Food TOXICOLOGY

Current Advances and Future Challenges

Editors Ashish Sachan | Suzanne Hendrich

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Edited by

Ashish Sachan, DVM, MVSc, PhD

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LIST OF ABBREVIATIONS

AD	antimicrobial division
ADHD	attention deficit hyperactivity disorder
ADI	acceptable dietary intake
AECOSAN	Spanish Consumer Agency for Food Safety and Nutrition
AhRs	aryl hydrocarbon receptors
AJs	adherent junctions
AMU	atomic mass units
AOP	adverse outcome pathway
APEs	alkylphenol ethoxylates
APs	alkylphenols
ASD	autism spectrum disorder
ASR	auditory startle reflex
ATSDR	Agency for Toxic Substances and Disease Registry United States
AuNPs	gold nanoparticles
BBB	blood–brain barrier
BCB	blood–cerebral spinal fluid barrier
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BMD	benchmark dose
BMP	bone-morphogenetic protein
BMR	benchmark response
BPA	bisphenol A
CCK	cholecystokinin
cEDI	cumulative estimated daily intake
CFR	Code of Federal Regulations
CFs	consumption factors
CFSAN	Center for Food Safety and Applied Nutrition
CI	confidence interval
CLA	conjugated linoleic acid
CNS	central nervous system
CS-UCNPs	core/shell upconversion nanoparticles
CTC	circulating tumor cells
DBP	di-*n*-butyl phthalate

DC	dietary concentration
DDD	daily dietary dose
DEHP	di-(2-ethylhexyl) phthalate
DiDP	di-isobutylpthalate
DILs	Derived Intervention Levels
DiNP	di-isononylpthalate
DL-PCB	dioxin-like polychlorinated biphenyls
DLPFC	dorsolateral prefrontal cortex
DnBP	di-*n*-butylpthalate
DNT	developmental neurotoxicity testing
DON	deoxynivalenol
DRCs	dioxin-related compounds
ECM	extracellular matrix
EDCs	endocrine-disrupting chemicals
EDI	estimated daily intake
EDs	endocrine disruptors
EECs	enteroendocrine cells
EFSA	European Food Safety Authority
EGF	epidermal growth factor
ELONA	enzyme-linked oligonucleotide assay
EMT	epithelial-to-mesenchymal transition
EPA	US Environmental Protection Agency
EPS	exopolysaccharides
ERs	estrogen receptors
EU	European Union
FAO/WHO	United Nations for Food and Agriculture/World Health Organization
FAP	Food Additive Petition
FCN	Food Contact Notification
FCSs	food contact substances
FCSS	food contact surface sanitizers
FDA	US Food and Drug Administration
FFQ	food frequency
FGF	fibroblast growth factor
FIFRA	Fungicide and Rodenticide Act
FOB	functional observation battery
FQPA	Food Quality Protection Act
FSIS	Food Safety and Inspection Service
GBS	Guillain–Barre syndrome
GIT	gastrointestinal tract

GJs	gap junctions
GL	Guideline Levels
GnRH	gonadotropin-releasing hormone
GPCRs	G-protein-coupled receptors
GR	glutathione reductase
GRAS	generally recognized as safe
HDAC	histone deacetylase
HEDP	1-hydroxyethane 1,1-diphosphonic acid
HGF	hepatocyte-growth factor
HPA	hypothalamic–pituitary–adrenal
HPG	hypothalamic–pituitary–gonadal
HRP	horseradish peroxidase
HTS	high-throughput screening
IARC	International Agency for Research on Cancer
IBD	inflammatory bowel disease
IGF	insulin-like growth factor
IQ	intelligence quotient
JAK	janus kinase
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LCR	lifetime cancer risk
LOD	limit of detection
LRET	luminescence resonance energy transfer
LSPR	localized surface plasmon resonance
MAPKs	mitogen-activated protein kinases
MEHP	mono(2-ethyl-hexyl) phthalate
MEP	monoethyl phthalate
MET	mesenchymal-to-epithelial transition
MiBP	mono-isobutyl phthalate
MnBP	mono-*n*-butyl phthalate
MNPs	magnetic nanoparticles
MOG	Modified One Generation
MPCs	maximum permissible concentrations
MWM	Morris Water Maze
NCGC	NIH Chemical Genomics Center
NM	nanomaterial
NOAEL	no observed adverse effect level
NP	nonylphenol
NPEs	nonylphenol ethoxylates
NTP	National Toxicology Program
OBs	osteoblasts

