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Full length article

## Cocktails of endocrine disruptors in the different diets of French consumers

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### ABSTRACT

With a view to identifying main endocrine disruptors (ED) mixtures to which French consumers are exposed through food, their main diets were modelled using an adapted dimension reduction method. Seven specific diets could be modelled for adults while only one overall diet was considered for children aged 3–17 years. The knowledge of the contamination levels of 78 known or suspected endocrine disrupting compounds in the foods constituting these diets, collected in the frame of the second French Total Diet Study, made it possible to explore the mixtures of EDs to which consumers are exposed. We have thus shown that the ED substances most present in mass concentration are comparable for the whole population, whatever the diet considered. However, a second approach made it possible to highlight, for a given diet, the substances whose exposure is statistically higher than in the diet of the general population. Thus, significantly different ED mixtures could be established for each diet. For example, diets with a high proportion of animal-based foods induce significantly higher exposures to some persistent organic pollutants (e.g., PCDD/F, brominated flame retardants), whereas these exposures are lower for Mediterranean-type diet. On the other hand, the latter, richer in fruits and vegetables, is the one for which pesticides represent a specific signature. These results now pave the way for studying the specific effects of these cocktails of endocrine disruptors, each of which is representative of a type of chronic exposure linked to specific diets.

### 1. Introduction

Individuals are exposed to a number of chemical substances on a daily basis through their environment and particularly through food. Such chronic exposure is known to be associated, in the short or long term, with public health issues. Food contamination by chemical substances can occur at any step of the food chain, including vegetal and animal productions as well as transformation, preservation, packaging, distribution and preparation processes. The result is the presence in food of diverse chemical contaminants, either of natural or anthropic origin. Among the substances of concern, some chemical contaminants are known or suspected endocrine disruptors (ED). Several lists of potential EDs have been drawn up in different parts of the world, based on various criteria and objectives. As a result, the number of substances on these lists varies considerably, from a dozen to several thousands. For example, the French Agency for Food, Environmental and Occupational Health Safety (ANSES) has drawn up a list of 906 substances of interest

for their potential endocrine activity, which includes a number of substances already banned or heavily regulated in Europe, and others that are not used in European countries. This list contains substances such as, e.g., Polycyclic Aromatic Hydrocarbons (PAHs), Dioxins and Polychlorinated Biphenyls (PCBs), Poly- and perfluorinated Compounds (PFAS), Brominated Flame Retardants (BFRs), Metals, Phytoestrogens, Mycotoxins and Pesticides (Agence nationale de s ecurit e sanitaire de l'alimentation de l'environnement et du travail (Anses), 2021).

The collection of food contamination data for risk assessment purposes is based on the implementation of two distinct strategies. The first enables the collection of contamination data from monitoring programs, carried out at specific country level to verify the conformity of foodstuffs with regard to contaminants (Ingenbleek et al., 2020), or surveillance programs to determine the levels of chemical substances in foods commonly consumed by the population. This approach has recently been encouraged through the Official Controls Regulation 2017/625/EC (European Parliament and Council 2017). An alternative to using data

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from surveillance and monitoring plans is the use of the Total Diet Study (TDS) approach. These studies are based on a standardized method recommended by the WHO, the Food and Agriculture Organization of the United Nations (FAO), and the European Food Safety Authority (EFSA): the stages characterizing a TDS include selecting food based on consumption data to best represent a typical diet, their preparation as consumed, and their analysis (European Food Safety Authority (EFSA), 2011).

The exposure of the population to substances present in food can be assessed by combining both food consumption and contamination data. At the French level, ANSES carries out national consumption studies (e.g., Individual and National Food Consumption Survey (INCA)) and total diet studies (TDS 1 and 2 available, 3 in progress) which respectively provide data on the dietary habits of the French population and concentration data for many chemical substances present in food consumed by the general population. The second French TDS studied about 440 chemicals (Siroto et al., 2009).

Current risk assessment of chemicals is most often carried out on a substance-by-substance basis or for substances belonging to the same chemical families (i.e., sharing a similar mode of action, e.g., dioxins) or by grouping substances according to their toxicity or specific effects on organs (e.g., dioxins and PCBs). However, the effects of these substances can be added to, cancelled out or even potentiated when they are mixed together, as is the case in food. Studying the potential effects of mixtures is now a challenge that is mobilising the scientific community because it involves a paradigm shift in the way risks are assessed. One of the key issues is to determine representative mixtures that are as close as possible to the main consumption patterns, and thus derive the “real” mixtures to which consumers are exposed (Escher et al., 2022).

Several strategies have been proposed to determine such mixtures. For instance, Crépet and co-authors proposed a statistical method based on a non-parametric Bayesian model to determine major mixtures from dietary exposures (Crépet et al., 2013; Crépet and Tressou, 2011; Crépet et al., 2013). This method made it possible to classify the population with regard to its exposure profiles and then define the mixtures based on correlations between pesticide exposures. As an alternative, a method based on non-negative matrix factorization (NMF) (Lee and Seung, 2001), consisting in reducing the size of the dataset before classification was implemented by Bechaux et al. (2013) and Traore et al. (2016) to identify chemical mixtures. The NMF method was further derived into the SNMU (Sparse and Unique Nonnegative Matrix Factorization) (Gillis and Plemmons, 2013) as implemented by Traore et al. (2018) to define real diet exposures. Most of those studies either focused on specific chemicals (e.g., pesticides (Bechaux et al., 2013; Rebouillat et al., 2021) or on specific populations (e.g., pregnant women (Traore et al., 2018), organic meat consumers (Tressou et al., 2017), women (Mancini et al., 2021)).

General population, including the most sensitive sub-populations such as children and pregnant women, is thus exposed to a mixture of known or suspected EDs through food. It is anticipated that the composition of this mixture may vary according to diet habits. The objective of this work was to define the different mixtures of EDs to which consumers are exposed *via* their main diets and compare with previous exposure profiles previously reported on the same data set, using different statistical methods. In practice, this work consisted i) in applying a SNMU-based approach to identify the diets of adults (18–79 years old) and children (3–17 years old), and ii) in highlighting the mixtures of chemical substances linked to those diets on the basis of a selection of known or suspected EDs whose levels of contamination in foodstuffs were assessed during the second French TDS. In comparison with existing work on defining chemical mixtures in food, this article broadens the scope of the results, either with regard to the type of chemical contaminants (e.g. previously limited to pesticide residues (Bechaux et al., 2013; Rebouillat et al., 2021), or the population of interest (e.g. previously focusing on pregnant women (Traore et al., 2018), organic meat consumers (Tressou et al., 2017), women (Mancini et al.,

2021). This work is also original in that it considers the critical effect as the key to selecting contaminants. Indeed, we chose to focus on known or suspected endocrine disrupting food contaminants, whatever their origin or chemical family.

## 2. Materials and methods

### 2.1. Data sets

#### 2.1.1. Consumption data

The second French « Individual and National Food Consumption Survey » (INCA 2) carried out by the French Food Safety Agency between late 2005 and April 2007 provided individual food consumptions data for both adults and children. The two independent associated random data sets included on the one hand 2,624 adults aged 18–79 years (Dubuisson et al., 2010) and on the other hand, 1,455 children aged 3–17 years (Lioret et al., 2010). Participants were initially selected in order to be representative of the French population using a three-stage random probability design stratified by region of residence, size of urban area and population category (adults and children). A sampling weight was then attributed to each subject. Their food consumptions were collected through a seven-day food record diary. Portion sizes were estimated through photographs compiled in a manual adapted from the Su-Vi-Max photographic booklet (Hercberg et al., 1994) or expressed by weight or household measures. Foods were coded according to the 1,280 food items of INCA 2 nomenclature. Demographic and socio-economic variables were also collected for each participant, such as age, body mass index (BMI) and the household monthly income.

Adults and children were considered independently in the present study. According to EFSA recommendations (European Food Safety Authority, 2009) and for the sake of comparison with previous studies, subjects who underestimated their consumption have been excluded from our final data set which led to the exclusion of 706 adults (26.9 % of the « adults » sample) and 11 children (0.8 % of the « children » sample). The average daily consumption for each food item in grams per day per kg body weight (bw) has been derived for each individual from the original data set for subsequent chronic exposure assessment. When the body weight values of the subjects were not provided, an imputation process based on regression and prediction models was applied using the weight of individuals of the same size/sex/age ( $\text{Lm}(\log(\text{weight}) \sim \text{size} + \text{sex} + \text{age})$ ).

