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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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ROYER Anne-Lise¹, GUITTON Yann¹, DESTOITS-LETHIMONIER Christelle^{2,3}, MAZAUD-GUITTOT Séverine^{2,3}, GALLART-AYALA Hector¹, HENNIG Kristin¹, MORVAN Marie-Line¹, JEGOU Bernard^{2,3}, LE BIZEC Bruno¹, ANTIGNAC Jean-Philippe¹

¹ Laboratoire d'Étude des Résidus et Contaminants dans les Aliments (LABERCA)
USC INRA 1329, Oniris, LUNAM Université, BP 50707, 44307 Nantes Cedex 3, France
Fax : +33 (0)2 40 68 78 78 - Tél : +33 (0)2 40 68 78 80
laberca@oniris-nantes.fr

² Inserm U1085 IRSET, SFR Biosit, Campus de Beaulieu, Rennes, France
Biosit - Université de Rennes 1 - Campus de Villejean - Bât. 8 - 2 avenue du Professeur Léon Bernard - 35043 Rennes Cedex
<http://www.irset.org/> - Tél : +33 (0)2 23 23 69 11

³ Université de Rennes I, Campus de Beaulieu, Rennes, France
2 rue du Thabor CS 46510 35065 Rennes cedex
<https://www.univ-rennes1.fr/> - Tél : +33 (0)2 23 23 61 23



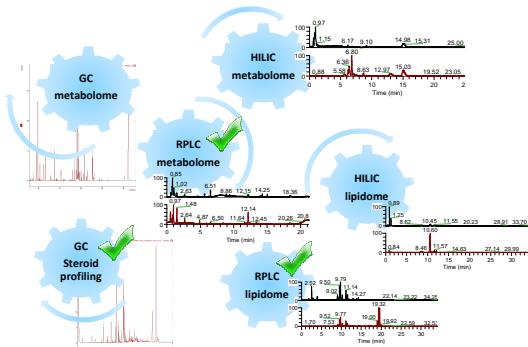
Introduction

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

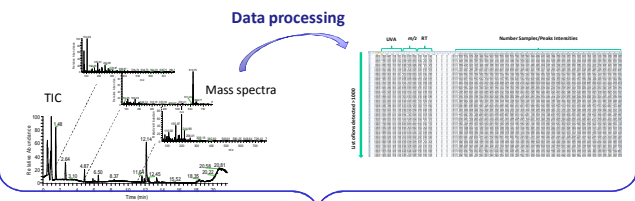
OMICS descriptors acquisition

➤ Several complementary characterization of sub-fraction of the metabolome



Data processing and signal annotation

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

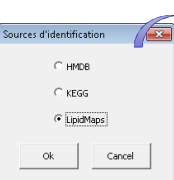


Excel macro
Metabolites ID: AM and RT
Automatic annotation

In-house Database ID:

name	SMILES	RT (min)	MS (m/z)
M281T431	C18H36O2	14.22	281
M281T432	C18H36O2	14.22	281
M281T433	C18H36O2	14.22	281
M281T434	C18H36O2	14.22	281
M281T435	C18H36O2	14.22	281
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M281T500	C18H36O2	14.22	281

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



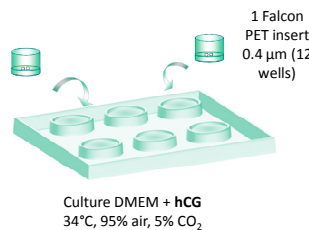
name	p-value	fold	identification
M281T431	0.00096247	3.148821967	[LIPIDMAPS020206-H]

Experimental

1 Experimentation



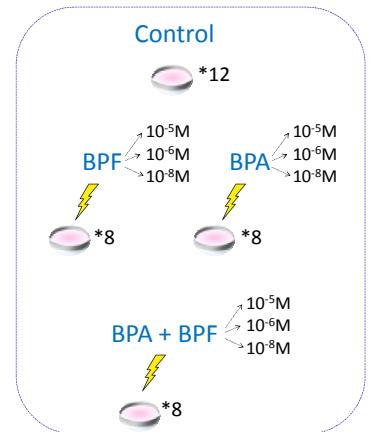
Testis collection & fragmentation into ≤ 3 mm³ pieces



Culture DMEM + hCG
34°C, 95% air, 5% CO₂

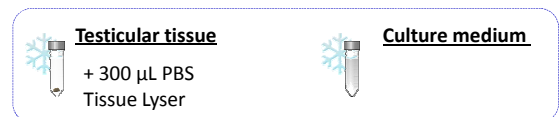
2 Exposure

➤ 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
Metabolomic

CHCl₃ + MeOH phase
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.