

Human Toxicology of Chemical Mixtures

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Toxic Consequences Beyond the Impact of One-Component Product and Environmental Exposures

Second Edition

Harold I. Zeliger



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*To my wife Gail. Your encouragement was the
catalyst that made this happen.*

Preface to the Second Edition

Since the publication of the first edition of this book in 2008, many new case studies addressing the human toxicology of chemical mixtures have been published. These studies are recognized and incorporated into the text here.

This book has been expanded to include new chapters on nanotoxicology and the toxicology of global warming. New advances in nanotechnology have brought with them new toxicological ramifications for those exposed to nanoparticles. Global warming is impacting people in many ways, including the acceleration of toxic chemical impact on human beings. The implications of these two new areas of toxicology are explored in the new chapters.

A new chapter on children's toxicology has also been added to this edition with the hope that it will bring recognition of the special effects that toxic chemicals have on the world's children. With that in mind, I rededicate this book to my grandchildren, Jessica, Will, Jack, Caroline, Meren, Sadie, and Nate, as well as to yours.

The publication of the first edition has stimulated new research into the human toxicology of mixtures. It is my hope that this book will encourage others to investigate this subject matter.

Harold I. Zeligier
West Charlton, New York
April, 2011

Preface to the First Edition

I have been a chemical toxicologist for almost 40 years. As such, I have studied and evaluated the toxicities of chemicals and the health effects produced by human exposure to chemical products and environmental chemicals.

This book really began over 30 years ago, when I was confronted with the first of scores of instances where individuals exposed to chemical mixtures subsequently developed symptoms and effects which could not be explained by the known toxicological effects of the individual chemical species. In some instances, these exposures led to effects far in excess of what would be expected from the exposure. In others, effects were noted following exposures to extremely low levels of chemicals and in still others the body organs targeted were not those known to be impacted by the individual chemicals. Stymied, I advised people to look for other causes of the conditions observed. These inquiries, however, led to my research into the area of toxic effects of chemical mixtures and ultimately to this book.

As time progressed, I began to think that the noted effects might in some way be related to the mixtures, but an explanation remained elusive. The breakthrough came while I was simultaneously investigating two separate, unrelated exposures. The first involved the exposures of several people to very low levels of herbicides and their carrier solvents that entered a building with air-conditioning uptake air. The second involved the exposure of an individual to chemicals off-gassing from newly installed carpeting in a home. In both instances, air sampling revealed airborne concentrations of all individual volatile chemicals to be less than 10% of the values known to affect people. Both exposures were to complex mixtures of chemicals and both exposures led to effects unknown for the individual chemical species.

These cases led me to hypothesize that exposures to chemical mixtures could produce “strange” effects. A review of the literature revealed many examples of unexplained health effects on humans following exposures to mixtures. A study of these showed that in every unexplained instance the mixture contained at least one lipophilic (fat soluble) and one hydrophilic (water soluble) chemical. The literature showed that all body tissues have lipophilic barriers surrounding them. This suggested that absorption of lipophilic chemicals should occur more easily than for hydrophilic species. This too was confirmed by the literature and it was then hypothesized that lipophiles facilitate the absorption of admixed hydrophiles. Accordingly, a greater quantity of a hydrophilic species would be absorbed if it were dissolved in a lipophile than would be taken up if the hydrophile were present alone. This, too, was confirmed by the literature. For example, lipophiles are commonly used to facilitate the absorption of hydrophilic pharmaceuticals. It was further hypothesized that greater absorption of hydrophiles might account for the enhanced low-level effects observed. What was not predicted at the time was the observed attack of lipophile/hydrophile mixtures on new target organs.

In multiple cases, however, human exposures to mixtures of lipophiles and hydrophiles showed attacks at organs not known to be targeted by the individual chemicals.

It was found that all bodily systems are affected by some lipophile/hydrophile mixtures. These include the reproductive (infertility), nervous, digestive, skin, musculoskeletal, filtering organ, digestive, respiratory, cardiovascular, immunological, and endocrine systems. A developing fetus or young child (with an incompletely developed immune system) is particularly vulnerable to attack by chemical mixtures.

The sources of lipophilic/hydrophilic chemical exposure include environmental pollution (air, water, and soil contamination), pesticide, herbicide, and fertilizer residues in foods and drinking water, excipients (non-active additives such as colors, flavors, rheological agents, etc.) in foods and pharmaceuticals, industrial chemicals, household chemical products, personal care products, cosmetics, and environmentally synthesized chemicals that are formed from reactions with released chemicals with each other and with naturally present species.

The subject of this book is effects on humans. Animal studies are occasionally cited, but conclusions are drawn primarily from the human experience.

This book is divided into four parts.