Finally, the consumption averages obtained for each food and each subject were standardised before being submitted to the SNMU in order to cancel out the differences in weight between foods as proposed in several previous studies (Bechaux et al., 2013; Traore et al., 2018). It aims to avoid “scale effects” related to the quantities consumed, which are not comparable across foods.

#### 2.1.2. Food contamination levels

The second French TDS 2 (Siroto et al., 2009) provides the contamination levels of 445 substances in 212 types of food (Arnich et al., 2012; Nougadere et al., 2012; Siroto et al., 2013; Siroto et al., 2012; Siroto et al., 2012; Veyrand et al., 2013; Riviere et al., 2014). Sampling was carried out using INCA2 data, considering 2 main criteria, (i) the most consumed foods, (ii) foods little consumed but likely to be highly contaminated. TDS 2 was therefore built on INCA 2 classification and covers about 90 % of the entire diet. For each of the 212 types of food, the sampling plan was drawn up to take into account consumption habits in France, e.g. flavour, product origin and place of purchase (supermarket or local market, for example). Each sample was purchased twice to cover potential seasonal variation from about 2007 to 2009. In total, around 20,000 items of food were purchased in some thirty towns and cities across the country. The foods were then mixed and prepared ‘as consumed’ to make-up 1,319 composite samples representative of consumers’ shopping baskets. These composite samples were analysed for 445 substances including additives, environmental chemical

contaminants, pesticide residues, trace elements and minerals, mycotoxins, phytoestrogens and acrylamide.

In the present work, the core foods consumed by less than 5 % of the population were excluded in order to select only foods likely to be highlighted by the statistical method used to identify the main diets (SNMU). This also avoids highlighting dietary behavior that is too specific or too isolated. Thus, 178 core foods were considered to build adults diets while 168 were selected for children.

Left censored data corresponding to concentrations below the analytical limits of detection (LOD) or quantification (LOQ) were substituted based on LB (Lower Bound) scenario (EFSA, 2010). National contamination data were used and the regional values were, therefore, averaged.

### 2.1.3. Endocrine disrupting compounds selection

In a first step, the chemical contaminants quantified at least in one food sample among the 445 screened in the TDS2 (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail (Anses), 2014) were selected. In order to select ED or potentially ED substances, these 191 substances were searched in the following lists or databases:

- CED - Danish Centre on Endocrine Disruptors, "List of endocrine disrupting chemicals", 2018 (Danish Centre on Endocrine Disruptors, 2020).
- European commission Priority list (Commission and List, 2020).
- BKH report 2000 - BKH (2000). Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption - preparation of a candidate list of substances as a basis for priority setting (BKH, 2020).
- BKH report 2002 - BKH (2002). Endocrine Disruptors: study on gathering information on 435 substances with insufficient data » (BKH, 2020).
- DHI report 2007 - DHI (2007) « Study on enhancing the Endocrine Disrupter priority list with a focus on low production volume chemicals » (DHI, 2020).
- ChemSec. (2019). SIN List (ChemSec, 2020).
- European Chemicals Agency. (2020). Substance evaluation – CoRAP (European Chemicals Agency, 2020).
- TEDX. (2018). TEDX List of Potential Endocrine Disruptors (TEDX).
- Candidate List of substances of very high concern for Authorisation (published in accordance with Article 59(10) of the REACH Regulation) (ECHA, 2020).
- EDSP21 database. CompTox Chemicals Dashboard (EDSP21 database, 2020).

The substances retrieved in at least one list were subsequently searched for in the DEDuCT database (DEDuCT database, 2020; Karthikeyan et al., 2019) in order to refine the list of substances of interest. Only the substances with a mode of action based on estrogen, androgen, thyroid and steroidogenic (EATS) modalities, based on information retrieved in any of the lists or databases above, were selected. A list of 112 ED or potential ED substances was obtained. For specific groups of substances, *i.e.*, polychlorinated biphenyls, dioxins, furans, it was considered more appropriate to select congeners representative either of the toxicity (e.g. dioxin) or of the contamination profiles usually observed (e.g. PCB).. Finally, the following 78 substances were considered in this work:

- 7 Polycyclic Aromatic Hydrocarbons (PAHs): phenanthrene (PHE), fluoranthene (FA), pyrene (PY), benz[a]anthracene (BaA), benzo[b]fluoranthene (BbF), benzo[a]pyrene (BaP), DiBenzo[a,h]anthracene (DBaA)

- 4 Dioxins and Polychlorinated biphenyls (PCBs): 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD 2378), 2,3,4,7,8-pentachlorodibenzofuran (PCDF\_23478), 2,3',4,4',5-pentachlorobiphenyl (PCB\_118), 2,2',4,4',5,5'-hexachlorobiphenyl (PCB\_153)
- 4 Perfluorinated compounds: perfluorooctanesulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA)
- 3 Brominated Flame Retardants (BFRs): alpha-hexabromocyclododecane (HBCD alpha), 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153), decabromodiphenyl ether (BDE-209)
- 4 trace elements and minerals: aluminium (Al), chromium (total) (Cr), cadmium (Cd), lead (Pb)
- 9 Phytoestrogens: daidzein, genistein, formononetin, biochanin A, glycitein, equol, enterolactone, coumestrol, resveratrol
- 1 Mycotoxin: zearalenone (ZEA)
- 46 Pesticides: azinphos-methyl, azoxystrobin, bifenthrin, captan, carbendazim, carbofuran, chlorfenvinphos, chlorothalonil, chlorpropham, chlorpyrifos-ethyl, chlorpyrifos-methyl, chlorthal-dimethyl, cyproconazole, cyprodinil, dimethoate, endosulfan-beta, endosulfan-sulfate, ethion, ethoxyquin, etofenprox, fenbuconazole, fenhexamid, fludioxonil, flutriafol, folpet, imazalil, iprodione, kresoxim-methyl, lambda-cyhalothrin, lindane (gamma-HCH), myclobutanil, omethoate, phosalone, phosmet, piperonyl-butoxide, pirimiphos-methyl, procymidone, propargite, pyrimethanil, pyriproxyfen, quinoxifen, tebuconazole, tetradifon, triadimenol, vinclozolin, 2-phenylphenol / O-phenylphenol

## 2.2. Methodology

### 2.2.1. Diets determination

The SNMU (Sparse and Unique Nonnegative Matrix Factorization) method which has already been described in details (Traore et al., 2018) has been applied to consumption data (§ 2.1.1) to determine the main diets of the French population.

The SNMU (Gillis and Plemmons, 2013) is a modified version of the NMF (Non-negative Matrix Factorisation). The NMF is a statistical method introduced by Lee and Seung (Lee and Seung, 2001) that consists in factoring a non-negative matrix. The principle is to use an optimisation method with a non-negativity constraint, which is corresponding, in the case of a work on a consumption matrix, to the minimisation of the following equation:

$$U \in \mathbb{R}^{F \times K}, V \in \mathbb{R}^{K \times N} \text{ such as } U \geq 0 \text{ and } V \geq 0$$

The aim of this minimisation is to get, when applied to a consumption matrix C (with  $F \times N$  dimensions) with a given number of factorial dimensions K (corresponding to the number of consumption systems), the optimal approximation U and V of dimensions ( $F \times K$ ) and ( $K \times N$ ).

The U matrix contains consumption systems. Each column represents a consumption system and each element  $U_{fk}$  gives the contribution of a given food in the consumption system k. The V matrix contains individual coefficients. Each element  $V_{kn}$  gives the contribution of the system of consumption k to the global consumption of an individual n.

