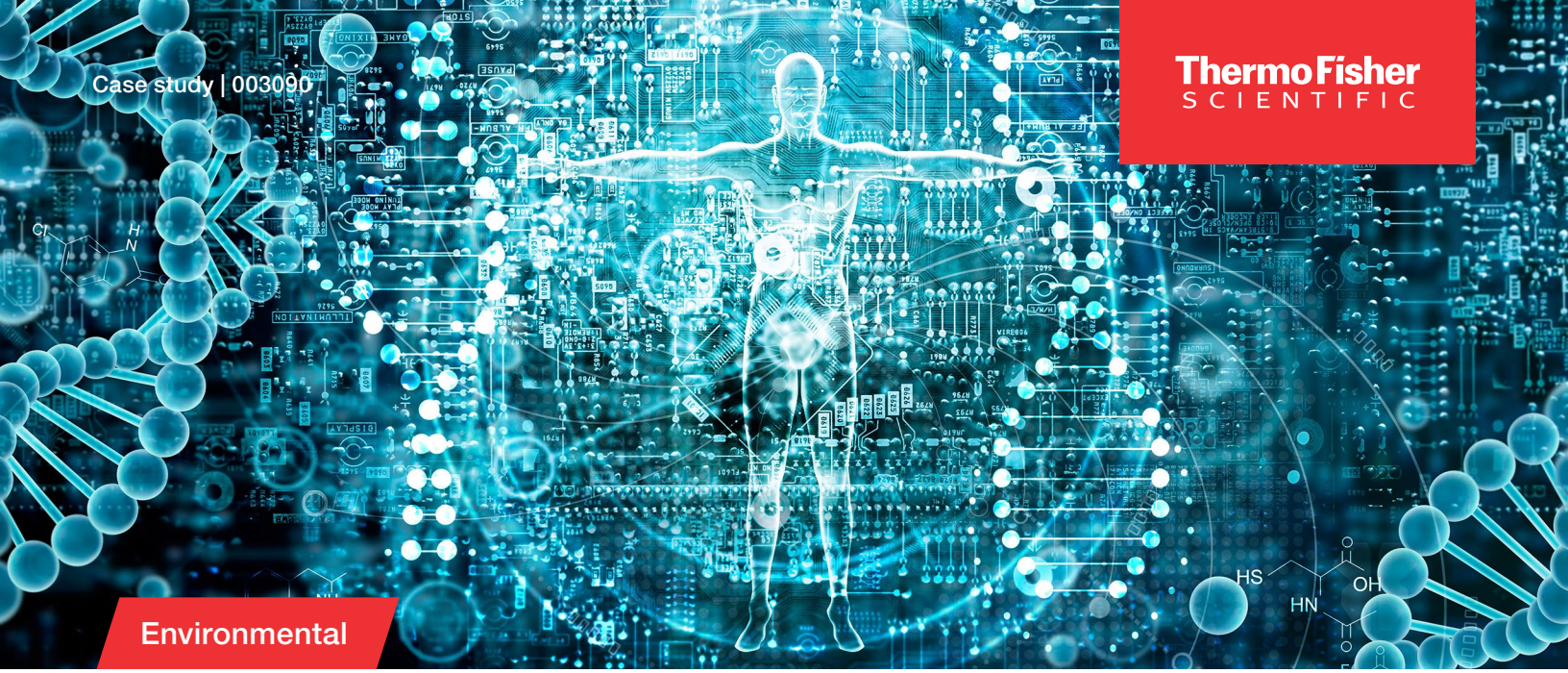

Supporting exposomics research with the Orbitrap Exploris GC 240 mass spectrometer

> "Our objective is to characterize the environment on a larger scale and to better understand the exposures that occur in human populations to mixtures of thousands of chemicals."
>
> – Associate Professor Douglas Walker, Emory University, Gangarosa Department of Environmental Health, Atlanta, GA, USA

What is exposomics?

The exposome, which is defined as the cumulative effect of environmental exposures and corresponding biological responses, helps to provide a comprehensive measure for evaluating non-genetic causes of disease. Exposomics is the study of the exposome that seeks to understand and quantify the totality of a human's lifetime exposure to various environmental factors, including chemical, physical, and biological agents. In essence, it involves assessing and analyzing the complex interactions between environmental exposures and an individual's genetic makeup, lifestyle, and other factors to understand their impact on human health and disease. By examining the cumulative effects of multiple exposures over time, exposomics provides valuable insights into the underlying mechanisms of disease development and can inform strategies for prevention and intervention.[1]

What are the challenges associated with exposomics research?

Determining the cumulative effect of exposure over an individual's lifetime comes with significant complications. Measurements of chemical exposure are compounded by the millions of estimated

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exposures that vary over a lifetime. The relationship between many of these exposures and health effects is unknown, highlighting the need to perform discovery studies that enable systematic characterization of the exposome and how it relates to health outcomes.

