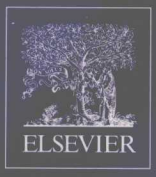

HUMAN TOXICOLOGY OF CHEMICAL MIXTURES

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

HAROLD I. ZELIGER

SECOND EDITION

Human Toxicology of Chemical Mixtures

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Second Edition

Harold I. Zeliger

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William Andrew is an imprint of Elsevier

William Andrew is an imprint of Elsevier
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK
225 Wyman Street, Waltham, MA 02451, USA

First edition 2008
Second edition 2011

British Library Cataloguing-in-Publication Data
A catalog record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN 978-1-4377-3463-8

For information on all William Andrew publications
visit our web site at www.books.elsevier.com

Typeset by MPS Limited, a Macmillan Company, Chennai, India
www.macmillansolutions.com

Printed and bound in the USA

11 12 13 14 15 10 9 8 7 6 5 4 3 2 1

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. Zeliger
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	Immunoglobin 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

PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-*p*-dioxins
PCDF	Polychlorinated dibenzofurans
PCP	Pentachlorophenol
PD	Parkinson's disease
PEL	Permissible exposure level
PET	Polyethylene terephthalate
PM2.5	Particulate matter less than 2.5 microns
PM10	Particulate matter less than 10 microns
PMP	Pharmaco-metabonic phenotyping
POP	Persistent organic pollutant
PPB	Parts per billion
PPM	Parts per million
PU	Polyurethane
PVC	Polyvinyl chloride
QAC	Quaternary ammonium compound
RADS	Reactive airways dysfunction syndrome
RF	Radio frequency
RO	Alkoxyl
ROO	Peroxyl
ROS	Reactive oxygen species
SAB	Spontaneous abortion
SBS	Sick building syndrome
SLE	Systemic lupus erythematosus
SO	Superoxide
SS	Systemic sclerosis
SSc	Scleroderma
STEL	Short-term exposure limit
SWCNT	Single-wall carbon nanotube
TAC	Toxic air contaminant
TCA	Trichloroacetic acid
TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
TCE	Trichloroethylene
THM	Trihalomethane
TRI	Toxic release inventory
TTHM	Total trihalomethanes
TLV	Threshold limit values
TWA	Time-weighted average
UCTD	Undifferentiated connective tissue disease
USDA	U.S. Department of Agriculture
UV	Ultraviolet
VOC	Volatile organic compound
WHO	World Health Organization

Contents

Part I

Introduction to Chemical Toxicology of Mixtures

1 Introduction

Chapter Outline
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What do Gulf War syndrome, Katrina cough, aerospace syndrome, and epidemic increases in the incidence of autism, attention deficit hyperactivity disorder (ADHD), birth defects, asthma, mailroom illness, spontaneous abortion (SAB), and many cancers have in common? Each of these can be associated with a single causative agent, but each can be associated with environmental exposure to chemical mixtures that do not contain any of the known causative agents.

No doubt that some of the increased numbers of the diagnoses being made for environmentally induced illnesses (such as asthma and ADHD) are due to improved methods of detection and reporting. The huge increases observed, however, cannot be accounted for by increased diligence only.

Many environmentally induced illnesses can be attributed to exposures to single chemical compounds. These have been and continue to be extensively studied and numerous references address them [1, 2]. Table 1.1 lists a few examples of single chemicals and the effects they are known to cause.

Single chemical effects will not be specifically addressed here. Rather, the focus here is on illnesses that ensue following exposures to mixtures of chemicals and that cannot be attributed to any one component of an exposure mixture. A good list summarizing the effects of approximately 2000 single chemicals has been made available by the State of Maine Department of Environmental Protection [3].

Traditionally and historically, toxicologists have addressed the effects of single chemicals. There are thousands of unnatural chemicals in our environment, in the home, and at the work place, and new ones are being constantly added. It is virtually impossible for a person to be exposed to a single chemical. The unborn fetus is exposed to numerous chemicals in utero and babies have been shown to be born with hundreds of synthetic chemicals in their bloodstreams. Nursing babies ingest large numbers of environmental toxins in mother's milk.