The SNMU (sparse NMU) approach introduced more recently by Gillis and Plemmons (Gillis and Plemmons, 2013) allows improving the decomposition compared to the NMF. SNMU is derived from an approach called NMU (Non-negative Matrix Under-approximation), proposing the use of a recursive algorithm based on Lagrangian relaxation to solve the NMF equation, introduced by Gillis and Glineur in 2010 (Gillis and Glineur, 2010). The principle of the recursive algorithm of the NMF, applied to a consumption matrix, is to highlight the main consumption systems one by one from the consumption matrix C. In order to guarantee the non-negativity, a new constraint has been to the

process of optimisation: the constraint of under-approximation (Gillis and Glineur, 2010). The principle is that each value of consumption  $C_{fn}$  has to be higher than his approximation  $U_{fkVkn}$ , i.e.,  $UV \leq C$ . A parcimony constraint has, then, been added (Gillis and Plemmons, 2013) to deal with the fact that certain substances exhibit small coefficients (i.e., coefficients which can vary from a system to another). The addition of a parcimony constraint consists to use a “sanction”  $\mu \geq 0$  on the consumption matrix  $C$  to reinforce the separation of the smallest contributors. Thus, the SNMU model is defined by the following optimisation problem (Gillis and Plemmons, 2013):

$$\min_{U \in \mathbb{R}^{FKK}, V \in \mathbb{R}^{FKK|C-UV|_p^2+\mu|U|_0} \text{ such as } U \geq 0, V \geq 0 \text{ and } UV \leq C$$

Finally, food mixtures constituting the diets were selected based on a classification depending on their decreasing contribution to each consumption system, expressed in percentages (% Food in Table 1). For practical purposes, it was chosen to present the most significant foods in each consumption systems (>1%).

The SNMU was implemented on R software (3.6.3 version) using the implementation algorithm on Matlab software (Gillis and Plemmons, 2013). The original code is available on their website (Gillis and Plemmons, 2020).

- Selection of the number K of consumption systems

In order to apply the SNMU, it is necessary to define a number of K factors, corresponding to the number of consumption systems, i.e., large groups of food items that will subsequently characterise a cluster (one cluster = one diet). A diet is then defined as a combination of several consumption systems (CS).

This parameter is crucial but there is no specific methodology to determine the optimal number of consumption systems, although some strategies may guide this step. First, graphical representations, such as the residual sum of squares representation (Zetlaoui et al., 2011) or the Bayesian information criterion (BIC) (Bai and Ng, 2002). The residual sum of squares representation is the most frequently used method. It consists of evaluating the sum of the residual squares between the original and the estimated matrix for different values of K and studying the resulting curve. If an inflection point is identified, then it can be used to choose the appropriate number of K. It is also possible to compare the results for several values of K by running the SNMU over several values (Traore et al., 2018). If one or more of the obtained consumption systems do not allow characterizing a cluster, then the chosen number K can be rejected. Thus, the number K of consumption systems is chosen based on the relevance and interpretability of the consumption systems in the clusters. In the present work, the consumption systems were defined according to their interpretability and the relevance of the different clusters obtained by comparison with the consumption systems previously reported by Traoré et al. (Traore et al., 2016) based on the same consumption data set.

- Clustering of individuals

A clustering method was applied after the SNMU to determine clusters of individuals with similar diets. The objective of this method was to obtain clusters of individuals with similar consumption patterns. In this study, a hierarchical agglomerative clustering was applied, using the function *hclust* (in R software) on the matrix H. The parameters used in this function are: the Euclidean distance and the Ward aggregation criterion. This method consists of several steps. In the first step, we start with N clusters (each individual n represents a cluster). Then, two clusters are grouped into a larger cluster according to their distance. After step N-1, a cluster is obtained consisting of all individuals. At each level of aggregation, some inter-class inertia is lost. The optimal number of clusters is the one before a significant loss is observed.

**Table 1**

Results of the clustering of 1,918 adults (age = 47, BMI = 25, %, Women = 59.5 % and income: % Low = 28.4, % Medium = 38.9, % High = 14.2, %NA = 18.4 %). Percentage of individuals (%N), individuals characteristics of the cluster, 2 main consumption systems (CS) of the clusters, major foods in each CS (>1%).

Cluster	Major CS	Description	Major Foods	% Food
Cluster 1 <i>Simplicity Diet</i>	CS 4 (40.0 %)	% N = 15 Age = 48 BMI = 24 % men = 50.5 Income: % Low = 30.9 % Medium = 40.4 % High = 13.3	Sugar	5.30
			Black coffee	3.90
			Butter	2.94
			Baguette	1.33
			Boiled potatoes	1.14
			Fried potatoes or chips	8.53
			Cooked ham	3.95
			Baguette	3.53
			Black coffee	1.15
			Beef steak	1.04
Cluster 2 <i>Mediterranean Diet</i>	CS 2 (33.0 %)	% N = 18 Age = 47 BMI = 24 % women = 80.4 Income: % Low = 29.1 % Medium = 40.9 % High = 12.8	Lettuce	
			Apple	
			Virgin olive oil	8.94
			Vegetable soup	8.49
			Tea or herbal tea	7.31
			Carrot	7.30
			Jam	7.15
			Clementine ou mandarin	5.22
			Kiwi	4.33
			Kiwi	3.23
Endive	3.04			
Fresh orange	2.87			
Boiled potatoes	2.79			
Vinaigrette	2.71			
Apple compote	2.19			
Honey	2.04			
Tap water	1.88			
Salmon	1.84			
Baguette	1.71			
Low-fat margarine	1.64			
Granary or wholemeal bread	1.61			
1.58	1.58			
Farmhouse bread	1.56			
Grapefruit	1.36			
Dried fruit	1.30			
Leek	1.23			
Black chocolate	1.08			
Oil seed	1.05			
Canned fruit in syrup	1.04			
Goat cheese	1.03			
Rice	1.01			
Whole milk yogurt				
	CS 8 (18.3 %)		Cf Cluster1	Cf Cluster 1
Cluster 3 <i>Dietetic Diet</i>	CS 3 (49.1 %)	% N = 20 Age = 52 BMI = 25 % women = 76.4 Income: % Low = 27.6 % Medium = 36.5 % High = 14.4	Tomato	9.06
			Cooked ham	8.59
			Lettuce	5.24
			Baguette	4.55
			Beans	3.21
			Virgin olive oil	2.98
			0 % yogurt	2.81
			Butter	2.62
			Non-light cream cheese	2.40
			Partly skimmed milk yogurt	2.18
2.10	2.10			
Melon	2.06			
Rice	1.93			
1.42	1.42			
Tap water	1.37			
Camembert and related cheeses	1.30			
Black coffee	1.29			
			1.27	

(continued on next page)

Table 1 (continued)

Cluster	Major CS	Description	Major Foods	% Food			
Cluster 4 Basic Diet	CS 2 (18.1 %)		Boiled potatoe	1.20			
			Peach	1.06			
			Spring water	1.01			
			Beef steak				
			Vinaigrette				
			Semi-skimmed milk				
			Cf Cluster 2	Cf Cluster 2			
			CS 8 (34.8 %)	% N = 20 Age = 46 BMI = 25 % women = 63.2	Cf cluster 1	Cf cluster	
			CS 1 (25.6 %)	Income: % Low = 31 % Medium = 38.9 % High = 11.6	Beef steak Pasta Butter Baguette Fresh cream	13.74 3.71 3.80 1.61 1.09	
			Cluster 5 Traditional Diet	CS 7 (48.1 %)		Camembert and related cheeses	8.70
Wine	6.62						
Oyster	3.52						
Scrambled egg, omelette	3.47						
Champagne	2.77						
Foie gras	2.19						
Black coffee	2.06						
Farmhouse bread	2.06						
Butter	1.81						
Cooked Ham	1.21						
Virgin olive oil	1.12						
Lettuce	1.00						
CS 8 (11.4 %)		Cf cluster 1	Cf cluster 1				
Cluster 6 Snacking Diet	CS 6 (45.1 %)		Hamburger	7.52			
			Soda	4.54			
			Beef steak	1.36			
			Fried potatoes or chips	1.10			
			Tap water	1.07			
			CS 8 (13.5 %)	% N = 9 Age = 31 BMI = 23 % women = 59.5 Income: % Low = 30.4 % Medium = 41.1 % High = 11.9	Cf Cluster1	Cf Cluster1	
			Cluster 7 Pleasant and convenient Diet	CS 5 (43.5 %)		Pizza	7.66
						Fried potatoes or chips	5.13
						Soda	3.02
						Tap water	2.10
Baguette	1.60						
Tomato	1.42						
Orange juice	1.34						
Chicken	1.22						
Lettuce	1.01						
CS 1 (11.8 %)	% Low = 27.3 % Medium = 36.7 % High = 16.7	Cf Cluster 4				Cf Cluster 4	

### 2.2.2. Generation of exposure data

Exposure was assessed by combining concentration values (TDS 2 data, §2.1.2) with consumption values (INCA 2 survey, § 2.1.1). The combined exposure to the 78 selected ED substances (§ 2.1.3) was calculated according to the formula:

$$e_{ij} = \frac{\sum_f q_{if} \times c_{fj}}{bw_i}$$

where  $e_{ij}$  is corresponding to the exposure to the contaminant  $j$  of the subject  $i$ ;  $q_{if}$  to the mean daily quantity of food  $f$  consumed by the subject  $i$  ( $f = 1$  to  $F$ ,  $F$  is the total number of different foods consumed by the subject  $i$  during the week);  $c_{fj}$  to the concentration level of contaminant  $j$  in food  $f$ ; and  $bw_i$  is the body weight of the subject  $i$ .

