APPLICATIONS OF BIOMARKERS IN TOXICOLOGY

Essay submitted for partial fulfillment of master degree in clinical toxicology

By

Reham Abdelnasser Mohamed Abdelhalim

M.B.B.Ch, Demonstrator in Forensic Medicine and Clinical Toxicology Department

Faculty of Medicine - Ain Shams University

Under the supervision of

Prof. Dr. Assmaa A. Fawzy Assaf

Professor in Forensic Medicine and Clinical Toxicology,
Faculty of Medicine, Ain Shams University

Prof. Dr. Manal Elsayed Abdelsalam

Professor in Forensic Medicine and Clinical Toxicology,
Faculty of Medicine, Ain Shams University

Prof. Rasha El-Hussaini Abou-Anza

Assistant professor in Forensic Medicine and Clinical Toxicology,

Faculty of Medicine, Ain Shams University

Faculty of Medicine Ain Shams University 2011



Acknowledgment

FIRST OF ALL, THANKS TO "ALLAH", THE MOST GRACIOUS AND THE MOST MERCIFUL

I would like to express my deepest appreciation and sincere gratitude to **Prof. Dr. Assmaa Fawzy Assaf**, Professor of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Ain Shams University, for her deep concern and enthusiastic encouragement throughout the study. I was truly honored to work under her supervision.

I do feel grateful to **Prof. Dr. Manal El Sayed Abd El Salam**, Professor of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Ain Shams University, for her active cooperation, continuous advice, great support as well as her helpful touches.

My grateful thanks to **Prof. Rasha El-Hussaini Abou Anza**, Assistant professor of Forensic Medicine and
Clinical Toxicology, Ain Shams University, for her support
and her valuable comments. They were of great help.

I would like to express sincere thanks to all staff members of Forensic Medicine and Clinical Toxicology department for their help, reinforcement and truthful advice.

I feel deeply indebted to My Family & My Husband, for their praying, care, patience and continuous encouragement.

Reham Abdelnasser Abdelhalim

List of Contents

Acknowledgment	i
List of Contents	ii
List of Tables	vi
List of Figures	vii
List of abbreviations	viii
Introduction	2
Aim of the work	8
Methodology	10
Literature review	
CHAPTER ONE	
Introduction to Biomarkers of Toxicity	13
Timeline of Biomarkers	13
Definitions of Biomarkers	18
The Ideal Biomarker	20
Sources of Biomarkers	22
Uses of Biomarkers	25
Limitations and Pitfalls of Biomarkers	28
Selection of Biomarkers	35
CHAPTER TWO	
Biomarkers of Toxicant Exposure	42
Introduction	42
A-Biomarkers of exposure	43
B-Biomarkers of susceptibility	51

List of Conte	nts	
C-Bion	markers of effect	54
В	iomarkers of the Respiratory System	55
	iomarkers of the Blood	
В	iomarkers of the Nervous System	60
В	iomarkers of the Renal System	63
В	iomarkers of the Liver	66
В	iomarkers of the Immune system	70
В	iomarkers of DNA damage	72
	iomarkers of Gene expression	
CHAP	TER THREE	
_	genomic and Toxicoproteomic App	
O	verview	78
V	/hat is Genomics?	79
V	/hat is Toxicogenomics?	80
	/hat is proteomics?	
V	Vhat is Toxicoproteomics?	82
V	/hat is Metabolomics?	83
V	/hat is Metabonomics?	83
V	/hat is Transcriptomics?	84
A	pplications of (omics) Technology in T	
CHAP	TER FOUR	
Applica	tions of Biomarkers in Clinical To	
Introd	vation	
mirodi	action	90

List of Contents	
Biomarkers for organophosphorus compounds (OI	PC) .90
Biomarkers for Acetaminophen Toxicity	101
Biomarker for Acute Iron Toxicity	116
Biomarkers for Scorpion Envenomation	119
Biomarkers for Carbon Monoxide Toxicity	123
CHAPTER FIVE	
Ethics, Regulatory Guidance and Validati Biomarkers of Toxicity	-
Introduction to Ethics	129
Ethics of Participation	129
Conduction and Interpretation of Results	130
Experiments on Terminally Ill Patients	131
Ethics Governing Biomarkers of Susceptibility	131
Quality Assurance and Quality Control	132
General concepts	133
Validation of Biomarkers of Exposure	138
Validation of Biomarkers of Effect	138
Validation of Biomarkers of Susceptibility	139
CHAPTER SIX	
Biomarkers of Chemical Warfare Agents	143
Introduction	143
Definition and Types	143
Importance of Detection of Biomarkers of ch Warfare	
Biomarkers for Nerve Agents	144
Biomarkers for Blistering Agents	148

