UNIVERSITAT DE BARCELONA

Assessment of the lipidomic effects of environmental pollutants on exposed organisms using chemometric and analytical methods

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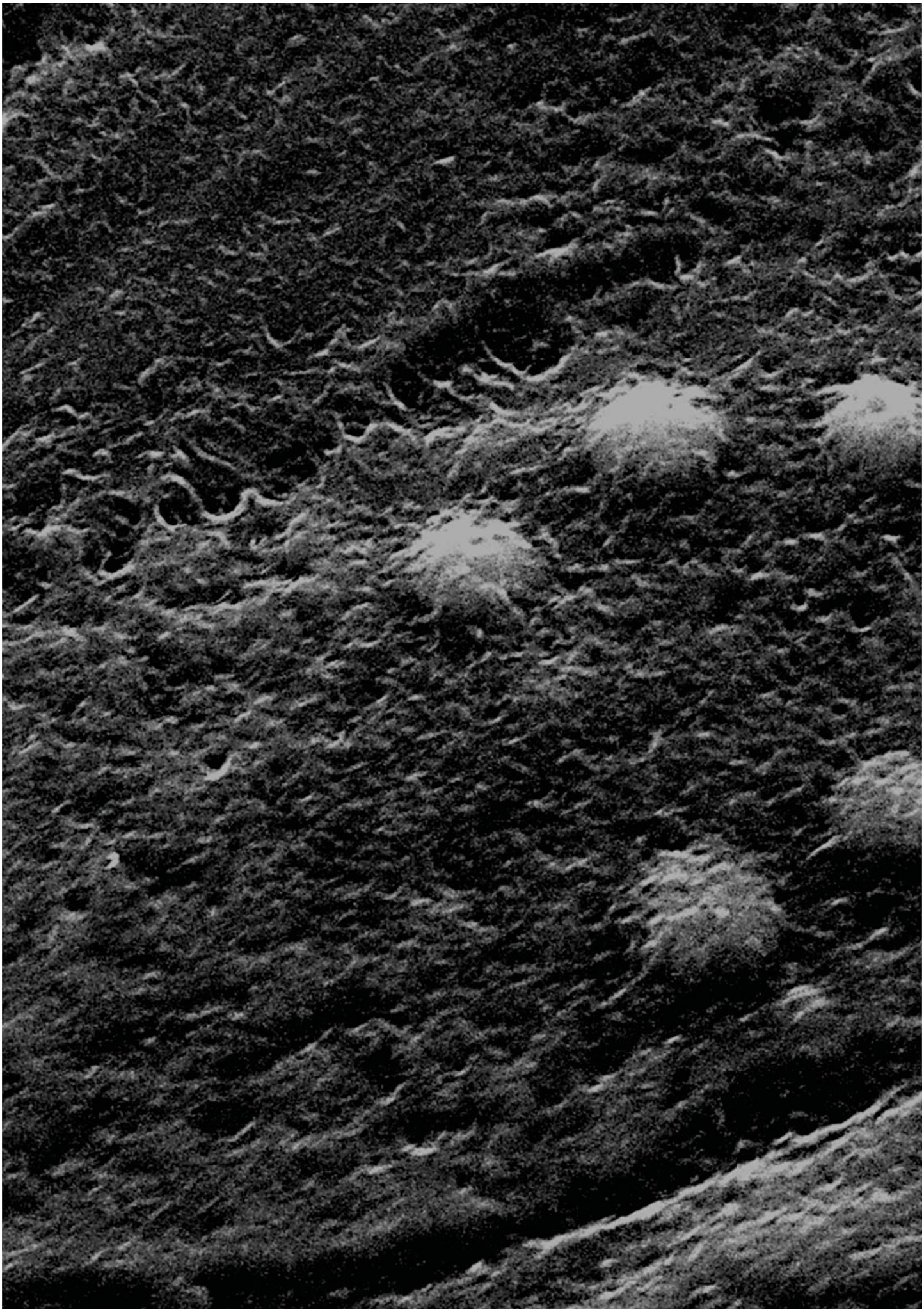