For a population of  $N$  individuals, the  $(P \times N)$  combined exposure matrix  $E$  is the product of the  $(P \times F)$  matrix  $C$  of contamination levels  $c_{fj}$ , the  $(F \times N)$  matrix  $Q$  of consumption quantities  $q_{if}$  and the  $(W \times W)$  diagonal weight matrix  $W$  corresponding to  $1/bw_i$  of each individual:  $E = CQW$ .

For the determination of ED mixtures in the diets, one of the two strategies described below (*i.e.*, scenario 2) was based on the use of the *catdes* function in R software. A standard threshold of significance of 0.05 was selected. Student  $t$ -tests have also been carried out in the same time. The  $p$ -values obtained matched with the one obtained with the *catdes* function which allowed to confirm and validate the use of this method. Two functions from the packages “epiR” and “epiDisplay” (“epi.descriptives” for quantitative variables and “tab1” for qualitative variables) have been used to retrieve individual characteristics (age, sex, BMI and incomes averages) per cluster.

## 3. Results and discussion

### 3.1. Diets and associated exposures to ED mixtures

Whereas previous studies using SNMU applied it directly to exposure matrices in order to identify chemical mixtures and deduce associated diets (Traore et al., 2018; Mancini et al., 2021), here we have opted for a reverse strategy, aiming to first define the main diets and then within each of them highlight the main EDs.

The residual sum of squares plots did not detect a significant decrease or inflection point for either the adult or children consumption data. The number of  $K$  was therefore chosen according to the interpretability of the results obtained and comparison with literature data. Several  $K$  scenarios were thus tested as described below.

#### 3.1.1. Adults

**3.1.1.1. Diets.** For the adult data, applying the clustering method to a first scenario with  $K = 7$  produced 4 clusters, and applying it to a second scenario with  $K = 8$  produced 7 clusters. The second scenario was chosen here because of the ease of interpretation associated with it, and because it was found to be consistent with previous studies. Table 1 details the 7 clusters (diets) thus obtained, the main consumption systems involved and the associated foods. Although all consumption systems are necessary to fully describe the different diets, only the two main systems forming each diet are shown here.

Of the total population of 1,918 adults included in this work, 59.5 % were women with an average age of 47 years and an average BMI of 25. Within this population, 28.4 % had a low income (less than 1,300 euros), 38.9 % a medium income (between 1,300 and 3,100 euros) and 14.2 % a high income (more than 3,100 euros) (18.4 % did not fill in this item).

**Cluster 1** represented 15 % of the total population. It has a balanced composition between men and women, with a slight over-representation of the former (50.5 %), with an average age of 48 years, an average BMI of 24 and a majority of medium income (40.4 %). Their diet consisted of 40 % of CS 4, which mainly contained the following foods: sugar, black coffee, baguette, butter, potatoes, pasta, dry sausage, rice and Gruyere cheese, and 16.4 % of CS 8, which mainly contained the following foods: fried or deep-fried potatoes, cooked ham, baguette, black coffee, beef steak, Gruyere cheese, spring water, lettuce, butter and carrot. These two CS corresponded to a diet labelled “Simplicity” in the literature (Traore et al., 2016), it was therefore decided to assign the same label to cluster 1.

**Cluster 2** represented 18 % of the total population. The vast majority

were women (80.4 %) with an average age of 47 years, an average BMI of 24 and a majority of medium income (40.9 %). Their diet was composed of 18.3 % of CS 8, (see cluster 1, “Simplicity” diet) and for 33.0 % of the CS 2 which contained mainly the following foods: lettuce, apple, virgin olive oil, vegetable soup, tea or herbal tea, carrot, jam, clementine or mandarine, kiwi and endive. It was decided that Cluster 2 corresponded to the “Mediterranean” diet based on the food items it contained.

**Cluster 3** represented 20 % of the total population. The majority were women (76.4 %) with an average age of 52 years, an average BMI of 25 and a majority of middle income (36.5 %). Their diet was composed for 18.1 % of CS 2 (i.e., “Mediterranean” diet and whose composition was detailed in the previous cluster) and for 49.1 % of CS 3 which corresponded to a “dietetic” diet and contained mainly the following foods: beans, vinaigrette, tomato, cooked ham, lettuce, baguette, virgin olive oil, apple, 0 % yoghurt and butter. As the latter CS was in the majority in the cluster, it was decided to consider cluster 3 as corresponding to the “Dietetic” diet.

**Cluster 4** represented 20 % of the total population. It is composed of a majority of women (63.2 %) with an average age of 46 years, an average BMI of 25 and a majority of average incomes (38.9 %). Interestingly, this cluster contained the highest proportion of low incomes (31 %). Their diet consisted of 25.6 % of CS 1 (which corresponded to a diet mainly composed of animal and cereal derived foods) and 34.8 % of CS 8 (i.e., “Simplicity” diet detailed above). It was decided that cluster 4 corresponded to the “Basic Consumer” diet in view of the foods it contained.

**Cluster 5** represented 11 % of the whole population. The vast majority were men (78.5 %) with an average age of 56 years, an average BMI of 26 and incomes mostly medium (38.4 %). This cluster corresponded to the highest proportion of high incomes (21.9 %). Their diet was composed for 11.4 % of CS 8 (“Simplicity” diet detailed above) and for 48.1 % of CS 7 associated to a “Traditional” diet including wine, camembert and related cheeses, oyster, scrambled eggs, omelette, champagne, black coffee, foie gras, cooked ham, farmhouse bread and butter. As the latter CS was in the majority in the cluster, it was allocated the “Traditional” diet.

**Cluster 6** represented 9 % of the whole population. It was composed of a majority of women (59.5 %) with an average age of 31 years, an average BMI of 23 and incomes mostly medium (41.1 %). Their diet was composed for 13.5 % of CS 8 (i.e., “Simplicity” diet detailed above) and for 45.1 % of CS 6, which corresponded to a “Snacking” diet and mostly contained the following foods: hamburger, sauteed potatoes or chips, soda, beef steak, tap water, chocolate croissant, chicken cordon bleu, dry chocolate biscuit, mayonnaise and chocolate instant drink. As this last CS was in the majority in the cluster, it was associated to the “Snacking” diet.

**Cluster 7** represented 8 % of the whole population. It was composed of a majority of men (64.7 %) with an average age of 42 years, an average BMI of 24 and incomes mostly medium (36.7 %). Their diet consisted in 11.8 % of CS 1 (detailed in cluster 4) and in 43.5 % of CS 5 which corresponded to a so called “Pleasant and convenient” diet and mostly contained the following foods: pizza, sauteed potatoes or chips, soda, tap water, baguette, tomato, orange juice, chicken, lettuce and tart or tartlet. As this last CS was in the majority in the cluster, it was decided to consider cluster 7 as corresponding to the “Pleasant and convenient” diet.