As used here, an unnatural chemical is one that is either synthesized by man and unknown in nature (e.g., polychlorinated biphenyls (PCBs), dichlorodiphenyl trichloroethane (DDT), and toluene diisocyanate (TDI)), or known in nature but introduced at concentrations that are much greater than those found in unpolluted environments (e.g., ozone, 1,3-butadiene, and asbestos). We all drink water, breathe air, and eat food that contains hundreds if not thousands of unnatural chemical compounds. Household cleaning and maintenance products, adhesives, paints, disinfectants, and pesticides are

Human Toxicology of Chemical Mixtures. DOI: 10.1016/B978-1-4377-3463-8.00001-1

Table 1.1 Single Chemicals and the Effects They Are Known to Cause

Chemical	Effects
Benzene	Leukemia
Bromoform	SAB
DDT	Liver and kidney damage
Dibenzofuran	Skin rashes and pigmentation changes
n-Hexane	Central nervous system (CNS) damage
Methylmercuric chloride	Irreversible brain damage
Trimellitic anhydride	Asthma

just some of the sources of chemical mixtures. Lesser known ones include disposable diapers, marking pens, air fresheners, fragrance products, mattress covers, pharmaceuticals, food flavors and colors, and chemicals inadvertently carried home on clothing of workers. Naturally occurring phenomena such as fires, petroleum seepage, and volcanoes are also sources of chemical mixtures. The interaction of electromagnetic radiation (EMR) with chemicals and the reaction of chemicals with other released or naturally occurring chemicals produce still more mixtures. Exposure to industrial chemicals affects very large numbers of people to wide varieties of single species and chemical mixtures.

Before 1828, it was believed that organic chemicals could only be formed under the influence of the vital force in the bodies of animals and plants. Vital force, also referred to as vital spark, energy and soul, is a tradition in all cultures, including Eastern as well as Western ones. Until 1828, this vitalism, and only it, was believed to be responsible for all factors affecting life, including the synthesis of all organic molecules. It was inconceivable that human beings could create such material. In 1828, Friedrich Wohler accomplished the first synthesis of urea, a naturally occurring component of human urine. Once it was demonstrated that such synthesis was possible, chemists were freed to pursue other such work, and since then, many other naturally occurring compounds have been synthetically prepared. Organic synthesis, however, has not limited itself to duplicating nature. Hundreds of thousands of new, previously unknown to nature, chemicals have been synthesized.

Each new chemical added to our environment potentially creates a vast number of new chemical mixtures with unknown health consequences. The number of compounds is multiplied by chemical reactions of newly released compounds with existing released compounds as well as with naturally occurring species to create yet more toxic molecules. Continual exposure to heat and/or EMR promotes further chemical reactivity and results in the creation of still more toxins. There are no meaningful experiments that can be done because the scope of the problem is undefined. The Earth's flora and fauna, including humans and guinea pigs, are afflicted by these toxicants and often do not understand the causes of these ailments. The results of these multiple exposures often only become evident after people are stricken. Research into

the toxic effects of single chemicals often produces conflicting results when investigators fail to consider the presence of species other than the ones being studied. For example, different effects have been reported following the inhalation of formaldehyde when it was admixed with other chemicals [4].

For single chemical exposures, we know that most individuals are affected by very high concentrations. Individuals who are genetically predisposed and/or have been previously sensitized react to lower concentrations of a chemical. Effects at different concentration levels are, for the most part, known and predictable, enabling proper precautions to be taken [5].

Exposures to mixtures of chemicals produce effects that are, for the most part, unknown and unpredictable. These are:

1. Enhanced effects
2. Low-level reactions
3. Unpredicted points of attack.

An enhanced effect is defined as one where exposure to a chemical mixture produces a reaction at a target organ that is anticipated for one of the chemicals in the mixture, but it is a reaction that is far in excess of that anticipated from the toxicology of the individual chemical species.

A low-level reaction is one where exposure to a mixture of chemicals in which each chemical is present at a concentration far below that known to produce a reaction does indeed impact a target organ that is known to be affected by one of the chemicals.

An unpredicted point of attack reaction occurs when exposure to a mixture of chemicals results in attack on an organ not known to be impacted by any of the individual chemicals in the mixture.

The human body is a complex mixture of chemicals. We have evolved and adapted over time to contacting, eating, drinking, and breathing the chemicals naturally present in our environment. We are not always prepared for the assault of "unknown" synthetic chemicals on our bodies. The introduction of a foreign chemical species (xenobiotic) challenges the body's natural defense mechanisms to defend against an unknown challenger. The body responds by trying to metabolize the invader so that it can be eliminated, and/or fights it with its immune system. Most people are thus able to defend against foreign chemical species. Mixtures, however, present a special challenge to the body's natural defenses. Often, one part of a mixture attacks a particular organ while a second species attacks a component of the defense mechanism trying to defend the body. This will be explored in more detail in later chapters.

Our inability to defend against new chemicals and mixtures often results in epidemics of disease. For example, asthma, autism, infertility, and many cancers affect different parts of the body and seemingly have different etiologies. All, however, can be related to a combination of genetic predisposition and environmental exposure to chemicals. All are less prevalent where chemical exposures are lower; for example, in rural areas. All have known single chemical exposure causes and all can also be related to low-level exposure to chemical mixtures. The toxic effects of chemical mixtures will be explored in the chapters that follow.