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Keeping Cocktail Effects Under Control is the Number One Challenge for the 21st Century

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The European Food Safety Authority (EFSA) published the following announcement on its website: Building on recent international developments and previous work at EFSA on pesticides and contaminants, our scientists have started to develop new approaches for assessing risks to humans and the environment from exposure to multiple chemicals in the food chain: "chemical mixtures" and their "cocktail effects". Chemical contaminant mixtures appear in our food, beverages and natural environment. They adversely affect the health of humans and wildlife. Also, there is a growing body of evidence that these chemicals can become more harmful when combined - a phenomenon known as the cocktail effect.

Migration from food contact and packaging materials might be the primary source of food contamination in terms of amounts and numbers of substances. Some 15 years ago, Grob [1] published an alarming conclusion: The number of substances migrating from food contact materials above the threshold of toxicological concern for genotoxic carcinogens is unknown but might be about 100,000.

Another health problem according to the Food and Agriculture Organisation is that mycotoxins contaminate nearly 25 % of the world's agricultural commodities. Aflatoxins and ochratoxins are the major contaminants, but several hundreds of different mycotoxins have been identified [2]. Exposure to mycotoxins can happen either directly by ingesting infected food or indirectly through the consumption of milk and other food products from animals that were fed contaminated feed. To be contaminated by a mycotoxin is bad enough, but the situation is even more disastrous when mycotoxins are mixed with pesticides [3]. And no-one will deny that pesticide residues are present in our diets!

It is now widely accepted that humans are exposed through their diet to a wide range of chemical contaminants. A highly original study [4] investigated 440 chemical substances and identified the major mixtures to which the French adult population is exposed. Six main consumption systems and their associated contaminant mixtures were determined. There are 11 to 19 contaminants in each of the mixtures - all of which are obviously contaminant cocktails - and the contaminant classes are heavy metals, mycotoxins, polycyclic aromatic hydrocarbons, pesticides and xenobiotics. In a follow-up study by Kopp., *et al*. [5], the genotoxic effects of the latter food contaminants were investigated using a bio-assay in human cell lines. Both the single molecules and the characteristic mixtures of the typical French diet were tested. Fourteen out of forty-nine individual organic contaminants demonstrated a positive genotoxic response. Additionally, two mixtures out of six triggered significant γH2AX induction after 24 hours of treatment and at concentrations for which the individual compounds did not induce any DNA damage. This confirms that the cocktail effect exceeds the sum of the individual effects because of the interactions between the chemicals. The authors conclude that two contaminant mixtures present in the French diet induce genotoxicity and mutagenicity and that the combined effects of single molecules present in the contaminant mixtures are not additive but synergistic.

Do exposures then really lead to adverse health effects or is the "machinery" of the human body so smart that it can repel chemical contaminant assaults? In his book, Sicker, Fatter, Poorer, Trasande [6] explains the science behind the escalating obesity, diabetes, learning disorders, autism, infertility, and food allergies, which result from chemicals in our food, homes, and personal care products: The chemicals with the strongest evidence of health effects are pesticides, flame retardants, plasticizer chemicals, and bisphenols, which are used to line food and beverage cans. At first it was thought that those chemicals had to persist in the body to cause harm, like a viral or bacterial infection. Now we realize that though the chemicals themselves are often excreted within a few days, they leave lasting effects. And here is the scariest piece: the effects of this chemical contact can reverberate years later and even be passed on to the next generation. That is what one calls the "hit-and-run" impact of these pernicious chemicals.

Exposure to toxic chemicals such as pesticides, polycyclic aromatic hydrocarbons, polychlorinated as well as polybrominated biphenyls, dibenzofurans and dibenzodioxins, and perfluorooctanoic acids (all substances in the plural) is a threat to global public health and is linked to numerous diseases, which can lead to significant effects on social endeavours and economic development. People can be exposed to mixtures of chemical toxins simultaneously and/or sequentially via multiple exposure routes, i.e. oral, dermal, and occupational. Exposure to these chemicals can trigger various cancers by disrupting the endocrine system, destroying DNA, damaging tissues, and switching genes on or off.

Protecting humans from harmful contaminated foods has become an urgent though daunting task. There can be no going back on the development that chemistry has undergone. Anthropogenic activities have introduced thousands of tons of chemicals into the environment knowing full well that all of us will be serving as human sponges and soaking up and storing the contaminants in our bloodstreams. Is there anything we can do to redress this global disaster, to defuse the ticking time bomb that has been inserted into our bodies without our consent? There is no simple answer to this question. There is no single miracle solution that can instantly cure all ills.

Molecule-specific analyses are the single pearls of instrumental analytical chemistry, but these techniques represent a heavy burden in terms of resources and time. Moreover, they do not tell us much about the non-target analytes, potentially very dangerous molecules whose presence in the contaminant cocktail is not even suspected. In order to complement these physicochemical analyses with bioanalytical methods, biosensors and other biological approaches have been developed since the end of the 20st century [7]. Unlike traditional physicochemical analysis, bio-analytical methods provide an overall value of the sample activity, but no information about the concentrations of individual molecules. These techniques measure the biological responses, e.g. the enzymatic activity, the antigen-antibody reaction, the hormonal activity, etc. The result of this type of analysis provides information on the effect of all the molecules present (the cocktails of contaminants), without however quantifying them individually.

Moreover, multi-residue analyses and in silico tools should complete the laboratory means for food quality control. Multi-residue analyses allow us to identify and quantify several hundreds of different molecules - pesticides, for example - in one single run [8]. This could be a great victory for analytical chemistry, but one that requires a sophisticated infrastructure and well-trained operators. In silico tools or mathematical modelling methods are now gaining considerable importance in toxicology, not only as a first-level screening tool, but also as a complement to *in vivo* and *in vitro* test results [9].

Tackling the contaminant cocktail requires a cocktail of techniques [10].

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