The results of this study consolidate the results obtained previously regarding the definition and composition of the different diets and dietary behaviours of the French population (Traore et al., 2016; Gazan et al., 2016). Indeed, we find here the same seven major diets as those previously described. However, our study identified eight consumption systems instead of the seven previously reported. In fact, the compositions of the CSs differ slightly from those described by Gazan (Traore et al., 2016; Gazan et al., 2016) and Traoré (Traore et al., 2016) for several reasons. In the latter study, the methodology was based on a

clustering method involving NMF while SNMU was used in the present study. Further, some parameters were slightly different (7 K vs 8 K, different sparsity parameter and number of iterations used). The statistical method used by Gazan et al. to derive the major diets was the same as in our study (SNMU) but a food clustering strategy was used.

**3.1.1.2. Exposures to ED mixtures.** Adult exposures to each of the 78 ED substances were then calculated for each of the 7 modelled diets (Table S1). In order to identify the mixtures of EDs specifically associated with a given diet, two scenarios were applied: one related to the mass contribution to exposure within a given diet, the other to the significance of exposure by comparing for each substance the average exposure in each diet with the one in the general population. Substances with statistically higher average exposure were identified and selected for each cluster, thus representing specific exposure profiles associated with these different diets. The result of this selection of EDs on the basis of these two distinct approaches is presented below.

- **Scenario 1** (mass contribution basis)

For each diet, the top 10 substances based on mass contribution scenario are shown in Table 2. The proportions for the 78 substances are presented in Table S1. According to this scenario, regardless of the diets considered, the main EDs to which consumers are exposed are trace metals (chromium, aluminium, cadmium and lead), pesticides (piperonyl butoxide, chlorpropham, imazalil, iprodione, propargite) and phytoestrogens (resveratrol, daidzein and genistein). Aluminium and chromium alone account for approximately 95 % of the contribution. The application of this strategy thus globally shows a mixture of EDs that is qualitatively quite similar between the different diets, composed on a mass basis of trace metals, pesticides and phytoestrogens. Differences between these diets are mainly related to phytoestrogens, especially daidzein and/or genistein, which are only represented in the top 10 substances in the Dietetic and Snacking diets, and to the absence of the pesticides propargite or chlorpropham and imazalil in the top 10 substances for Snacking or Dietetic diets, respectively.

- **Scenario 2** (*p*-value)

When looking specifically at the EDs for which the exposures induced by the different diets are significantly higher than those induced by the general population diet, the compounds found are very different between the diets studied, thus highlighting specific ED mixtures for given diets, as detailed below and in Table 2 and Table S1:

- **Cluster 1 - Simplicity diet.** Through their diet, the individuals of this cluster were more exposed than the general population to trace elements chromium (Cr) and cadmium (Cd), the mycotoxin zearalenone (ZEA), POPs such as the dioxin TCDD2378, HBCD-alpha and BDE209, pesticides such as piperonyl butoxide and pirimiphos methyl.
- **Cluster 2 – Mediterranean diet.** Through their diet, the individuals of this cluster, mainly women (>80 %) were more exposed than the whole population to 5 pesticides: ethion, folpet, ethoxyquin, captan and flutriafol.
- **Cluster 3 – Dietetic diet.** The individuals of this cluster (>76 % women) were more exposed than the whole population to 28 pesticides (Table S1): vinclozolin, procymidone, cyprodinyl, chlorothalonil, phosmet, lambda cyhalothrin, fludioxonil, pyrimethanil, pyriproxyfen, chlorpyrifos ethyl, iprodione, bifenthrin, cyproconazole, propargite, carbendazim, captan, phosalone, azinphos methyl, tetradifon, tebuconazole, fenhexamid, myclobutanil, triadimenol, etofenprox and quinoxifen; 6 phytoestrogens: coumestrol, genistein, daidzein, glycitein, biochanin a and formononetin; 2 perfluorinated

**Table 2**

List of main EDs specifically associated with the 7 adult diets, two scenarios were applied: 1/ contribution to exposure on a mass basis expressed as % of the sum of the exposures of the 78 EDs, 2/ significance of exposure compared to general population expressed as *p*-value.

Clusters / Diets		Scenario 1		Scenario 2	
		Contribution to exposure on mass basis (% of the sum of the 78 ED' exposure levels)		EDs presenting significantly higher exposure compared to the general population ( <i>p</i> -value)	
1	Simplicity	Aluminium	85,23	Chromium	1,38E-05
		Chromium	10,21	Piperonyl butoxide	9,22E-03
		Resveratrol	0,58	Cadmium	6,00E-03
		Propargite	0,49	Pirimiphos methyl	3,69E-02
		Piperonyl butoxide	0,42	ZEA	1,66E-03
		Cadmium	0,38	BDE209	7,03E-03
		Lead	0,38	HBCD alpha	4,18E-03
		Iprodione	0,35	DBahA	4,63E-02
		Chlorpropham	0,35	TCDD_2378	2,71E-02
		Imazalil	0,25		
2	Mediterranean	Aluminium	87,35	Ethion	1,55E-07
		Chromium	8,43	Folpet	9,30E-03
		Resveratrol	0,62	Ethoxyquin	9,30E-03
		Propargite	0,57	Captan	1,53E-02
		Iprodione	0,39	Flutriafol	3,96E-02
		Piperonyl butoxide	0,33		
		Cadmium	0,32		
		Lead	0,31		
		Imazalil	0,24		
		Chlorpropham	0,23		
3	Dietetic	Aluminium	86,14	Coumestrol	2,07E-108
		Chromium	8,57	Genisteine	4,52E-107
		Propargite	0,69	Vinclozolin	1,57E-107
		Iprodione	0,56	Daidzeine	6,13E-104
		Daidzeine	0,48	Glyciteine	2,01E-29
		Genisteine	0,44	Procymidone	8,24E-23
		Resveratrol	0,42	Cyprodinyl	2,83E-17
		Lead	0,33	Chlorothalonil	1,39E-16
		Cadmium	0,32	Phosmet	7,08E-16
		Piperonyl butoxide	0,31	Lambda Cyhalothrin	2,06E-15
4	Basic	Aluminium	86,07	Chlorpropham	<0,0001
		Chromium	9,25	Cadmium	<0,0001
		Resveratrol	0,53	Imazalil	<0,0001
		Chlorpropham	0,47	ZEA	8,34E-04
		Propargite	0,44	DBahA	4,16E-03
		Piperonyl butoxide	0,39	BDE153	4,35E-02
		Iprodione	0,39	TCDD_2378	3,72E-02
		Cadmium	0,38		
		Lead	0,34		
		Imazalil	0,31		
5	Traditional	Aluminium	85,84	Chromium	1,20E-03
		Chromium	9,45	Iprodione	<0,0001
		Resveratrol	0,60	Lead	<0,0001
		Propargite	0,56	Pyrimethanil	1,55E-02
		Iprodione	0,54	BaA	1,75E-02
		Lead	0,51	BbF	<0,0001
		Cadmium	0,34	HBCD alpha	7,82E-03
		Piperonyl butoxide	0,33		
		Chlorpropham	0,27		
		Imazalil	0,21		
6	Snacking	Aluminium	85,90	Piperonyl butoxide	<0,0001
		Chromium	10,16	Chlorpropham	1,39E-03
		Piperonyl butoxide	0,51	PHE	<0,0001
		Chlorpropham	0,42	Chlorpyrifos methyl	<0,0001
		Cadmium	0,35	BDE209	<0,0001
		Resveratrol	0,34	BDE153	8,69E-03
		Lead	0,33	PCDF_23478	1,10E-02
		Iprodione	0,32		
		Imazalil	0,24		
		Daidzeine	0,18		
7	Pleasant & Convenient	Aluminium	86,84	Zearalenone	5,16E-16
		Chromium	9,21	BaA	3,28E-10
		Piperonyl butoxide	0,42	PHE	4,03E-08
		Iprodione	0,36	FA	2,03E-07
		Resveratrol	0,35	PY	3,58E-06
		Propargite	0,35	BDE 209	7,38E-06
		Cadmium	0,34	BbF	8,96E-06
		Lead	0,34	Pirimiphos methyl	3,01E-05
		Chlorpropham	0,29	DBahA	8,97E-05
		Imazalil	0,19	Piperonyl butoxide	2,87E-06

phenanthrene (PHE), fluoranthene (FA), pyrene (PY), benz[a]anthracene (BaA), benzo[b]fluoranthene (BbF), benzo[a]pyrene (BaP), DiBenzo[a,h]anthracene (DBahA), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD\_2378), 2,3,4,7,8-pentachlorodibenzofuran (PCDF\_23478), alpha-hexabromocyclododecane (HBCD alpha), 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153), decabromodiphenyl ether (BDE-209), zearalenone (ZEA).



compounds: PFOA and PFHxS and Aluminium (Al). The 10 most specific EDs to this diet are listed in [Table 2](#).

