass analyzers with higher resolution power and chromatographic resolution are needed in these applications [202]. In the other hand, a high-resolution time-of-flight mass spectrometer has been demonstrated as a powerful tool for reliable detection and accurate quantification of pesticide residues even at very low concentration levels. The performance characteristics obtained in many respects exceed those achievable by conventional MS analyzers [203].

Schurek et. al. [204] in their study, compares the extracts of solid phase micro extraction (SPME) analyzed using conventional GC HP 6890 and GC×GC, both coupled to a high-speed TOFMS Pegasus III detector with BPX-5 column and SupelcoWax (table 8).

Table 8: Detectability comparison for α endosulfan and other organochlorines in GC/TOFMS and GC×GC/TOFMS system under optimal conditions

| Pesticides | Quantification (bold) and identification ions | Enhancement factor | MS match factor (Similarity/reverse) | |
|---|---|---|---|---|
| | | | GC | GC×GC |
| Alpha BHC | 181,217,219 | 9.4 | 807/886 | 935/940 |
| Beta BHC | 109, 183, 219 | 6.9 | 735/875 | 758/889 |
| Gamma BHC | 181, 183, 219 | 10.2 | 798/874 | 851/898 |
| Heptachlor | 237, 272, 372 | 1.2 | - | 913/801 |
| Alpha endosulfan | 195, 241, 339 | 2.4 | 768/860 | 885/890 |
| Dieldrin | 79, 149, 263 | 7 | - | 927/942 |
| DDD | 165, 199, 212 | 3.5 | - | 892/897 |
| DDE | 316, 318, 246 | 7.1 | - | 897/915 |
| DDT | 165, 235, 237 | 4 | 859/870 | 867/908 |
| Aldrin | 109, 263, 265 | 15.2 | 876/864 | 905/906 |
| Endrin | 263, 261, 317 | 8 | 872/895 | 901/915 |

Source: Schurek et. al. [204]. Adapted.

When employing one-dimensional GC/TOFMS, confirmation based on the mass spectrum "MS correspondence" factors with the NIST library could not be achieved (the value of this parameter greater than 600 was defined as a minimum requirement) for 9 of 36 pesticides (peak at 50g.kg$^{-1}$ level) due to many coelutions. The quantification limits (LOQs) were higher than the maximum residue limits (MRLs) of the European Union. A significant improvement in the quality of the mass spectra and a distinct increase in the S/N ratios (decrease in LOQs) was achieved by the application of the GC×GC separation being demonstrated through the improvement factor. The improvement factor is defined as the ratio between S/N of the pesticide peak in GC×GC and GC. In addition, GC×GC had all analytes identified and 79% of the “MS compatibility” factors were above 850 [204,205]. The comparison of detection capabilities in GC /TOFMS and GC×GC/TOFMS can be seen in Table 8.

In the determination of multiple pesticide residues, the GC×GC/TOFMS proved to be a powerful tool to solve problems with the reliable verification of pesticide residues at very low concentration levels, applicable for the analysis of endosulfan alpha, beta and endosulfan sulfate [206]. Hoh et al. [207] described a non-target analytical method using the direct introduction of samples coupled with GC×GC/TOFMS, which could characterize a wide spectrum of non-polar contaminants (for example, PCBs, PBDEs, and PBBs) in the fat of the common Atlantic dolphin for example. Misselwitz et. al. [208], provided a good separation of the complex matrix (tobacco) of the pesticides of interest with the GC×GC/TOFMS, using a QuEChERS extraction. Analyzes of pesticides in water are reported in Table 9.

Table 9: Analysis of pesticide trace in water by GC×GC/TOFMS

| **Author** | **Extraction** | **Chromatography** | **Column** | **Analysis time** | **LOD ηg.L$^{-1}$** | **LOQ ηg.L$^{-1}$** |
|---|---|---|---|---|---|---|
| Wooding et. al. [18] | Stir bars (SBSE)<br>61 compounds | GC×GC<br>7890A<br>GC×GC-TOFMS | 1D – RTX-CLPesticides II<br>30mx0.25mmx0.2µm<br>2D - Rxi-17Sil MS<br>1.1mx0.25x0.25 µm | 34.5 min. | 0.001 - 0.19 | 0.003 - 0.63 |
| Gómez et. al. [209] | SBSE<br>27 pesticides (endosulfan) | GC×GC<br>7890A<br>GC×GC-TOFMS | 1D – Rtx-5<br>10mx0.18mmx0.20µm<br>2D – Rtx-17<br>1mx0.1mmx0.1 µm | 19 – 26 min. | - | 0.05 – 2.3 |
| Gómez et. al. [210] | SBSE<br>54 compounds (endosulfan) | GC×GC<br>7890A<br>GC×GC-TOFMS | 1D – DB-5<br>10mx0.18mmx0.20µm<br>2D – BPX-50<br>1mx0.1mmx0.1 µm | 19 – 26 min. | 0.17 - 1.96 | 0.56 - 6.53 |
| Ochiai et. al. [211] | SBSE<br>23 organochlorines | GC×GC-TOFMS | 1D - DB-5<br>10mx0.18mmx0.18µm<br>2D - TRB-50HT<br>2mx0.1mmx0.1µm | 25 min. | 0.012 – 0.044 | N.I. |
| Matamoros et. al. [212] | SPE<br>97 coumpounds<br>12 organochlorines | HP 6890N<br>GC×GC-TOFMS | 1D - TRB-5ms<br>30mx0.25mmx0.25µm<br>2D - TRB-50HT<br>2mx0.1mmx0.1µm | 48 - 53 min. | 2 - 6 | 3 - 15 |

It is observed that the detection limits for analyzing traces of pesticides in water are very low. The analytical response of comprehensive two-dimensional gas chromatography with time-of-flight mass spectrometry reaches limits as low as routine analysis equipment such as GC-MS/MS. However, little research on the water matrix of pesticides such as endosulfan has been developed in recent years.

## CONCLUSION

The evolution of analytical methods concerning the analysis of endosulfan and its metabolites in environmental samples was evaluated in the context of multiresidue pesticide analysis, together with the history of chromatography and mass spectrometry.

It was not possible to observe a single analytical solution in terms of sample preparation and analytical instrumentation. Methodologies vary in seeking excellent results with different columns, detectors, and extraction methods. Extraction methods have evolved a lot and have become more efficient, easier, faster, and more economical. Techniques such as SBSE and SPME have become promising in the analysis of endosulfan in water and the SPME method as well as SPE are widely used mainly with one-dimensional chromatographs.

Concerns about the matrix effect are also important for the choice of method. For complex matrices, the application of GC×GC/TOFMS showed improvements to solve co-eluted compounds. Cheaper and less complex chromatographs for routine analysis and detectors with greater sensitivity to achieve lower and lower LODs become more important. Comprehensive two-dimensional chromatography with time-of-flight mass spectrometry is capable of scanning divergent polarities and is best suited for analyzing all endosulfan metabolites, including endosulfan diol. Concerns about the matrix effect are also important for the choice of method. For complex matrices, the application of GC×GC/TOFMS showed improvements to solve co-eluted compounds.

The most used columns for endosulfan analysis are low polarity for the first dimension for any GC and medium polarity for the second dimension for GC×GC. For the analysis of new endosulfan analytes, two-dimensional chromatography is sought due to divergent polarities, as in the case of endosulfan alcohol.

When it comes to the best LOD results, Gas Chromatography Tandem Mass Spectrometry has shown good results with ranges from 10 to 270 pg $L^{-1}$.

## ACKNOWLEDGMENTS

This study was financed in part by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brazil (CAPES).

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