Part I contains an introduction, a discussion of chemical toxicology and mechanisms of chemical absorption and of interaction with various body tissues on macro and molecular levels. Also discussed are the body's protective responses to xenobiotic intrusion, including metabolism, immune system, and endocrine system actions.

Part II discusses where the exposures to chemical mixtures come from, including chemical product and environmental sources. Included are air pollution, water pollution, foods, chemicals used in food production, pharmaceutical products, and electromagnetic radiation.

Part III examines the specific effects of mixtures on different body systems and organs and addresses predicting what the effects of uncharacterized mixtures will be. Case studies of specific effects of chemical mixtures on humans are listed and described.

Part IV is devoted to regulatory requirements for toxic chemicals, warnings for chemicals and chemical products, and the need to adjust recommended exposure levels for products containing chemical mixtures. This part also contains suggestions for limiting mixture exposures in the products we use and recommendations for limiting environmental exposures to toxic chemical mixtures.

I wish to acknowledge the encouragement of my children and their spouses, David, Jennifer, Joseph, Christine, Michael, Katie, Laura, and Jeremy, during the research and writing of this book. David and Jennifer, I cannot thank you enough for your critical review. Your scientific focus, intellect, and rigor were invaluable. Jeremy, thank you for your editing and computer skills. These helped immeasurably in the writing of this book.

This book is dedicated to my children and grandchildren as well as to yours and those of everyone else with the hope that they will all live in a healthier world.

Harold I. Zeliger
West Charlton, New York
April, 2008

List of Abbreviations

2,4-D	2,4-Dichlorophenoxyacetic acid
2,4,5-T	2,4,5-Trichlorophenoxyacetic acid
ACD	Allergic contact dermatitis
ACGIH	American Conference of Governmental and Industrial Hygienists
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
AMI	Acute myocardial infarction
AOT	Air odor threshold
ASD	Autism spectrum disorder
BaP	Benzo[a]pyrene
BET	Brunauer, Emmett, and Teller (surface area)
BFR	Brominated flame retardant
BHA	Butylated hydroxyl anisole
BHT	Butylated hydroxyl toluene
CDC	U.S. Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
CNS	Central nervous system
CNT	Carbon nanotube
COPD	Chronic obstructive pulmonary disease
CVS	Cardiovascular system
DBP	Disinfection (or decontamination) by-products
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DE	Diol-epoxide
DEP	Diesel exhaust particles
DES	Diethyl stilbesterol
DEET	Diethyltoluamide
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNAPL	Dense nonaqueous-phase liquid
DOT	U.S. Department of Transportation
EAFUS	Everything added to food in the United States
EDC	Endocrine-disrupting compound
EDTA	Ethylenediaminetetra-acetic acid
ELF	Extremely low frequency
EMR	Electromagnetic radiation
EPA	U.S. Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-To-Know Act of 1986
ET	Electron transfer
ETS	Environmental tobacco smoke
EWG	Environmental working group

FAS	Fetal alcohol syndrome
FDA	U.S. Food and Drug Administration
FD&C	Food Drug and Cosmetic Act
FEMA	Flavor and Extract Manufacturers Association
FHSA	U.S. Federal Hazardous Substances Act
FM	Fibromyalgia
GC/MS	Gas chromatography/mass spectrometry
GRAS	Generally regarded as safe
GSH	Glutathione
H	Hydrophilic compound
HAA	Haloacetic acid
HAN	Haloacetonitrile
HPT	Hypothalamic-pituitary-thyroid (axis)
IARC	International Agency for Research on Cancer
IDLH	Immediately dangerous to life or health
IgE	Immunoglobulin E antibodies
IPA	Isopropyl alcohol
ISW	Industrial waste sites
K_{ow}	Octanol:water partition coefficient
K_p	Permeation coefficient
L	Lipophilic compound
MCL	Maximum contaminant level
MCS	Multiple chemical sensitivity
MIBK	Methyl isobutyl ketone
MND	Motor neuron disease
MOAEL	Minimal-observed-adverse-effect-level
MPCM	Milligrams per cubic meter of air
MS	Multiple sclerosis
MSDS	Material safety data sheet
MSG	Monosodium glutamate
MSW	Municipal solid waste
MWCNT	Multi-wall carbon nanotube
NDD	Neurodegenerative disease
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No-observed-adverse-effect-level
NOEC	No-observed-effect-concentration
NP	Nanoparticle
NSDWR	National secondary drinking water regulations
OA	Occupational asthma
OH	Hydroxyl
OS	Oxidative stress
OSHA	U.S. Occupational Safety and Health Administration
PAH	Polynuclear aromatic hydrocarbon
PB	Pyridostigmine bromide
PBB	Polybrominated biphenyl