- **Cluster 4 – Basic diet.** Through their diet, the individuals of this cluster were more exposed than the general population to chlorpropham and imazalil (pesticides), cadmium (inorganic contaminant), zearalenone (mycotoxin), DBaH (PAH), TCDD2378 (dioxin) and BDE 153 (BFR).
- **Cluster 5 – Traditional diet.** Through their diet, the individuals of this cluster, mainly composed of men (>78 %) were more exposed than the whole population to inorganic contaminants lead (Pb) and chromium (Cr), pesticides iprodione and pyrimethanil, PAHs BbF and BaA and the BFR HBCD-alpha.
- **Cluster 6 – Snacking diet.** Through their diet, the individuals of this cluster were more exposed than the whole population to BFRs BDE 209 and BDE 153, the PAH PHE, pesticides piperonyl butoxide, chlorpyrifos methyl and chlorpropham and to the dioxin PCDF 23478.
- **Cluster 7 - Pleasant and convenient diet.** Through their diet, the individuals of this cluster were more exposed than the whole population to the mycotoxin ZEA, PAHs BaA, PHE, FA, PY, BbF and DBaH, pesticides piperonyl butoxide and pirimiphos methyl, the BFR BDE 209 and inorganic contaminants chromium (Cr) and aluminium (Al).

These results show very clearly that diets with more animal foods (e.g., Simplicity, Traditional, Snacking ...) ([Table 1](#)), those where men are in the majority, induce significantly higher exposures to some persistent organic pollutants (e.g., PCDD/F, brominated flame retardants) than the general diet. Exposures to these substances were not specifically associated with the Mediterranean and Dietetic diets. On the other hand, the latter two diets, where women are in the majority, which are richer in fruit and vegetables, are also those for which pesticides represent a specific signature, associated in the case of the Dietetic diet with certain phytoestrogens, already identified as such on the basis of their mass contribution in the scenario n°1 above. These results thus highlight the specificities of exposure linked to the diets of men and women.

Other studies have attempted to identify major chemical mixtures to which the population or specific population is exposed through the diet ([Crépet et al., 2013](#); [Crépet and Tressou, 2011](#); [Crépet et al., 2013](#); [Traore et al., 2016](#); [Traore et al., 2018](#); [Mancini et al., 2021](#)). However, as mentioned above, most of these studies, although using the same tools, operated differently from ours. Regarding the methodology, they first identified mixtures of compounds and then associated them with diets, whereas here we wanted to first consolidate diets to specifically study ED compounds and then derive exposure mixtures. However, even if the methodology is different, the results regarding the definition of diets are very similar, which supports both strategies, on the one hand in the definition of diets, on the other hand in the exposure trends. In particular, and although our study included more families of contaminants with a focus on ED and/or concerns a larger population than those previously published, we can compare what is common, such as exposure to pesticides. In spite of methodological differences between our study and the previous ones as detailed above, all studies showed how consumption of fruit and vegetables is associated with higher exposure to pesticides ([Traore et al., 2016](#); [Mancini et al., 2021](#)), as observed in the present study in clusters 2 (Mediterranean) and 3 (Dietetic). Interestingly, a recent study specifically dedicated to the characterization of pesticide exposure in the general population also ([Rebouillat et al., 2021](#)), but using other consumption and contamination databases, showed similar results, while identifying women as being mainly concerned (87 % of women in their Cluster 4); our observations in Mediterranean and Dietetic diets point in the same direction, with women representing 80.4 % and 76.4 % of the population, respectively.

Otherwise, [Mancini et al. \(Mancini et al., 2021\)](#) identified 8 main chemical mixtures from E3N cohort involving > 70,000 French women. It is thus possible to compare the mixtures determined here for each specific diet with those highlighted in their study. Although the

populations characterised are not identical (general population vs. middle-aged women), as well as the selected substances (78 vs. 197 food contaminants) an exercise to compare the chemical mixtures to which the populations are exposed can be attempted. For instance, they reported Cr and Cd as associated in the same mixture (Mixture 1) consistent with the specific exposure profile induced by cluster 1 (simplicity diet) in the present study. Similarly, their mixtures 3 (mycotoxins, pesticides and PAHs) and 8 (mycotoxins and PAHs) echoes the exposure, respectively induced by clusters 7 (Pleasant and convenient diet) and 4 (basic diet) described in the present work. The exposure induced by certain diets can also be described by several mixtures identified in [Crépet's work \(Crépet et al., 2013\)](#); e.g., mixtures 5 (pesticides#1) and 6 (pesticides#2) provide a good description of the exposure induced by the dietetic diet (cluster 3) with regard to pesticides, phytoestrogens and PFAS compounds.

### 3.1.2. Children

The application of the SNMU to children consumption data did not allow identifying specific diets. Therefore, exposures were calculated for the overall diet of children aged 3 to 17 years. Afterwards, these exposure data were compared to the exposure of the general population of adults ([Table 3](#)).

On the basis of their mass contribution to the mixture of 78 EDs, the 10 most contributing substances were trace elements aluminium (Al), chromium (Cr), cadmium and lead (respective contribution to exposure of 85.06 %, 10.35 %, 0.34 % and 0.31 %), phytoestrogens resveratrol, enterolacton and equol (respective contribution to exposure of 0.66 %, 0.34 % and 0.28 %) and pesticides piperonyl butoxide, chlorpropham and propargite (respective contribution to exposure of 0.43 %, 0.41 % and 0.26 %).

A statistically significant increasing difference between the exposure values of the general population of children and the general population of adults could be observed for almost all investigated ED substances (n = 66 out of 78) ([Table 3](#)). The 12 compounds with no exposure difference between adults and children all are pesticides ([Table 3](#)): endosulfan beta, endosulfan sulfate, ethion, ethoxyquin, etofenprox, fenhexamid, folpet, kresoxim methyl, myclobutanil, procymidone, pyrimethanil and quinoxifen.

These results of a clear overexposure of children to most EDs should be put in perspective with the weight of children compared to adults which mathematically leads to a high exposure value. The explanation for the exception relating to some pesticides may be sought in the lower consumption of fruits and vegetables by this part of the population, although this was not investigated further in this study.

### 3.2. Strengths and limitations of the study

The strengths of the present study lies in the robust and validated data set used for either consumption or contamination data. In particular, the TDS data were the most comprehensive and recent data available on food contamination for the French consumers. Moreover, the sampling covered more than 90 % of food consumption in France (the remaining 10 % corresponded to minority foods in the French diet, such as quenelles, avocado, duck meat, etc.).

Secondly, the SNMU is a dimension reduction method that is particularly well suited to consumption data since it was specifically developed for matrices composed of non-negative real numbers (and therefore composed of positive values) and is particularly well suited to matrices containing many zeros, which was the case for consumption data. Moreover, it is a method that has the advantage of being more advanced than other previously developed dimension reduction methods (such as the NFM, for example, see § 2.2.1). The present study therefore enables to compare the methodological performance of the SNMU with that of the NFM, which had previously been applied to the same data sets.

Finally, the added value of our work relates to the fact that the

Table 3

Results of the comparison of exposure levels for the 78 EDs studied between the general population of adults and the general population of children aged between 3 and 17 years. The exposure unit is in *mg/kg bw/day*.

