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Assessment of food toxicology

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Abstract

The interest in food toxicology is evident by the dependency of humankind on nutrition by virtue of their heterotrophic metabolism. By means of modern biochemistry, molecular and cell biology, computer science, bioinformatics as well as high-throughput and high-content screening technologies it has been possible to identify adverse effects and characterize potential toxicants in food. The mechanisms of toxicant actions are multifactorial but many toxic effects converge on the generation of oxidative stress and chronic inflammation resulting in cell death, aging and degenerative diseases. Integration of food toxicology data obtained throughout biochemical and cell-based *in vitro*, animal *in vivo* and human clinical settings has enabled the establishment of alternative, highly predictable *in silico* models. These systems utilize a combination of complex *in vitro* cell-based models with computer-based algorithms. A decrease of rodent animal testing with its limitations of high costs, low throughput readouts, inconsistent responses, ethical issues and concerns of extrapolability to humans have led to an increased use of these but also alternative lower hierarchy surrogate animal models (*e.g. Drosophila melanogaster*; *Caenorhabditis elegans* or *Danio rerio*) and efforts to integrate organotypic systems and stem cell-based assays. Despite those achievements, there are numerous challenges in various disciplines of food toxicology.

Keywords: Food toxicology; Oxidative stress; Inflammation; *In vitro*, *in vivo* and *in silico* models; Alternative models

1. Overview

The history of food toxicity might have started as early as Hippocrates made the statement "Let food be thy medicine and medicine thy food" which presaged the modern science by over two millennia ago. With the development of modern biochemistry, molecular biology, cell culture techniques, computer science and bioinformatics, it has been possible to identify and characterize potential toxicants in food [1–7]. Mechanistic insights gained by toxicity assessment of food using different models ranging from *in vitro* biochemical, cell-based *in vitro*, animal *in vivo* to clinical settings have led to a better food safety. The growing interest in this area is reflected by a stunning 6280 publications in PubMed as of February 2016 when combining "food, toxicity, review" in searches and the exploding numbers of around 200 reviews per year on these topics starting from 2002 (Fig. 1).

There are two different related areas in the measurement of toxicants and toxicity in food: (1) actual measurements of the effects of toxicants in different models ranging from *in vitro* biochemical systems, cell-based *in vitro* systems, animal *in vivo* models to clinical settings analyzing systemic or organ-specific toxicity and (2) assessment and/or predictions of potential toxicants in food. These two are interrelated since the mechanistic knowledge gained by the actual assessment of the effects of toxicants can lead to the identification of other potential toxicants in food. The majority of assessment systems for food toxicology were developed in the field of pharmacology [5,6,8,9]. Pharmacology and nutritional science share common roots since many of the world's most commonly used drugs are derived from natural products as illustrated by the term "nutraceutical" [10].

The mechanisms of toxicant effects are multifactorial interacting intrinsically and extrinsically with key molecules which

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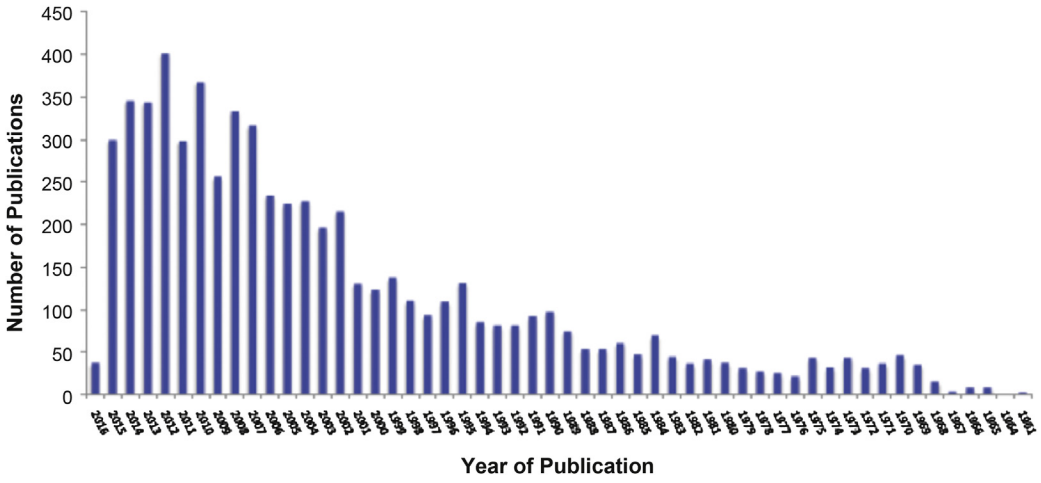