A major challenge in in exposomics research is achieving accurate and reproducible sample analysis within the diverse sample matrices encountered. These matrices include environmental (i.e., soil, air, water), food, and biological samples, all with a high degree of matrix complexity and variability. Methods used during sample extraction, instrumental analysis, and data reporting need to be capable of detecting targeted compounds while screening for other known/unknown compounds with high sensitivity and selectivity. Douglas Walker, Associate Professor, Emory University, explains that they *"address these challenges by developing analytical approaches that allow us to measure the exposome on a scale that is consistent with its importance to human health."* He goes on to say, *"We developed different analytical methods that leverage powerful Thermo Scientific™ HRAM MS to allow us to systematically characterize biological samples for the presence of thousands to tens of thousands of exposures."*

How does Thermo Fisher Scientific support this growing area of research

For many years, laboratories have deployed targeted analytical approaches using triple quadrupole mass spectrometry (MS) instrumentation for targeted contaminant quantification. This technology covers a wide range of chemical classes and provides the required level of sensitivity and selectivity. However, GC-MS/MS is limited to only detecting those compounds in the method acquisition list, and exposomics requires a holistic collection of information on compound presence or absence and concentration. Although GC-MS (nominal mass instruments) can provide full scan data, it lacks the selectivity for unknown screening in complex matrices.

High-resolution accurate mass (HRAM) mass spectrometry (MS) technology brings distinct advantages to meet the ever-changing demands in modern analytical research. The technology is being used by the Comprehensive Laboratory for Untargeted Exposome Science (CLUES) in the Gangarosa Department of Environmental Health at Emory University. Use of HRAM MS provides sensitive and selective non-targeted acquisition and surpasses quadrupole instruments in non-targeted applications. According to Dr. Walker, *"Orbitrap technologies have allowed us to go from measuring hundreds of exposures in a sample to now being able to screen for up to 100,000 different exposures."* This technology has provided the research group with the necessary workflow to develop robust methods for compound identification, structure elucidation, and quantitation across a variety of chemical classes within various matrices.

Thermo Scientific™ Orbitrap™ MS-based instruments offer unmatched resolving power (up to 240 000 at *m/z* 200), mass accuracy greater than 1 ppm, wide linear dynamic range, and high sensitivity.[2] However, to fully realize the benefits of a HRAM system, powerful software is essential to convert high quality data into scientific discovery. Thermo Scientific™ Compound Discoverer™ software is designed to process large non-targeted data sets acquired using Thermo Fisher Scientific's high-resolution mass spectrometry instruments. The software contains a wide range of tools for unknown compound identification and statistical analysis.

"Orbitrap GC has allowed us to go from measuring hundreds of exposures in a sample to now being able to screen for up to 100,000 different exposures."

– Douglas Walker

"Due to the high-resolution, accurate mass capabilities, combined with incredible reliability and high sensitivity for low level exposures, these instruments have transformed our ability to measure the exposome in human populations."

- Douglas Walker

Making accurate compound identifications

Once a peak or feature in the data is isolated, the next question is "what is the compound?" To answer this, the Thermo Scientific™ Orbitrap™ GC-MS Contaminants Library can be used alongside nominal mass libraries such as NIST 2023 for identification. This library is an HRAM spectral library for electron ionization (EI) GC-MS. It contains more than 1,200 retention-indexed spectra from more than 940 compounds. When used in combination with powerful Orbitrap technology and unique Thermo Scientific software data processing tools, including Thermo Scientific Compound Discoverer software, the complex challenges associated with spectral annotation are greatly reduced, providing time efficient and accurate results.

Summary

The ability to measure the complexity of the exposome has been limited by the available analytical technology to detect complex exposures patterns at varying concentrations. By using untargeted approaches with high-resolution mass spectrometry, it is possible to detect and identify ongoing exposures that may have not been expected or characterized.

High-resolution, full scan mass spectrometry using Orbitrap technology provides a solution for:

- Detection and quantification of compounds using an untargeted full scan acquisition that is both highly selective and sensitive.
- Identification and elucidation of the chemical composition of unknown compounds.
- Retrospective analysis of samples long after data acquisition.

The combined capability of both the Orbitrap Exploris GC 240 mass spectrometer and Compound Discoverer software with spectral libraries is an excellent tool to support exposomics research.