Substances	Family	Adults N = 1,918			Children N = 1,444			p-value	
		Mean	P95	P99	Mean	P95	P 99		
PHE	PAH	7.39E-06	1.40E-05	1.99E-05	1.19E-05	2.42E-05	3.16E-05	<0.0001	
FA		2.86E-06	5.10E-06	6.37E-06	4.05E-06	8.52E-06	1.13E-05	<0.0001	
PY		6.49E-06	1.13E-05	1.45E-05	9.58E-06	1.95E-05	2.67E-05	<0.0001	
BaA	Dioxins, PCBs	2.77E-07	5.60E-07	7.79E-07	3.79E-07	7.97E-07	1.13E-06	<0.0001	
BbF		2.41E-07	6.04E-07	1.05E-06	2.94E-07	6.03E-07	8.42E-07	<0.0001	
BaP		1.44E-07	3.01E-07	4.54E-07	1.85E-07	4.19E-07	5.51E-07	<0.0001	
DBaHA		3.60E-08	6.90E-08	9.31E-08	5.77E-08	1.22E-07	1.68E-07	<0.0001	
TCDD_2378		1.53E-11	3.08E-11	4.43E-11	2.33E-11	5.48E-11	7.16E-11	<0.0001	
PCDF_23478		1.09E-10	2.08E-10	2.86E-10	1.64E-10	3.65E-10	4.68E-10	<0.0001	
PCB_118		2.60E-07	6.43E-07	9.55E-07	3.84E-07	9.31E-07	1.52E-06	<0.0001	
PCB_153		6.47E-07	1.69E-06	2.53E-06	8.96E-07	2.29E-06	3.99E-06	<0.0001	
PFOS		Perfluorinated compounds	3.58E-08	1.16E-07	1.88E-07	4.50E-08	1.45E-07	2.73E-07	<0.0001
PFHxS			1.81E-08	6.80E-08	1.07E-07	2.45E-08	8.08E-08	1.29E-07	<0.0001
PFOA	1.16E-08		3.20E-08	4.76E-08	1.45E-08	3.91E-08	6.29E-08	<0.0001	
PFNA	BFRs	1.25E-09	6.90E-09	1.25E-08	8.43E-10	5.04E-09	1.03E-08	<0.0001	
HBGD alpha		1.53E-07	3.67E-07	5.15E-07	2.04E-07	5.17E-07	7.89E-07	<0.0001	
BDE153		1.15E-08	2.44E-08	3.30E-08	1.71E-08	3.88E-08	5.58E-08	<0.0001	
BDE209		3.07E-07	6.17E-07	8.33E-07	5.84E-07	1.40E-06	2.11E-06	<0.0001	
Aluminium		Trace elements and minerals	3.64E-02	6.52E-02	9.01E-02	5.05E-02	9.77E-02	1.28E-01	<0.0001
Chromium			3.88E-03	5.81E-03	6.99E-03	6.15E-03	1.21E-02	1.49E-02	<0.0001
Cadmium			1.46E-04	2.54E-04	3.38E-04	2.04E-04	3.90E-04	5.02E-04	<0.0001
Lead		Phytoestrogens	1.51E-04	2.66E-04	3.33E-04	1.86E-04	3.73E-04	4.77E-04	<0.0001
Daidzein			9.91E-05	2.98E-04	4.84E-04	1.31E-04	4.02E-04	6.96E-04	<0.0001
Genistein			8.52E-05	2.75E-04	4.44E-04	1.12E-04	3.74E-04	6.28E-04	<0.0001
Formononetin	4.26E-06		1.46E-05	2.00E-05	1.39E-05	4.29E-05	7.60E-05	<0.0001	
Biochanin A	1.74E-06		4.63E-06	6.22E-06	4.41E-06	1.28E-05	2.19E-05	<0.0001	
Glycitein	1.79E-05		5.33E-05	8.07E-05	4.77E-05	1.44E-04	2.26E-04	<0.0001	
Equol	4.46E-05		1.85E-04	2.76E-04	1.67E-04	5.38E-04	8.84E-04	<0.0001	
Enterolacton	5.04E-05		2.16E-04	3.16E-04	2.04E-04	6.60E-04	1.12E-03	<0.0001	
Coumestrol	1.90E-05		6.28E-05	1.00E-04	2.60E-05	8.52E-05	1.44E-04	<0.0001	
Resveratrol	2.15E-04		1.61E-03	2.97E-03	3.90E-04	2.68E-03	2.68E-03	<0.0001	
Zearalenone	Mycotoxins	5.56E-06	1.03E-05	1.37E-05	9.99E-06	2.06E-05	2.65E-05	<0.0001	
Azinphos-methyl		Pesticides	3.58E-06	1.51E-05	2.53E-05	2.62E-06	1.18E-05	2.12E-05	<0.0001
Azoxystrobin			1.07E-06	5.52E-06	1.39E-05	1.40E-06	7.18E-06	1.75E-05	0.004
Bifenthrin			1.89E-06	5.92E-06	9.85E-06	1.30E-06	5.00E-06	10.00E-06	<0.0001
Captan			1.63E-06	6.45E-06	1.06E-05	1.22E-06	5.18E-06	9.54E-06	<0.0001
Carbendazim			1.09E-05	4.26E-05	7.20E-05	8.11E-06	3.35E-05	6.29E-05	<0.0001
Carbofuran			5.41E-07	3.83E-06	8.63E-06	3.70E-07	2.87E-06	9.31E-06	0.005
Chlorfenvinphos			4.95E-08	3.50E-07	7.88E-07	3.38E-08	2.62E-07	8.50E-07	0.005
Chlorothalonil			1.49E-06	5.50E-06	8.74E-06	1.79E-06	7.15E-06	1.21E-05	0.0004
Chlorpropham			1.31E-04	3.26E-04	4.75E-04	2.46E-04	6.14E-04	8.87E-04	<0.0001
Chlorpyrifos-ethyl	9.44E-06		3.79E-05	9.08E-05	6.75E-06	3.11E-05	6.81E-05	<0.0001	
Chlorpyrifos-methyl	1.83E-06	7.83E-06	1.41E-05	2.25E-06	7.94E-06	1.61E-05	<0.0001		
Chlorthal-dimethyl	1.24E-07	8.75E-07	1.97E-06	8.45E-08	6.55E-07	2.13E-06	0.005		
Cyproconazole	3.25E-07	1.04E-06	1.60E-06	2.15E-07	8.93E-07	1.59E-06	<0.0001		
Cyprodinyl	2.39E-05	7.38E-05	1.46E-04	1.78E-05	5.89E-05	1.06E-04	<0.0001		
Dimethoate	7.50E-06	1.02E-05	2.18E-04	3.72E-08	2.27E-07	7.96E-07	<0.0001		
Endosulfan-Beta	6.70E-07	4.41E-06	1.31E-05	8.38E-07	5.52E-06	1.68E-05	0.11		
Endosulfan-Sulfate	2.68E-07	1.76E-06	5.23E-06	3.35E-07	2.21E-06	6.73E-06	0.11		
Ethion	2.38E-06	1.07E-05	1.77E-05	2.17E-06	1.08E-05	2.01E-05	0.15		
Ethoxyquin	8.94E-07	5.33E-06	1.29E-05	7.46E-07	5.70E-06	1.13E-05	0.09		
Etofenprox	6.30E-07	3.78E-06	1.25E-05	4.93E-07	3.56E-06	1.11E-05	0.09		
Fenbuconazole	3.22E-06	4.45E-06	9.53E-05	nd	nd	nd	<0.0001		
Fenhexamid	1.48E-05	8.41E-05	2.33E-04	1.34E-05	8.76E-05	2.03E-04	0.34		
Fludioxonil	6.87E-05	1.96E-04	3.12E-04	4.75E-05	1.64E-04	2.81E-04	<0.0001		
Flutriafol	8.57E-07	5.29E-06	1.97E-05	4.89E-07	2.22E-06	1.45E-05	0.0006		
Folpet	1.05E-06	6.24E-06	1.52E-05	8.73E-07	6.67E-06	1.32E-05	0.09		
Imazalil	1.01E-04	3.19E-04	5.48E-04	1.37E-04	4.02E-04	6.43E-04	<0.0001		
Iprodione	1.81E-04	5.17E-04	8.34E-04	1.15E-04	3.99E-04	7.33E-04	<0.0001		
Kresoxim-methyl	1.34E-07	8.82E-07	2.62E-06	1.68E-07	1.10E-06	3.37E-06	0.11		
Lambda-Cyhalothrin	4.21E-06	1.36E-05	2.65E-05	2.75E-06	1.01E-05	1.81E-05	<0.0001		
Lindane	6.81E-07	2.77E-06	4.88E-06	8.55E-07	3.10E-06	6.55E-06	<0.0001		
Myclobutanil	8.34E-07	4.63E-06	1.39E-05	7.16E-07	4.24E-06	1.28E-05	0.21		
Omethoate	3.22E-06	4.45E-06	9.53E-05	0.00E + 00	0.00E + 00	0.00E + 00	<0.0001		
Phosalone	4.67E-06	1.90E-05	3.18E-05	3.44E-06	1.47E-05	2.69E-05	<0.0001		
Phosmet	4.07E-06	1.48E-05	3.12E-05	2.98E-06	1.26E-05	2.25E-05	<0.0001		
Piperonyl-butoxide	1.57E-04	3.53E-04	5.08E-04	2.58E-04	5.62E-04	8.05E-04	<0.0001		
Pirimiphos-methyl	6.46E-05	1.28E-04	1.86E-04	9.27E-05	1.93E-04	2.71E-04	<0.0001		
Procymidone	1.93E-05	5.31E-05	9.78E-05	1.81E-05	6.00E-05	9.79E-05	0.08		
Propargite	2.14E-04	8.56E-04	1.44E-03	1.56E-04	6.69E-04	1.20E-03	<0.0001		
Pyrimethanil	1.65E-05	5.17E-05	9.14E-05	1.58E-05	5.65E-05	1.07E-04	0.35		