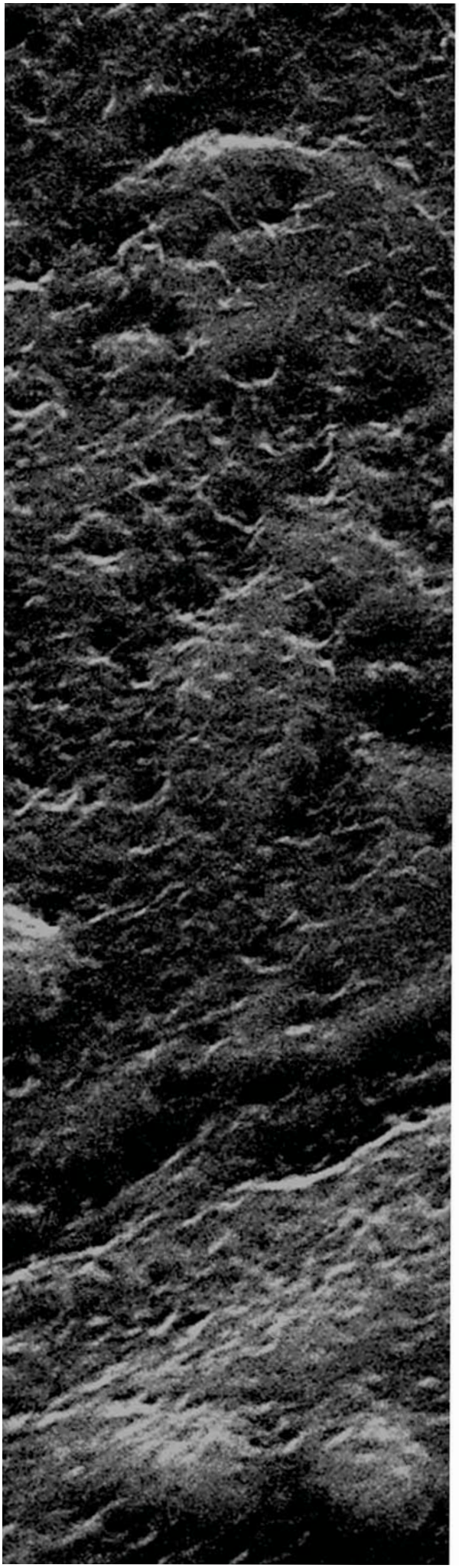

Conclusions

In the present Doctoral Thesis, the suitability of *Chemometrics* to analyse the lipidomic data generated by different analytical techniques (*i.e.*, LC-MS, IR and Raman) to further draw significant conclusions of the effects of environmental pollutants on human and environmental model-biosystems has been demonstrated.

From the scientific research performed in this Thesis, the following general conclusions can be extracted:

- The large amount of information generated in lipidomic experiments makes data analysis a complex task, which can be notably facilitated with the use of chemometric tools, as demonstrated in this Thesis. The application of chemometrics in lipidomic data analysis mainly covers the steps of: data pre-processing (to make data more computationally manageable and to correct for sample size and experimental bias), exploratory analysis (to extract and visualize the global variation of the data), data profiling and resolution (to solve chromatographic problems such as peak coelutions), feature detection (to detect potential lipid biomarkers) and variance source exploration (to evaluate the influence of the distinct factors in multifactorial designs). Among them, special attention has been paid in this Thesis in the steps of data pre-processing (data compression) and resolution. Concerning data compression, ROI search has been proven to be the most adequate strategy to compress LC-MS data sets, allowing the reduction of data dimensions with no loss of spectral accuracy. Regarding data resolution, MCR-ALS has been proven to successfully resolve chromatographic peaks, providing notable advantages compared to other LC-MS data analysis packages (*e.g.*, XCMS) that generally require peak shaping and chromatographic alignment, two steps that might have an associated error. Overall, the chemometric strategy for LC-MS metabolomic data analysis developed in this Thesis, named ROIMCR, has intended to provide an alternative approach to analyse own-generated data outside feature detection packages, and has pretended to enable a proper understanding of the nature of LC-MS omic data while analysing them.