Fig. 1. Reviews referenced in PubMed (www.PubMed.gov) as of February 2016 when combining "food, toxicity, review" in search.

play major roles in cell integrity, metabolism, signaling pathways, gene expression and translation. For a variety of toxicants their effects appear to converge on the generation of electrophilic species (ES) leading to oxidative stress and chronic inflammation [11–15]. Oxidative reactions induced by toxicants lead to an accumulation of damaged macromolecules thus harming cells, tissues and organs. Therefore, toxicants may play central roles in cell death, chronic inflammation, aging and degenerative diseases such as Alzheimers, Parkinsons and Huntingtons diseases, as well as multiple sclerosis, myocardial infarction, arteriosclerosis, diabetes, rheumatoid arthritis, sterility, cataracts and many others [13,14,16–23].

For *in vitro* assessment a variety of biochemical systems have been developed to analyze damaging effects on integrity or activity of key biomolecules. Such molecules are important in cell integrity, metabolism, signaling pathways, as well as gene expression and translation. The list of affected molecules is extensive and includes enzymes, receptors, membrane lipids, nucleic acids and/or or factors involved in gene expression [3–6,24–29]. On cellular level, a variety of viability assays are routinely used to quantify effects of potential food toxicants for extrapolation of range of dosages used for maximal tolerated concentrations for *in vivo* animal models and also clinical settings [3–6,30–32]. For more mechanistic insights, several cell-based *in vitro* systems were developed in combination with targeted *in vitro* analyses which focus on cell-specific key enzymes and receptor-dependent pathways. *In vivo* rodent models still appear to be the gold standard for toxicity assessment but there are limitations of such traditional testing such as high costs, low throughput readouts, inconsistent responses, ethical issues and concerns of extrapolability to humans [2,5,6,8]. Consequently, new strategies have been developed and the paradigm in toxicology has switched from the traditional apical endpoint approach as determined in animal models to a mechanism-based approach by *in silico* methods [6,7,29,33,34].

In silico screening systems, a combination of focused *in vitro* cell-based models and computer based algorithms employ a variety of different high-throughput and high-content screening technologies. Cell-specific biomarkers on gene, protein or metabolite levels can be measured by toxicogenomics, toxicoproteonomics or toxicometabonomics, respectively [6,27,35–40]. The integration of food toxicology data obtained *via in vitro* biochemical, cell-based, *in vivo* animal models and *in silico* systems have led to a mechanistic knowledge of systemic or organ-specific toxicity in humans and the identification and use of specific surrogate biomarkers in clinical settings.

Although complex *in vitro* cell culture systems integrated with *in silico* systems provide unique mechanistic insights into *in vivo* toxicology more relevant to humans, they will never completely model the higher level complexity of cross-talk throughout different pathways present in an intact organism [1,2,4–6,8,41]. Another refinement in toxicity assessment is the installation of alternative lower hierarchy surrogate animal models such as zebrafish (*Danio rerio*), fruit flies (*Drosophila melanogaster*) or nematodes (*Caenorhabditis elegans*). These models offer an advantage in terms of ethical concerns, high throughput and genetic manipulation over traditional rodent models [4–6,42,43]. The value of using alternative sub-mammalian vertebrate and invertebrate models became evident by the surprising discovery of the high degree of homology of genes between humans and zebrafish, fruit flies or nematodes [5,43–49].

Overall, the achievements in food toxicology have significantly improved the prediction rate of drug and food safety in dimensions as unimagined only a decade ago [4–6,8,50–52]. The deeper understanding of the molecular mode of action on key targets of biological pathways have enhanced the predictivity and robustness of *in vitro* cell-based toxicity models and thus led to the improvement of food safety. Moreover, although in early development, stem cell-based screening or three-dimensional organotypic models will further increase the predictivity of acute toxicity and help to answer fundamental biological questions and/or enable testing of novel therapeutic approaches [6,7,53–57].

Despite those achievements, at present there are still huge challenges to increase the rate of predictivity in various areas such as reproductive and developmental toxicity, neurotoxicity,