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Review

State of the art on public risk assessment of combined human exposure to multiple chemical contaminants

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ABSTRACT

Background: Concern about the effects on health of exposure of combined chemicals present in food, air or water are increasing nowadays. However, mechanism and effects of combined chemical contaminants are still poorly know.
Scope and approach: This review deals with the variety of routes of these chemicals when enter the human body. The gaol is the development of a mechanism-based and quantitative framework for risk assessment to estimate the impact on human health and prevent exposure to multiple chemicals.
Key findings and conclusions: It has been shown that new studies should be developed taking into account cumulative effect of these substances and different tiers as external exposition, dietary exposition, lifestyle, age and economic factors. New techniques must also be implemented, mainly "omic" techniques, bioassay systems, mathematical modelling, quantitative structure-activity relationship models, and threshold of toxicological concern to develop databases. In conclusion, several programs should continuously be developed by different health agencies to have a better understanding of the effect of these substances and to develop a unified policy.

1. The importance of the effects of the combination of multiple chemicals contaminants

We are exposed in our daily lives to several contaminants, and food is one of the reservoirs where is possible the presence of chemical contaminants. For the Codex Alimentarius, contaminant means any substance not intentionally added to food, which is present in such food because of the production (including operations carried out in crop husbandry, animal husbandry and veterinary medicine), manufacture, processing, preparation, treatment, packaging, transport or holding of such food or because of environmental contamination. The term does not include insect fragments, rodent hairs and other extraneous matter (Codex Alimentarius Commission, 2010). The European Chemicals Agency (ECHA) Technical Guidance (ECHA, 2008) defines that "A chemical category is a group of chemicals whose physicochemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity". Nowadays different studies have highlighted the exposure of humans and wildlife to several chemicals contaminants, but these studies were mainly developed with one type of chemicals contaminants.

According to the preliminary annual report by RASFF (Rapid Alert System for Food and Feed), the 2015-notifications by hazard category of chemical contaminants were mainly for mycotoxins, industrial contaminants, heavy metals, pesticide residues, and residues of veterinary medicinal products (RASFF, 2015). In promoting the exchange of information regarding dangerous consumer products, the EU uses RAPEX - a rapid alert system for dangerous consumer products (excluding food, pharmaceutical and medical devices, which are covered by other mechanisms). RAPEX publishes the notifications from National Contact Points, regarding the dangerous product type, the country of origin, and the measures taken to eliminate the risks, on the internet. The most frequent notifications were received for toys (33%), followed by the reporting of dangerous electrical appliances (11%) and motor vehicles (11%). Other noteworthy categories include clothing, textiles and fashion items (8%) and childcare articles and children's equipment (6%).

Effects of the mixture or the cocktail of chemical contaminants have also been studied in several works (Table 1) (EEA, 2012; Carvalho et al., 2014; Kortenkamp, 2009). The point of view was altered when it was discovered that effects do also occur when

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Acronyms

aHI	Adjusted HI
AhR	Aryl hydrocarbon receptor
ATSDR	Agency for Toxic Substances and Disease Registry
CA	Concentration addition
Cefic	European Chemical Industry Council
CSAFs	Chemical-specific adjustment factors
CYP	Cytochrome P450
DEBs	Dynamic energy budgets
DLCs	Dioxin-like compounds
E	Exposome
ECHA	European Chemicals Agency
ED	Effective dose
EDCs	Endocrine Disrupter Compounds
EFSA	European Food Safety Authority
EPA	United States Environmental Agency
FDA	United States of Food and Drug Administration
G	Genome
GI	Gastrointestinal
HBM	Human Bio-Monitoring
HI	Hazard index
HQ	Hazard quotients
IA	Independent action
LADD	Lifetime average daily dose
LOCs	Levels of Concern
MCR	Maximum cumulative ratio
MECs	Multiple chemical sensitivity
MOE	Margin of exposure
NCGC	National Institutes of Health Chemical Genomics Centre
NIEHS	National Institute of Environmental Health Sciences
NOEL	No-Observed-Effect Level
NTP	The US National Toxicology Program
PCBs	Polychlorinated Biphenyls
PCDDs	Polychlorinated Dibenzo-p-Dioxins
PCDFs	Polychlorinated Dibenzofurans
PEC	Predicted environmental concentration
PEF	Potency equivalency factor
PNEC	Predicted no effect concentration
PODI	Point of departure index
RAPEX	Rapid Alert System for Dangerous Consumer Products
RASFF	Rapid Alert System for Food and Feed
RfPI	Reference point index
RPF	Relative potency factor
RV	Reference value
TEF	Toxic equivalency factor
TUs	Toxic units
UF	Uncertainty factor
WoE	Weight of evidence

organisms are exposed even at low levels; as a consequence new studies of cumulative risk assessment have been triggered (EPA, 2008; EFSA, 2013). With the aim to consider the presence of chemical contaminants from various sources, the European Commission developed in 2003 a Strategy on Environment and Health, and in the period of 2004–2010 developed the Environment and

Table 1
Previous studies about the toxicity of the combined exposure to chemical contaminants.

Toxicological tests	Chemical contaminants	Toxic effects	Reference
Clinical	PCBs	Combinations and/or individual congeners appeared to have adverse effects on liver, thyroid, immunological function, reproduction function, behaviour, and are carcinogenic	Sirot et al. (2012)
In vivo	PCBs, Dioxins, Pesticides, Metals	Observed different effect according to the type of contaminants: Additivity, synergy, potentiation, or antagonism	Moretto et al. (2008)
In vitro tests	7 Mixtures of Pesticides	The toxic effects observed on human cells cannot be easily predicted based on the toxic potential of each compound.	Crépet et al. (2013)
In vitro Tests	Four different combinations of chemicals: a group of three similar acting model compounds: flutamide, procymidone and vinclozolin, all well-known antagonists of the AR. group of four model compounds: Finasteride, mono-(2-ethylhexyl) phthalate (MEHP), prochloraz and vinclozolin. The third consists of parabens: methyl paraben, ethyl paraben, propylparaben, butyl paraben and isobutyl paraben. The fourth group consists of the azole fungicides: epoxiconazole, propiconazole and tebuconazole.	In vitro mixture (epoxiconazole, propiconazole and tebuconazole) showed close to additive AR antagonistic effects with some variation over the concentration range. The mixture of parabens (methyl-, ethyl-, propyl-, butyl- and iso-butyl paraben) exhibited AR antagonistic effects.	Kjærstad, Taxvig, Andersen, and Nelleman (2010)
In vitro	Zn + Vit C	Vit C increased the cytotoxicity significantly. Exists synergistic toxicity	Wang et al. (2014)
In vitro	Mixtures of pesticides	- Isomalathion acted as a potentiator of the malathion toxicity by inhibiting the carboxylesterase responsible for the detoxication of the insecticide - Potentiation of OPs toxicity by organochlorine insecticides. - Potentiation of carbaryl toxicity by Ops - Synergism between PYRs and carbamate compounds	Hernández et al. (2013)
In vivo and clinical	Dioxins and PCBs	Large amounts of these chemical substances represent a real risk for food safety, because of their bioaccumulation thought the food chain	Ghimpeteanu, Militaru, and Scippo (2014)
Clinical	Eleven toxic compounds (acrylamide, arsenic, lead, mercury, chlorpyrifos, permethrin, endosulfan, dieldrin, chlordane, DDE, and dioxin)	Children in their preschool and primary school years exceed benchmark levels for a number of contaminants with known effects on health.	Vogt et al. (2012)