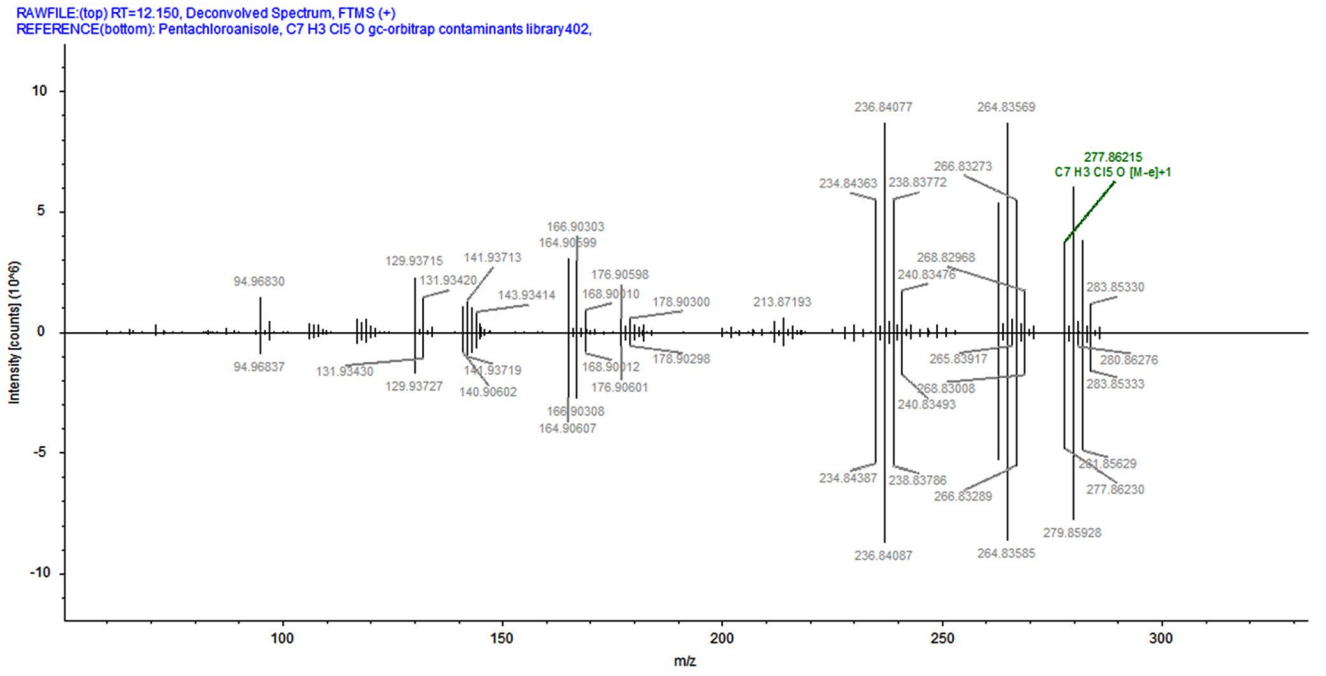

Figure 1. Compound Discoverer software with compound (Pentachloroanisole) matched with the Orbitrap GC-MS HRAM contaminants library

About Douglas Walker

Douglas Walker, PhD, is an Associate Professor in the Gangarosa Department of Environmental Health at Emory University and an adjunct Assistant Professor at Utrecht University. Before joining Emory University, Dr. Walker was an Assistant Professor in the Department of Environmental Medicine and Public Health at the Icahn School of Medicine in New York. He is an environmental engineer and analytical chemist with training in metabolomics and developing EWAS (exposome-wide association study) methodologies for environmental health and precision medicine research. He received his PhD in Environmental and Water Resources Engineering from Tufts University. At Emory University, Dr Walker's research focuses on continued development and application of advanced analytical strategies for measuring the occurrence, distribution, and magnitude of previously unidentified environmental exposures and assisting in delineating the mechanisms underlying environment-related diseases in humans. The approaches he developed show it is possible to measure over 100,000 chemical signals that include exposure biomarkers, nutrients, dietary chemicals, and associated biological response in a high-throughput and cost-effective manner, establishing a foundation for operationalizing the exposome framework for precision medicine. Ongoing research projects are now focused on using high-throughput exposome methods to establish disease-exposome atlases and development of methods for measuring biomarkers of complex exposures of emerging concern, including microplastics, e-waste, and polyfluorinated chemicals. Dr. Walker leads the Comprehensive Laboratory for Untargeted Exposome Science (CLUES), which was established to provide high-quality, untargeted screening of biological samples for nutrition, precision medicine, and environmental health research.

About Gangarosa Department of Environmental Health, Emory University

By adopting an interdisciplinary approach, the Gangarosa Department of Environmental Health (EH) focuses on chemical, physical, and microbial hazards present in natural and built environments that range from the molecular to planetary and local to global scales. The breadth of research in the department reflects the diversity of backgrounds and interests of our faculty, students, and alumni. We tackle complex environmental health concerns from multiple angles with a variety of methods. Our department has particular strengths in air pollution, toxicology, chemical exposures, climate change, and water, sanitation, and hygiene (WASH). We pride ourselves on our dynamic partnerships with other universities, governmental agencies, non-profit organizations, and private companies. Our department is also home to a number of research centers tackling many of the most pressing environmental health issues facing our world today.

References

1. Fuentes, et al. Operationalizing the Exposome Using Passive Silicone Samplers. *Current Pollution Reports* **2002**, *8,* 1–29.
2. Thermo Fisher Scientific Technical Note 10730: Mass resolving power of 240,000: for confident compound identification, 2021. https://assets.thermofisher.com/TFS-Assets/CMD/Technical-Notes/tn-10730-gc-ms-power-confident-compound-identification-tn10730-en.pdf

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