Mixtures prioritization based on exposure and hazard

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Example: dietary exposure

Individuals are exposed to various substances which can interact

~ 200 Pesticides  ~ 30 Inorganic contaminants and minerals
~ 10 Additives  ~ 10 Phyto-oestrogens  ~ 20 Mycotoxins
~ 50 Dioxins, PCB, furans, brominated flame retardants, Perfluoroalkyl acids

French Total Diet Study 2, Anses, 2011

Unrealistic to test all possible combinations:
Pesticides: $2^{200} = 1.6 \times 10^{60}$ Combinaisons !!!

How to prioritize mixtures? $\rightarrow$ need methods to identify mixtures
Current approaches for mixture selection

Based on toxicological data (Efsa, US-EPA)
Targeted organ / specific effect / mode / mechanism of action
✓ Chemical families (Dioxins and PCB-DL, Triazoles, Organophosphates,...)
✓ Cumulative assessment group, CAG, EFSA
✓ Common mechanism group, CMG, US-EPA

Based on exposure data (Périclès*, French ANR project)
✓ Directly from dietary co-exposure 1
✓ Through cluster diet 2

Based on toxicological and exposure data 3

*Crépet A., et al. (2013) The PERICLES research program: an integrated approach to characterize the combined effects of mixtures of pesticides residues to which the French population is exposed. (Toxicology).
Mixture selection from exposure and cluster diet
In real life: more than 2 chemicals
Define combinations from a large number of chemicals

Combined exposures to two pesticides

- Individuals weakly exposed to both pesticides
- Individuals highly exposed to both pesticides
- Highly exposed to Maleic Hydrazide
- Weakly exposed to Chlorprophane

Number of exposed individuals

Density

Exposure levels

++

Maleic hydrazide

Chlorprophane
Method

Individuals are exposed to mixtures because
✓ They combine different food during a meal, a day, life...
✓ One food can contain several substances

The population can be divided in different subgroups
✓ Due to particular combinations of consumed food: specific diet
✓ Due to particular contamination: regionality, high contaminated sites

Mathematical methods

Cluster individuals with similar profiles in subgroups
Extract mixtures by studying correlations/latent variables

➢ Crépet A., Tressou J. (2011). Bayesian nonparametric model for clustering individual co-exposure to pesticides found in the French diet. Bayesian Analysis. 6(1), 127:144.
Concentrations of food substances in individuals combined exposures to substances $i=1, \ldots, n$.

Groups

- Low exposures to $j$ substances
- High exposures to $k$ substances
- High exposures to $l$ substances and low exposures to $m$ substances

Selection Criteria
- High Exposures
- High Correlations

Mixtures linked to meat and pasta
Mixtures linked to fruits and vegetables
Mixtures linked to junk food

Food vectors of mixtures?

Concentrations of food substances
A food substance
A food substance in individuals
Combined exposures to substances $i=1, \ldots, n$
Substances $s=1, \ldots, S$
Low exposures to $j$ substances
High exposures to $k$ substances
High exposures to $l$ substances and low exposures to $m$ substances

Food diet
- High consumers of meat and pasta...
- High consumers of fruits and vegetables...
- High consumers of junk food
Mixture selection method

A combination of Sparse Non-negative Matrix Underestimation (SNMU) and hierarchical classification

Matrix U shows mixtures

Matrix V shows how individuals are exposed to mixtures

Balance between

- Exposure Correlations
- Exposure levels
- Similar exposure profiles
- Cluster diet
- Relative potency factors

Matrix U

Weight in total exposure

3 groups
Chronic exposures to 153 substances (TDS 2, Anses 2011)
6 groups of individuals combining 1 or 2 of the 6 major consumption systems (CS) and therefore exposed to 1 or 2 mixtures among the 6 major mixtures

<table>
<thead>
<tr>
<th>Group</th>
<th>% of CS</th>
<th>Major Consumption Systems</th>
<th>Mixtures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>36%</td>
<td>Soda, Pizza, Sandwich, Hamburger, Chocolate spread, Sauteed potatoes or chips Salted potato crisp, etc.</td>
<td>PHE, FA (PAHs), Zer (Mycotoxins), Pirimiphos-methyl, Piperonyl Butoxide PBDEs Co, Acrylamid, Ni, etc.</td>
</tr>
<tr>
<td></td>
<td>22%</td>
<td>Baguette, Beef steak, Pasta, Butter, Camembert, Sugar, Eggs, etc.</td>
<td>HT2, Don, Niv, Zer (Mycotoxins), BPA, PY, PHE (PAHs) Cd, Co, Te, Pb, etc.</td>
</tr>
<tr>
<td>Group 3</td>
<td>49%</td>
<td>Peach, Melon, Abricot, Tomato, Cucumber, Vinaigrette, Bean, Radish, Strawberry, etc.</td>
<td>Α-Cyhalothrin, Chlorpyrifos-ethyl, Acrinathrin, Procymidone, Phosmet, Chlorothalonil, Cyprodinil, etc.</td>
</tr>
</tbody>
</table>