(continued on next page)

Table 3 (continued)

Substances	Family	Adults N = 1,918			Children N = 1,444			p-value
		Mean	P95	P99	Mean	P95	P 99	
		Pyriproxyfen		3.29E-07	1.27E-06	2.04E-06	3.75E-07	
Quinoxifen		3.50E-07	2.10E-06	6.97E-06	2.74E-07	1.98E-06	6.15E-06	0.10
Tebuconazole		5.11E-07	3.24E-06	1.04E-05	1.91E-07	1.41E-06	3.82E-06	<0.0001
Tetradifon		2.10E-07	1.40E-06	2.78E-06	3.87E-07	2.35E-06	5.04E-06	<0.0001
Triadimenol		7.95E-07	4.44E-06	1.46E-05	6.03E-07	4.05E-06	1.23E-05	0.04
Vinclozolin		3.51E-06	1.21E-05	1.95E-05	4.50E-06	1.58E-05	2.77E-05	<0.0001
2-Phenylphenol / O-phenylphenol		1.45E-05	5.86E-05	1.36E-04	3.82E-05	1.80E-04	3.53E-04	<0.0001

contaminants of interest were selected on the basis of a common toxicological effect, which makes it possible to contribute to the evaluation of chemical mixtures of endocrine disruptors, moreover, for the general population and not only for a specific population.

With regard to the limitations of the study, the interpretation of the results must be set against the reference years of the databases used (TDS 2 2007–2009) and INCA 2 (2006–2007). French diets are likely to have changed since then, particularly with the emergence of new practices (e.g., vegan) or production methods (organic), as are contamination levels (e.g. pesticides, mycotoxins in particular), which may have increased or decreased depending on the contaminant, the period, etc. A study relating to the characterization of dietary exposure to pesticides of French adults having a variable proportion of organic foods in their diet recently showed an inverse correlation between exposure to pesticides through food and the proportion of organic foods in the diet (Rebouillat et al., 2021). It will therefore be necessary in the future to update this picture by using the new consumption data (INCA 3 study) recently available (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail (Anses), 2021) with that of the TDS 3 currently underway in the territory, which takes into account the organic aspect of production. Those more recent consumption data (INCA3), however, could not be used in the present study for strictly methodological reasons. Indeed, the classification of foods is not the same as in TDS2. Only INCA2 and TDS2 data can be associated since they are based on the same classification. Only future TDS3 data currently in progress can be combined in the future with INCA3 data.

Although these two sets of data do not represent the snapshot of the current French population, the study provides date of exposure in the general population around 2006–2009; the occurrence of chronic pathologies being distant from exposure, these data could thus be useful to assess the health impact on the population 15 years later, that is to say nowadays. More specifically, it was chosen to exclude the 5 % of the least consumed foods, which led to the exclusion of certain substances likely to be present in large quantities in certain less consumed foods. For instance, all soy-based foods were automatically excluded from this study, even though these foods are the main vectors for phytoestrogen exposure. An underestimation of phytoestrogen exposure may therefore be expected. Otherwise, fish consumers were not well represented in the TDS2 data as only 52.3 % of fish consumption was sampled, which may have led to an underestimation of exposure to some substances such as POPs. Also, we chose to exclude under-declarers in order to continue the exploitation of TDS2 and INCA2 data in the same way as in previous studies. This led to the exclusion of 25 % of adults, which can be considered as a bias in the study, since different results could have been obtained by including these individuals. Future studies should integrate recent general recommendations for managing consumption data.

The list of 78 known or suspected ED food contaminants was established based on substances included in TDS2 and lists and databases of known or suspected EDs and is therefore non exhaustive. Indeed, despite the number of substances analyzed in TDS2, some substances with potential ED properties were not studied, such as for example substances migrating from food contact materials. These were included in the subsequent infant TDS (Sirot et al., 2021). Moreover, lists

and databases of potential ED substances are expected to be incremented as knowledge evolves. Other substances, not included either in TDS2 or in lists and databases of known or suspected EDs, could therefore contribute to dietary exposure to EDs.

Despite being one of the most sensitive stages of life to EDs exposure, children under 3 years of age could not be included in this study. Indeed, it would have been necessary to use the infant TDS data that are available but we did not have access to the associated consumption data. Also, a reason why no specific diets could be identified for the children group may be related to the fact that adolescents diets are certainly closer to adults ones than children's. The INCA2 dataset, which defined 2 populations, namely two independent random samples of 3- to 17-year-old children and 18- to 79-year-old adults, therefore drove the age classes used in the present study and in any relying on this national database.

Finally, the censoring management scenario chosen also presents some limitations. Indeed, it was chosen to turn to a LB scenario, *i.e.*, to replace non-detected concentrations by 0 and detected but unquantified concentrations by the LOD, which leads to the exclusion of substances that could have been present or to underestimate certain exposures.

#### 4. Conclusion

The main diets of the French population could be modelled and are in agreement with previously developed and published models, although the methodology used here is significantly different. The knowledge of the levels of contamination of 78 known or suspected endocrine disrupting compounds, belonging to 8 different chemical families, in the foods constituting these diets allowed to explore the mixtures of EDs to which consumers are exposed. Two scenarios were investigated to define these mixtures and we were able to show that an approach by mass contribution led to the definition of qualitatively close mixtures, whereas a statistical approach allowed to identify mixtures of exposure that were significantly different between diets, showing specific exposures related to gender. The application of the SNMU method provided new information that is also comparable to that of previous studies using the NMF approach. These studies had reported different exposure profiles depending on the diet, however, without the specific notion of endocrine disruptors or that of mixture having been specifically addressed, as is the case here in a complementary way. These results now pave the way for the study of the specific effects of these mixtures, work that is currently being carried out via the implementation of various endocrine activity tests.

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#### CRedit authorship contribution statement

**Gaud Dervilly:** Conceptualization, Investigation, Methodology,

Supervision, Validation, Writing – original draft, Writing – review & editing. **Manon Bourdeau**: Data curation, Formal analysis. **Manon Pruvost-Couvreur**: Methodology. **Isabelle Severin**: Conceptualization, Writing – review & editing. **Anne Platel**: Conceptualization, Funding acquisition, Writing – review & editing. **M.C. Chagnon**: Conceptualization, Writing – review & editing. **Fabrice Nessler**: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Bruno Le Bizec**: Supervision, Validation, Writing – review & editing. **Hélène Moche**: Conceptualization, Funding acquisition, Project administration, Investigation, Supervision, Validation, Writing – review & editing.

### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dervilly Gaud reports financial support was provided by National Agency for Food Environmental and Occupational Health and Safety.

### Data availability

Data will be made available on request.

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### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2023.108408>.

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