List of Tables
Biomarkers for Respiratory agents148
Biomarkers for Blood Agents150
A Final Word151
CHAPTER SEVEN
Applications of Biomarkers in Toxic Tort and Forensic Litigation155
Introduction155
A Dilemma and a Potential Solution157
Potential Applications of Biomarkers in Toxic Tort and Litigation
Biomarkers of exposure and Toxic Tort Litigation 159
Biomarkers of Effect and Toxic Tort Litigation161
Biomarkers of Susceptibility and Toxic Tort Litigation
Summary
Conclusion
Recommendations
References
ب العلجي العربي

List of Tables

	1:Examples			_			-
	2:Examples ads			_			-
Table :	3:Biomarkers	of re	enal effects	s		• • • • • • •	65
Table 4	4 :Biomarkers	of iı	nmunotoxi	city in hun	nans		71

List of Figures

Figure 1: The interrelationship between different types of Biomarkers of toxicity
Figure 2: Factors that influence the interaction between the host and xenobiotic
Figure 3: The types of biomarkers of toxicity and their relationship to the source of exposure
Figure 4 :Biomarkers for internal dose for chemicals for which the major mechanism of action occurs through molecular interaction47
Figure 5 :Relationship among different biomarkers of exposure with respect to their levels and time of appearance after a single dose50
Figure 6:General Structure of OPCs, R=methyl, ethyl or isopropyl, X=leaving group
Figure 7 :Distribution of taurine levels in three different groups, 1 acetaminophen-poisoned patients, 2- non-acetaminophen poisoned patients, 3- healthy controls
Figure 8:Schematic diagram of acetaminophen metabolic pathway108
Figure 9 :Scorpion venom effect on catecholamines, neuropeptide Y (NPY), endothelin-1 (ET-1) and atrial natriuretic peptide (ANP)121

List of abbreviations

ABG	Arterial Blood Gases
AchE	Acetylcholinesterase enzyme
ALAD	Delta-aminolevulinic acid dehydra- tase
ALT	Alanine transaminase
ANP	Atrial Naturetic Peptide
AP	Attributable Proportion
APOE-€4	Apolipoprotein E-€4
ARDS	Adult Respiratory Distress Syndrome
AST	Aspartate aminotransferase
ATCA	2-aminothiazoline-4-carboxylic acid
ATP	Adenosine-5'-triphosphate
BAL	Bronchoalveolar fluid
BG	β-glucuronidase
BuChE	Butyrylcholinesterase
CC16	Clara Cell Protein 16
Cd	Cadmium
CD3,4,8etc.	Cluster of differentiation protein

СО	Carbon Monoxide
СОНь	Carboxyhemoglobin
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CtnI	Cardiac Troponin I
CWA	Chemical Warfare Agents
CWC	Chemical Weapons Convention
CYPs	cytochrome P450
DDT	Dichlorodiphenyltrichloroethane
DILI	Drug Induced Liver Injury
DILIN	Drug Induced Liver Injury Network
DNA	Deoxyribonucleic acid
EBC	Exhaled Breath Condensate
ELISA	Enzyme-linked immunosorbent assay
EP	Epinephrine
ET-1	Endothelin-1
FPN	Ferroportin
gm	Gram

GBM	Glomerular Basement Membrane
GSH	Glutathione
HAVCR1	Hepatitis A virus cellular receptor 1
НВО2	Hyperbaric oxygen
HDL	High Density Lipoprotein
Hg	Mercury
HLA	Human Leukocytic Antigen
HMWP	High Molecular Weight Protein
HPLC	High Performance Liquid Chromatography
HPLC-EC	High-performance liquid chromatography with electrochemical detection
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-8	Interlukin-8
IPCS	International Programme for Chemical Safety

KDa	Kilo-Dalton (unified atomic mass		
	unit)		
Kim-1	Kidney Injury Molecule 1		
L	Leucine		
LC-MS	Liquid Chromatography mass spectrometry		
LKM	Liver Kidney Microsomes		
LMWP	Low Molecular Weight Protein		
M	Methionine		
MAO	Monoamine Oxidase		
MAO-A	Monoamine Oxidase A		
МАО-В	Monoamine Oxidase B		
mg	Milligram		
ml	Milliliter		
miRNA	Micro RNA		
mRNA	Messenger Ribonucleic acid		
NAC	N-acetylcysteine		
NAG	β-N-acetyl-D-glucosaminidase		
NAPQI	N-acetyl-p-benzo-quinone imine		

NE	Norepinephrine
NIEHS	National Institute of Environmental Health Sciences
NO	Nitric Oxide
NPY	Neuropeptide Y
NTE	Neuropathy Target Esterase
ОС	Organochlorines
OCT	ornithine carbamyltransferase
OP	Organophosphate
OPC	Organophosphorus Compounds
OPIDN	Organophosphate- Induced Delayed Neuropathy
Pb	Lead
PCR	polymerase chain reaction
PhD	Doctor of Philosophy
PON1	Paraoxonase enzyme
Ppm	Part per million
Q	Glutamine
R	Arginine