- The capacity of some PFASs, of TBT and of some proautophagic drugs to produce lipidomic alterations in two human model-biosystems has been demonstrated in this

Thesis. On the one hand, the capacity of a mixture of eight PFASs (*i.e.*, PFBA, PFBS, PFHxA, PFHxS, PFOA, PFOS, PFNA and PFDoA) to interact with cellular membranes, producing an increase in the amount of membrane lipids, has been demonstrated on human placental choriocarcinoma JEG-3 cells. Moreover, the cytoxicity assessment of PFASs on these cells has evidenced a relation between the cytoxicity of the compounds and the length of their fluorine carbon tail, being the most cytotoxic compounds the longer ones. Also, the uptake study of these chemicals has proven a connection between their capacity to enter the cells and the elongation of their fluorocarbon chain, being the longer PFASs the ones showing higher residues in JEG-3 cells after 24 h of exposure. Finally, the evaluation of the capacity of PFASs to inhibit aromatase CYP19 activity has highlighted the ability of PFBS and PFHxS to inhibit aromatase at low endogeneous cellular concentrations. Then, the obesogenic properties of TBT have been confirmed in JEG-3 cells, producing in the latter an increment in the amount of TAG and DAG species. On the other hand, the five proautophagic drugs tested (*i.e.*, CCX, PXD, RV, GTE and XM462) have been proven to cause lipid disruption on the human glioblastoma T98G cell line by generating an increase in some phospholipid species and a relative decrease of some phospholipids containing polyunsaturated acyl groups. The latter results suggest an inhibitory capacity of proautophagic drugs of some fatty acid desaturases.

- The lipidomic (and metabolomic) alterations caused by four PFASs and of five CBNs have been evidenced in two environmental model-biosystems. First, the capacity of four PFASs (*i.e.*, PFBS, PFOA, PFOS and PFNA) to alter the metabolites and lipids (mainly fatty acids) of *Xenopus laevis* A6 kidney epithelial cells has been demonstrated. Such alterations have been observed to be different depending on the cell differentiation status (*i.e.*, monolayer or domes), the moment of exposure (*i.e.*, pre- or post-dome formation) and the cell population. The toxicity assessment of the four PFASs on A6 cells has evidenced the capacity of PFOS and PFOA to inhibit cell proliferation, producing maximum cell depletion after 48 h of treatment. Secondly, the capacity of five CBNs (*i.e.*, C_{60}, SWCNT, short MWCNT and long MWCNT) to disrupt the lipids of brain, gonads and gastrointestinal tracts of male and female zebrafish (*Danio rerio*) has been proven. Specifically, it has been evidenced an impact of CBNs on cellular membrane lipids,

suggesting an autodefence mechanism of cellular membranes against CBN-induced oxidative stress. Moreover, it has been demonstrated the capacity of short MWCNTs and SWCNTs to increase global genomic methylation in female zebrafish tissue samples.

- The recent advances in analytical techniques allow improved performance of lipidomic studies with enhanced lipid characterization. In this Thesis, the adequacy of LC-MS techniques together with spectroscopic techniques (*i.e.*, IR and Raman) to perform lipidomic experiments has been demonstrated. Also, it has been proven that the information generated by these two analytical approaches is different, although complementary. While IR and Raman spectroscopic fingerprints provide global information of lipid molecules, LC-MS provides a higher degree of structural information, leading to the identification of the molecular formulas of lipid species. However, it can be concluded that the lower identification power of spectroscopic techniques is compensated with the advantages associated to the easier sample arrangement that they require and their non-destructive nature compared to LC-MS.

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