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Characterization of pesticide metabolites to study their effects on health

Emilien Jamin^{1,2}, Romain Vuillaume^{1,2}, Carla Orlandi^{1,2}, Ndeye Khoyane Dieng^{1,2}, Nicolas Loiseau^{1,3}, Anne Fougerat^{1,3}, Clémence Rives^{1,3}, Laurence Gamet-Payrastrre^{1,3}

1- Toxalim (Research Center in Food Toxicology), Toulouse University, INRAE, ENVT, INP-Purpan, Toulouse, France

2- MetaboHUB-MetaToul, National Infrastructure of Metabolomics and Fluxomics, Toulouse, France

3- Toxicology and Integrative Metabolism, UMR1331 Toxalim (Research Centre in Food Toxicology), Toulouse University, INRAE, ENVT, INP-Purpan, UPS, 31027 Toulouse, France

Introduction:

The exposome concept has led to the toxicological assessment of pollutant mixtures. To assess the metabolic consequences of chronic dietary exposure to a pesticide cocktail, a preclinical study was performed in mice fed a standard or a western diet and exposed to the individual admissible daily intake (ADI) of 4 pesticides in mixture. Thus, the characterization of residues (active substance and its metabolites) would not only support exposure but also provide a better insight of the observed effects. However, in a context of low-dose exposure and in the absence of commercial standards, detecting, identifying, and quantifying metabolites is challenging.

Experimental design to study the combined effects of pesticides and western diet on metabolic diseases:

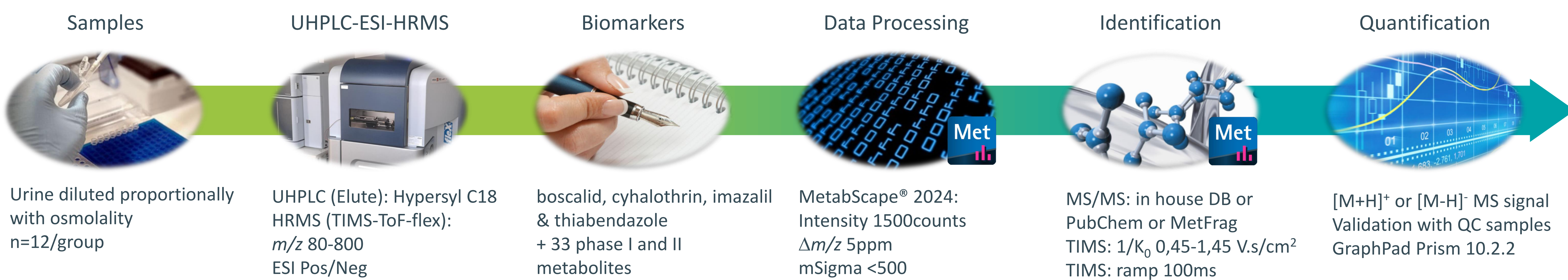
Cocktail effect of 4 pesticides : **boscalid, cyhalothrin, imazalil & thiabendazole**

2 diets : **Western Diet (WD)** enriched with fat and sugar vs **Chow Diet (CD)**

Mice unexposed (0) or exposed to the ADI or 10 times ADI of each pesticide in each diet

Collection of urine after 15 weeks of exposure

Material and Method:



Experimental Results:

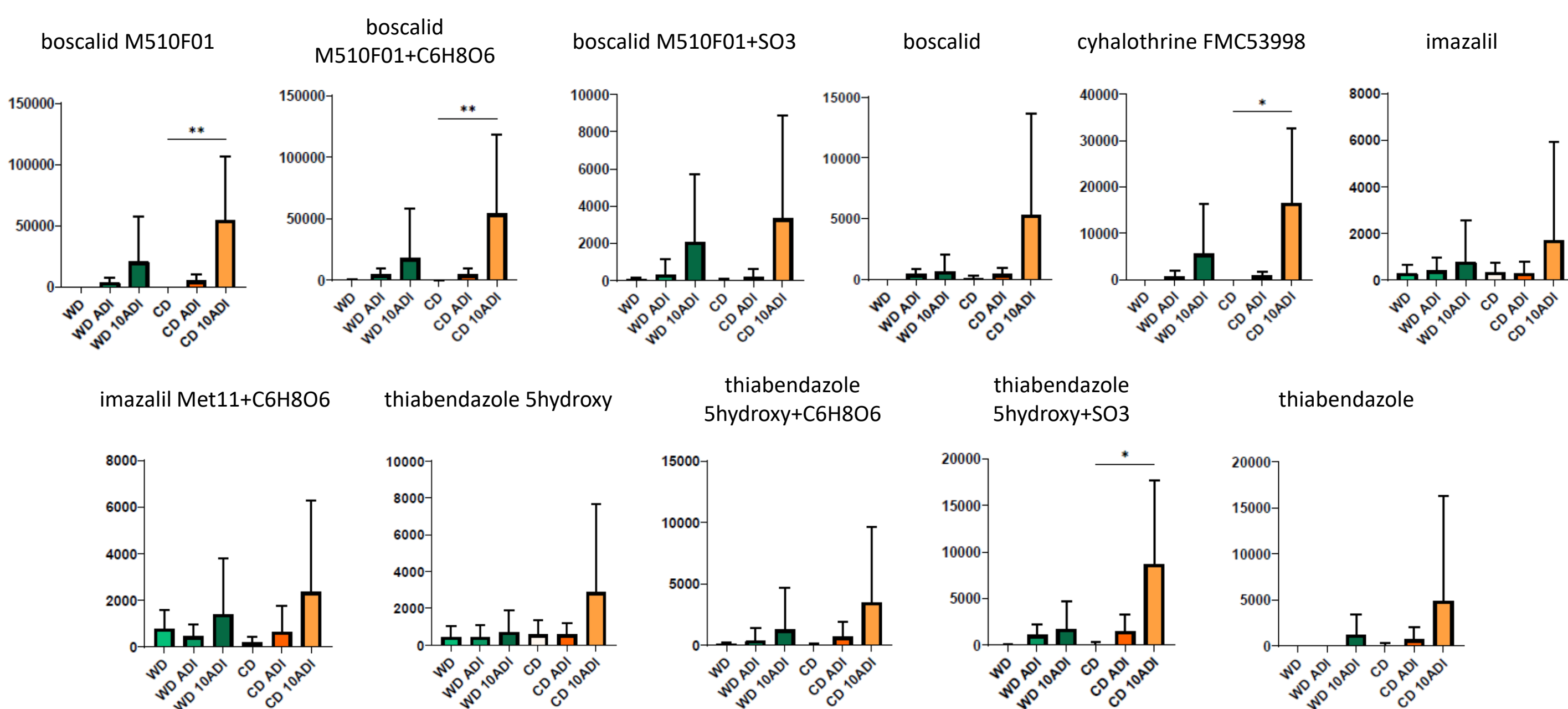
- Identified and quantified exposure biomarkers:

Name	Chemical Formula	Identification level*	Annotation confidence**	Inchi
boscalid M510F01	C18H12Cl2N2O2	2	b,c,f,g,h,i	InChI=1S/C18H12Cl2N2O2/c19-12-5-9-11(4-6-12)15-10-13(2)7-8-16(15)22-18(2)14-2-1-9-21-17(1)4(2)0/h1-10,23H,(H,22,24)
boscalid M510F01 +C6H8O6	C24H20Cl2N2O8	2	b,c,f,g,h,i	InChI=1S/C24H20Cl2N2O8/c25-12-5-3-11(4-6-12)15-10-13(35-24-19(31)17(29)18(30)20(36-24)23(33)34)7-8-16(15)28-22(32)14-2-1-9-27-21(4)26/h1-10,17-20,24,29-31H,(H,28,32)(H,33,34)
boscalid M510F01 + SO3	C18H12Cl2N2O5S	3	b,c,i	InChI=1S/C18H12Cl2N2O5S/c19-12-5-3-11(4-6-12)15-10-13(27-28(24,25)26)7-8-16(15)22-18(2)14-2-1-9-21-17(1)4(2)0/h1-10H,(H,22,23)(H,24,25,26)
boscalid parent	C18H12Cl2N2O	1	a,b,c,d,h,i	InChI=1S/C18H12Cl2N2O/c19-12-5-9-11(4-6-12)15-10-13(2)7-8-16(15)22-18(2)14-2-1-9-21-17(1)4(2)0/h1-10H,(H,22,23)
cyhalothrine FMC53998 +C6H8O6	C15H18ClF3O8	2	b,c,f,h,i	InChI=1S/C15H18ClF3O8/c1-14(2)4(3-5)16(15)17(18)19(16)12(25)27-13-9(2)7(20)8(21)10(26-13)11(23)24/h3-4,6-10,13,20-22H,1-2H3,(H,23,24)/b5-3
imazalil	C14H14Cl2N2O	1	a,b,c,d,h,i	InChI=1S/C14H14Cl2N2O/c1-2-7-19-14(9-18-6-5-17-10-18)12-4-3-11(15)8-13(12)16/h2-6,8,10,14H,1,7,9H2
imazalil Met11 +C6H8O6	C17H18Cl2N2O7	3	b,c,i	InChI=1S/C17H18Cl2N2O7/c18-8-1-2-9(10)19(5-8)11(6-21-4-3-20-7-21)27-17-12(15)24(25)13(22)14(23)14(23)14(23)17/h1-5,7,11-14,16-17,22-23,26H,6H2,(H,24,25)
thiabendazole 5hydroxy	C10H7N3OS	2	b,c,f,h,i	InChI=1S/C10H7N3OS/c14-6-1-2-7-8(3-6)13-10(12-7)9-4-15-5-11-9/h1-5,14H,(H,12,13)
thiabendazole 5hydroxy + C6H8O6	C16H15N3O7S	2	b,c,f,g,h,i	InChI=1S/C16H15N3O7S/c20-10-11(21)13(15)23(24)26-16(12)10(22)25-6-1-2-7-8(3-6)19-14(18-7)9-4-27-5-17-9/h1-5,10-13,16,20-22H,(H,18,19)(H,23,24)
thiabendazole 5hydroxy + SO3	C10H7N3O4S2	2	b,c,e,g,h,i	InChI=1S/C10H7N3O4S2/c14-19(15,16)17-6-1-2-7-8(3-6)13-10(12-7)9-4-18-5-11-9/h1-5H,(H,12,13)(H,14,15,16)
thiabendazole	C10H7N3S	2	b,c,e,h,i	InChI=1S/C10H7N3S/c1-2-4-8-7(3-1)12-10(13-8)9-5-14-6-11-9/h1-6H,(H,12,13)

* Sumner et al., Metabolomics (2007)

** (a) RT=standard, (b) m/z=theory, (c) isotopic pattern=theory, (d) MS/MS=standard, (e) MS/MS=onlineDB, (f) MS/MS=expertise or MetFrag, (g) annotated in ESI+ and ESI-, (h) CCS=in silico, (i) in concordance with biological design

- Relative quantification of exposure biomarkers:



Conclusions:

Following a dietary exposure of mice to a mixture of 4 pesticides, 11 biomarkers of exposure were identified according to chromatography, HRMS, MS/MS, ion mobility, and quantified in urinary samples. Obviously, exposure levels were higher in animals fed a CD and exposed to the highest dose (10ADI). Interestingly animals fed a western diet presented lower levels of pesticide residues compared to animals fed a CD. Experiments are under progress to understand this influence of diet on the bio-availability of pesticides.

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