OCPs	organochlorine pesticides
OECD	Organization for Economic Cooperation and Development
OP	octylphenol
OPP	Office of Pesticide Programs
OPPTS	US EPA's Office of Prevention, Pesticides, and Toxic Substances
OSHA	US Occupational Safety and Health Administration
PAGs	Protective Action Guides
PAHs	polycyclic aromatic hydrocarbons
PAs	protective actions
PBBs	polybrominated biphenyls
PBDEs	polybrominated diphenyl ethers
PC	phosphatidylcholine
PCBs	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-*p*-dioxins
PCR	polymerase chain reaction
PFC	prefrontal cortex
PFCs	perfluorinated compounds
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PKC	protein kinase C
PMTDI	provisional maximum tolerable daily intake
PNDs	postnatal days
POD	point of departure
POPs	persistent organic pollutants
PPARs	peroxisome proliferator-activated receptors
ppb	parts per billion
PPI	prepulse inhibition
PTSs	persistent toxic substances
PTWI	provisional tolerable weekly intake
PVC	poly(vinyl chloride)
QD	quantum dots
Ras/ERK	Ras-extracellular signal-regulated kinase
RBE	relative biological efficiency
RNS	reactive nitrogen species
ROS	reactive oxygen species
RTK	receptor tyrosine kinase
RT-PCR	reverse-transcription polymerase chain reaction
RXRs	retinoid X receptors
SCFAs	short-chain fatty acids

SFB	segmented filamentous bacteria
SOD	superoxide dismutase
ssDNA	single-stranded DNA
TAS	total antioxidant status
TBT	tributyltin
TCDD	2,3,7,8-tetrachlorodibenzodioxin
TDI	tolerable daily intake
TEQs	TCDD equivalents
TGF-β	transforming growth factor beta
TH	thyroid hormone
TJs	tight junctions
TK	toxicokinetic
TMA	trimethylamine
TMAO	TMA N-oxide
TOR	Threshold of regulation
TPT	triphenyltin
TRs	thyroid receptors
TSCA	Toxic Substances Control Act
TWI	tolerable weekly intake
UCNPs	upconversion nanoparticles
URF	unit risk factor
US	unauthorized substances
USDA	US Department of Agriculture
WHO	World Health Organization
ZEN	zearalenone

PREFACE

The objective of this book is to offer academia, government, regulatory agencies, consumers, and those in the food industry knowledge of the breadth and depth of the multifaceted field of food toxicology. There are more than seven billion people and counting in the world today, and advances in food toxicology have a direct bearing on food safety issues that are of concern to all of humanity for the foreseeable future. Massive globalization, industrialization, and commercialization have affected every aspect of food production, the food supply chain, and food consumption. The challenge of sustainable and safe food for everyone needs a multidisciplinary and multi-sectorial approach from related industries and the government sector alike.

This volume, Food Toxicology: Current Advances and Future Challenges, offers important global perspectives of scientists and experts in areas related to biomarkers and nanosensors in food toxicology, toxicology of nanomaterials, chemicals in sanitation and packaging, food additives, mycotoxins, endocrine disruptors, radionuclides, toxic metals, and waste-burning residues in food. The fourteen chapters in this the book effectively cover this broad range of topics. The discussion on biomarkers in food toxicologyprovides interesting information surrounding the biomarkers of exposure, effect, carcinogenesis, and susceptibility. The chapter on the mucosal exposome delivers an interesting perspective on the effect of dietary components on the endogenous mucosal microenvironment affecting host physiology. This chapter also discusses biomarkers involving responses ofthe mucosal exposome to toxicants.

The toxicity of engineered nanomaterials used in food additives and food packaging is discussed in the chapter on the toxicity of ingested nanomaterials. Food incorporates numerous potentially toxic chemicals in its path from raw material to ingestion. Safety evaluation for such chemicals, especially during the processing and packaging of food, is detailed in the chapter on safety evaluation of chemistries used in the food and beverage processing and packaging industries. The chapter also puts in detailed context the direct and indirect dietary exposure of food contact substances as regulated primarily by the United States Food and Drug Administration (FDA) and the United States Environmental Protection Agency (EPA).