*significantly different from the whole population

T. Traoré, C. Béchaux, V. Sirot, A. Crépet. 2016 To which chemical mixtures is the French population exposed? Mixture identification from the second French Total Diet Study, Food and chemical toxicology
Concentrations

A food substances

Consumption

A food n individuals

Combined Exposures

Substances i=1,…,...,…..,n

j substances

k substances

l substances

m substances

Exposure Profiles

Groups

1

n individuals

2

3

Selection Criteria

High Exposures

High Correlations

Selection Criteria

High Consumption & concentrations

Substances associated to diet

Food diet

High consumers of meat and pasta...

High consumers of fruits and vegetables...

High consumers de junk food

New mixtures

Mixtures linked to meat and pasta

Mixtures linked to fruits and vegetables

Toxicological properties

Combined Exposures

Substances toxicity?

Selection Criteria

High Exposures and Correlations

Common effect and high toxicity
Mixture selection from co-exposure and hazard

EFSA, Cumulative Assessment Groups (CAGs)

For Pesticides

- Level 1: targeted organ
- Level 2: specific effect
- Level 3: mode of action
- Level 4: mechanism of action

Level 1 and 2 done
Done for 16 organs
EFSA reports 2012, 2015

NOAELs (no observed adverse effect)

Relative potency factors (RPFs)
Convert each substance in toxicity of an index compound

\[ RPFs = \frac{\text{NOAEL}_i}{\text{NOAELs}} \]
Mixture selection strategy

EFSA, Cumulative assessment groups (CAGs)

\[ RPF_s = \frac{NOAEL_i}{NOAEL_s} \]

Combined exposure

\[ E_{s,i} \times RPF_s \]

Selection Criteria
- High Exposures and Correlations
- Common effect and high toxicity

Mixtures from co-exposures and hazard
Risk based mixtures

Euromix
Applied to pesticides and liver CAG

EFSA, Cumulative assessment groups (CAGs)

- Level 2: Steatosis, 144 pesticides

Combined exposure

France, 194 pesticides, Chronic, adults, 2010-2014

\[ E_{s,i} \times RPF_{s} \]

120 pesticides

70 pesticides \( \geq LOD \)
with censored value= 0

Mixtures from co-exposures and hazard
Risk based mixtures

Selection Criteria

- High Exposures and Correlations
- Common effect and high toxicity

Crépet et al. Mixtures of chemicals that European populations are exposed to: selection from dietary exposure and hazard data, in progress
Steatosis, Adults, Chronic exposure (France)

<table>
<thead>
<tr>
<th>Substances</th>
<th>SNMU weight</th>
<th>Exposure µg/kg bw.d</th>
<th>RPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imazalil</td>
<td>84%</td>
<td>0.75</td>
<td>2.53</td>
</tr>
<tr>
<td>Dithiocarbamates</td>
<td>12%</td>
<td>0.14</td>
<td>0.35</td>
</tr>
<tr>
<td>Carbendazim and benomyl</td>
<td>1%</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>1%</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>1%</td>
<td>0.02</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Variance explained by the mixture: 77.2%
Compounds of the main mixture per country

Food drivers
Imazalil: oranges, grapefruit, mandarins, bananas
Dithiocarbamates: fungi, wine grapes, lettuce, apple and concumbers for Greece
Conclusions and limits

The developed methods lead to identify mixtures
✓ Based on observed combined exposures
✓ Considering dietary habits
✓ Identifying populations exposed to specific mixtures
✓ Using toxicological information such as CAG and NOEAL
→ Could be applied to environmental/aggregated exposure, contamination and biomonitoring data

Results depend of the data
✓ A snapshot at a given time → need actualized data at European level
✓ Censored data → need appropriate method for mixtures
✓ CAG → continue efforts, extend to other substances than pesticides
Thanks to my coworkers

Anses-DER: Thiéma Traore, Marie Vanacker, Louis Trocellier, Véronique Sirot

PERICLES participants: Fanny Héraud, Jean-Charles Leblanc, Jessica Tressou, Vanessa Graillot, etc.

Euromix partners: in particular Jacob van Klaveren, Corinne Sprong, Hilko van der Voet, Waldo de Boer, Ad Peijnburg, Emiel Rorije, Angelo Moretto etc.

Thank you for your attention
Concentrations of substances in food consumption by individuals. Combined exposures of substances to different groups: high exposures to $k$ substances, high exposures to $l$ substances, and low exposures to $m$ substances. Selection criteria for new mixtures: high exposures and correlations. Toxicological properties and combined exposures to food diets (high consumers of meat and pasta, fruits and vegetables, and junk food).