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Integrated metabolomic, lipidomic and steroidomic profiling for revealing signatures and markers of effect induced by bisphenols exposure on human testicular function

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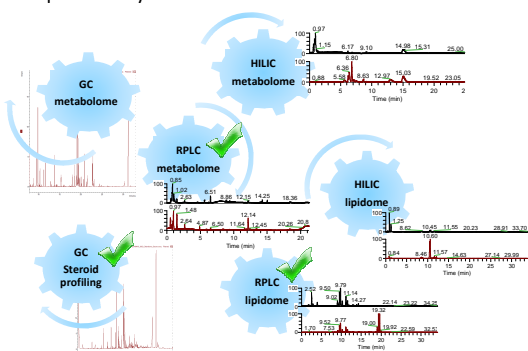
Introduction

The Newplast research project (ANR-13-CESA-0012-01) focuses on substitutes of bisphenol A (BPA) which are used in the manufacture of polycarbonate and epoxy resins, including food contact materials. The effect of BPA and related substitutes (BPS and BPF) on testicular function was assessed on adult (TEXAS) models using an integrated metabolomic, lipidomic and steroidomic profiling approach. Three complementary workflows were then combined to generate a unique set of biological signatures as a support for markers of effect discovery. A sample preparation permitted to fractionate each characterized sample into one polar fraction for metabolomic profiling, and one apolar phase for lipidomic and steroidomic profiling. Moreover a comprehensive characterization from both culture medium (exo-metabolome) and testicular tissue (endo-metabolome) was achieved.

Multi-analytical platform and automatic annotation

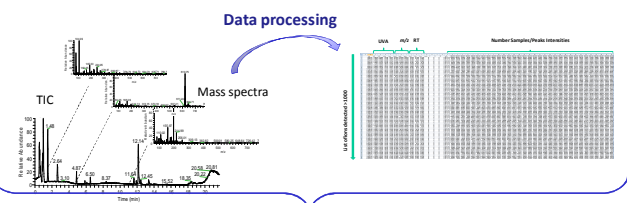
OMICS descriptors acquisition

➤ Several complementary characterization of sub-fraction of the metabolome



Data processing and signal annotation

➤ A semi automated process from data normalization, to peak annotation



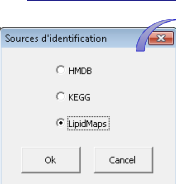
Excel macro
In-house Database ID:

name	rt	rt max	rt min
M281T431	0.00096247	3.148821967	

Metabolites ID: AM and RT
Automatic annotation



Other databases ID (HMDB, KEGG and LIPID MAPS):



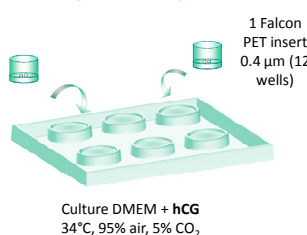
name	p-value	fold	identification
M281T431	0.00096247	3.148821967	[LIPID01020206-H]

Experimental

1 Experimentation



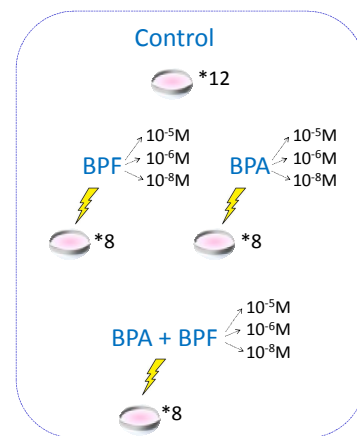
Testis collection & fragmentation into ≤ 3 mm³ pieces



1 Falcon PET insert 0.4 μm (12 wells)
Culture DMEM + hCG 34°C, 95% air, 5% CO₂

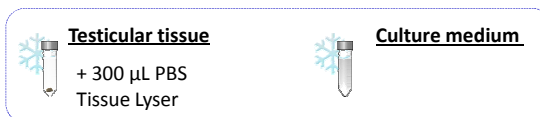
2 Exposure

➤ Assessment of BPA, BPF and BPA+BPF mixture effect



3 Sampling

➤ Complementary characterization of endo and exo metabolome



30 μL of matrix

+ 190 μL MeOH (vortex 20 s)
+ 380 μL Chloroform (vortex 20 s)
+ 120 μL Water (vortex 20 s)
Equilibration room temperature 10 min
Centrifugation (8000 g, 10 min, T 10 °C)

MeOH + Water phase

CHCl₃ + MeOH phase

Metabolomic

Steroidomic

Lipidomic

Conclusion

The complementary multi-platform approach to sample preparation step and fingerprints acquisition allows a comprehensive characterization of samples. The development of an experimental spectral database greatly facilitates metabolite identification based on retention time, accurate mass and fragmentation pattern. This workflow is applied to the Newplast research project. The data are still being processed however pre-tests have already revealed significant differences between the treated groups and controls, particular molecules belonging to fatty acids and amino acids.