The succeeding chapter on developmental neurotoxicity considerations for food additive safetyprovides adetailed overview of the developmental neurotoxicity (DNT) caused by food additives and theevolution of regulatory approaches for risk assessment through DNT testing methodologies. In context the chapter also sheds light on the structural neural development and the susceptibility of the developing brain to neurotoxicity.

The chapter on the protective effect of food-grade lactic acid bacteria highlights the importance of exogenous antioxidants in our daily diet against oxidative stress due to reactive oxygen species (ROS) and reactive nitrogen species (RNS). In this volume the information on mycotoxins focuses on the important aspect of the fungal contamination of food grains and discusses risk assessment procedures and current and future mycotoxin mitigation strategies. The information in the book on endocrine disrupting chemicals lays out the common endocrine disruption chemicals in food harmful to human health along with an example-based exposure assessment of such chemicals. Further, the chapter on radionuclides in food provides an interesting and detailed perspective surrounding the pathways of human exposureand related health risks due to radionuclides through food sources.

The information in the book on metal toxicity delineates recent advances in assessment of heavy metals in food affecting human health. The chapter on waste-burning residues in foods focuses on toxicological risks due to improper waste management in low-income countries. The chapter focuses on the routes of exposure and adverse health effects due the toxic residues found in food because of open-air solid waste burning. The chapter on epithelial to mesenchymal transition (EMT) provides an excellent overview on the biological process of EMT and explains its developing role as a valuable marker in ecotoxicology and food toxicology. Subsequently, the chapter on pesticide residues provides a great overview of the regulatory challenges, residue monitoring in food and water, and the detrimental impact of such pesticide residues to human and animal health. Finally the book also provides introduction to aptamers and focuses on the use of aptamers as powerful nanosensing tools in food toxicology.

The book has involved the diligent efforts of 36 scientists and experts from 11 countries around the globe. It provides informative research for food scientists and researchers and others involved with food safety and toxicology.

—**Ashish Sachan,** Canada
—**Suzanne Hendrich,** USA

CHAPTER 1

BIOMARKERS IN FOOD TOXICOLOGY

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ABSTRACT

Major food toxicological interests arise from the need to estimate exposure, early effects, and individual variation in sensitivity reflecting the interaction between exogenous and endogenous factors in the human body. To this end, "biomarkers" represent tools to measure response(s) (functional, physiological, and biochemical) at the cellular or molecular level reflecting interactions between a biological system and a potential hazard of a chemical, biological, and physical nature. Overall, three classes of biomarkers are identified: *biomarkers of exposure*, *biomarkers of effect*, and *biomarkers of susceptibility*. Selection of appropriate "priority" biomarkers is of critical importance to assess the risk and possible health-related outcomes of exposure to individuals and population subgroups. The usefulness and characteristics of pertinent analytical methods and technical considerations of each are discussed. Additionally, dietary toxicants which target gut microbiota can significantly impact different organs and tissues. Any adverse effect on the gut microbiota, which plays an important role in metabolism, can potentiate some of these toxicants. Importantly, developmental processes during perinatal period in the nervous system are especially vulnerable by some food toxicants at doses that may not be toxic to mature systems. This chapter summarizes the current knowledge about biomarkers suitable for application to the hepatic, renal, hematological, immune, pulmonary, reproductive, developmental, nervous system, and cognitive functions and those associated with carcinogenic mechanisms, as well as the assessment of risk to human health derived from food toxicants.

1.1 INTRODUCTION

In recent years, the nutritional richness of some foods as well as the innovative marketing of several other fortified foods with potentially beneficial defined ingredients for health constituted an important driving force favoring their worldwide commercialization. For example, there is an increasing interest in some kinds of seaweed as a source of fiber and minerals as well as foods fortified with phytochemicals because of their hypocholesterolemic and antioxidant effects. However, these foods can be a source of naturally occurring toxicants such as heavy metals (i.e., arsenic, cadmium, lead) and/or oxidized products produced during food processing and storage (i.e., phytosterol oxides). Moreover, the consumption of some staple foods also constitutes a significant source of some toxicants, for example, rice as source of inorganic arsenic, and potentially immunogenic components, including gluten-containing cereals as innate modulators for celiac and overweight/obese patients.

The toxicity and resulting threat to human health of food toxicant(s) is, of course, related to its concentration in the food. Increasing research efforts have been made to better understand and estimate exposure levels of naturally occurring food toxicants or those produced during food processing and storage.[1,2] Several scientific studies reveal that traditionally held viewpoints of food toxicology in evaluating the concentration, physicochemical species, and evolution of the toxicant(s) as well as questionnaires about food frequency (FFQ) consumption usually overestimate toxicant(s) intake meanwhile food records often underestimate their dietary intake. Thus, FFQ need to be corrected according to physiological factors (i.e., biotransformation or factors that can affect the absorption of food/toxicant) to better compile toxicological information and predict health-risk assessments.

Food toxicological risk assessment implies major challenges because of the low doses to which humans are frequently exposed, so limiting the usefulness of experimental in vivo and in vitro models. Biomarkers constitute biological parameters reflecting interactions between a biological system and a hazard (physical, chemical, and biological or their metabolites) at cellular and molecular level.[3,4] These biomarkers are, among others, tools to evaluate the risk and possible health-related outcomes to individuals and population subgroups. Because of their increasing availability and sensitivity, biomarkers are increasingly being used to explore the links between exposure and effect in order to establish causality.[5] The contrast between individual variability and common characteristics becomes important to understand how behavioral phenotypes, constructed as an environmentally driven diet physiological adaptation, influence susceptibility to food toxicants.

Analysis of tissues and body fluids for defined chemicals or derived metabolites as well as enzymes and other biochemical substances to identify the interaction of toxicant(s) with biological systems has been used.[6] Measurement of biomarkers has been recognized as an advantageous tool directly linking exposure with an internal concentration and potential outcomes as relevant to the health-risk assessment. In this scenario, data from experimental in vivo and in vitro models can be compared to the biomarkers response(s) to establish and refine biological parameters that may be used in hazard identification and exposure potentially approaching biological response(s) in humans. The reaction and health outcome to toxicant(s) exposure through food consumption highly depends on inherited or behavioral patterns, life-style, chemical form(s) of the toxic, and how it is affected by household processes. Moreover, the critical dose–response relationship is difficult to estimate because of the physiological accumulation and biotransformation into tissues and organs as well as toxicant(s)-induced phenotype adaptations of these that will condition health outcomes to future exposure. Beyond risk factors, recent data suggest that food composition and its influence—on and interaction—with other dietary components as well as gut microbiota, and finally their crosstalk with the host's intestinal immune system are important determinants of food toxicant(s).[7,8]

Importantly, there is a growing body of evidence that the intrauterine or early childhood exposure to food toxicants induce phenotype changes and important health outcomes later in life. Currently, this information is foremost limited to heavy metals exposure through rice and water consumption (i.e., arsenic),[9–11] but it is largely inferential after long-term consumption of some oxidized derived phytochemicals and immunogenic components such as gluten. Thus, it points out the enormous importance to establish preventive nutritional intervention strategies stressing the need to limit the dietary intake of such components and the use of such foods as part of a balanced diet.

In this chapter, we summarized current knowledge about biomarkers suitable for application to several different physiological compartments and relevant systems. Additionally, identification of practicable biomarkers associated with different toxic end points or outcomes and usefulness and characteristics of pertinent analytical methods and technical considerations of each are discussed.

1.2 TAXONOMY OF BIOMARKERS

The term biomarker was first used in relation to a search for several classes of porphyrins in an attempt to establish the antiquity of terrestrial life.[12] This term receives different meanings depending upon the focus of the study. Currently, the most relevant biomarkers refer to exposure, effect, carcinogenesis, and susceptibility to other disease endpoints or adverse conditions and will be explained in further sections in this chapter. The National Institutes of Health Biomarkers Definitions Working Group defined the term biomarker as "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[13] According to this definition, biomarkers are not only used as indicators of the state/progress/impact of a toxic process but is also as an important instrument to investigate the relevance of the underlying toxicological mechanisms (Fig. 1.1).