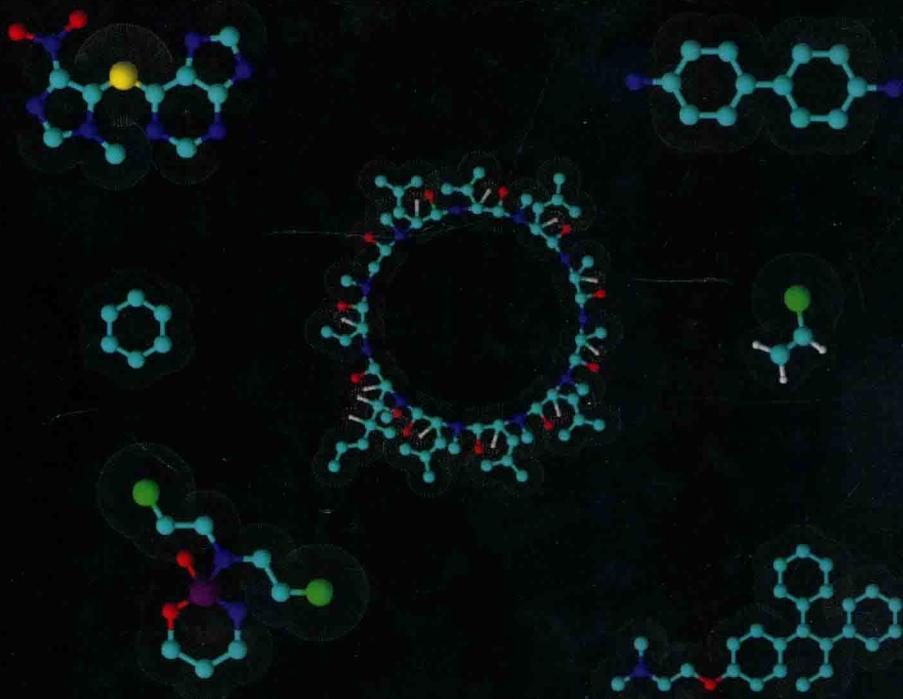


# CANCER RISK ASSESSMENT

*Chemical Carcinogenesis,  
Hazard Evaluation,  
and Risk Quantification*

Edited by

*Ching-Hung Hsu and Todd Stedeford*



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# *CANCER RISK ASSESSMENT*

Chemical Carcinogenesis, Hazard  
Evaluation, and Risk Quantification

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CHING-HUNG HSU  
TODD STEDEFORD



 **WILEY**

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About the cover: The cover structures are chemicals classified as known human carcinogens in the U.S. National Toxicology Program's Annual Report on Carcinogens (<http://www.ntp.niehs.nih.gov/>). The center structure is cyclosporin A (CASRN 59865-13-3). The outer structures going clockwise are benzidine (92-87-5), vinyl chloride (CASRN 75-01-4), tamoxifen (CASRN 10540-29-1), cyclophosphamide (CASRN 50-18-0), benzene (CASRN 71-43-2), and azathioprine (CASRN 446-86-6). These structures were prepared using ACD/ChemSketch (ACD/Labs Release: 11; Product Version: 11.01; <http://www.acdlabs.com>).

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*CANCER RISK  
ASSESSMENT*

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# PREFACE

Cancer risk assessment is an ever-changing discipline with standard regulatory practices and defaults giving way to ever-increasing breakthroughs in scientific discovery. The scientific literature is, however, replete with reports of toxicant-induced changes, but discriminating between those reports that are irrelevant or relevant to humans and those that are compensatory versus truly adverse can be an arduous task. This book aims to inform and to provide interpretive guidance on evaluating toxicological data and understanding the relevance of such data to hazard evaluation and cancer risk estimation.

The topics presented herein begin with Part I, which provides an overview of cancer risk assessment, followed by a discussion on science policy. The regulatory frameworks for industrial chemicals and biocides are presented along with the general approaches for developing standards for chemicals in air, water, food, soil, and consumer products. In Part II, basic concepts in cancer biology, chemical carcinogenesis, hormesis, and experimental evidence of thresholds for genotoxic carcinogens are provided. Thereafter, Part III describes the testing guidelines and regulations for *in vitro* and *in vivo* genotoxicity testing, and Part IV offers interpretive guidance on assessing the human relevance of chemical-induced tumors from rodent studies, along with the necessary criteria for evaluating data from epidemiological studies. Commonly observed modes of action from experimental animal studies, including PPAR- $\alpha$ ,  $\alpha_{2u}$ -globulin, and so on, are then discussed. In Part V, methods for informing cancer risk quantification, including quantitative structure-activity relationships (QSAR), physiologically based pharmacokinetic (PBPK) modeling, “-omics”, and computational toxicology are discussed. Finally, Part VI addresses general approaches for quantifying cancer risks including linear and nonlinear low-dose extrapolations, summing tumors, and exposure reconstruction for cancer risk estimation.

The foregoing topics are critical for keeping abreast of changes that are taking place in cancer risk assessment, as well as in the fields of toxicology and risk assessment in general. For example, with the increased emphasis on describing a chemical's mode of action for both cancer and noncancer endpoints, an understanding of the human relevance framework is essential, as is the role of rapidly developing technologies (e.g., “-omics”) for informing mode(s) of action. Therefore, readers of this text will take away knowledge that is applicable to cancer risk assessment and more broadly to toxicology and risk assessment. The resources that formed the bases for this text include: peer-reviewed scientific articles, regulatory guidance documents, validated test guidelines, and the many years of experience conveyed throughout by the contributing authors.

The editors are truly grateful to the contributing authors of this text, who provided their expertise on a gratis basis. If it were not for their dedication and commitment to advancing the knowledge and understanding of cancer risk assessment, the extensive coverage provided herein would not have been possible.

*Taipei, Taiwan*  
*Baton Rouge, Louisiana*  
*April 2010*

CHING-HUNG HSU  
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# ABBREVIATIONS AND ACRONYMS

AAF	2-Acetylaminofluorene
4-ABP	4-Aminobiphenyl
ACF	Aberrant crypts foci
ACO	Acyl-CoA oxidase
ACToR	Aggregated chemical toxicity resource
ADAF	Age-dependent adjustment factor
Ade	Adenine
ADI	Allowable daily intake
ADME	Absorption, distribution, metabolism, and excretion
AFC	Altered foci cells
AHF	Altered hepatic foci
AhR	Aryl hydrocarbon receptor
AI	Artificial intelligence
AMS	Accelerator mass spectrometry
ANOVA	Analysis of variance
AOM	Azoxymethane
apo	Apolipoprotein
ARB	Air Resources Board, California EPA
ARNT	Ah receptor nuclear translocator
ATSDR	U.S. Agency for Toxic Substances and Disease Registry
AUC	Area under the curve
B[a]A	Benz[a]anthracene
BBDR	Biologically based dose-response
BDA	Bayesian data analysis
BE	Biomonitoring equivalents
BEEL	Biological environmental exposure limit
BEIs	Biological exposure indices
BMD	Benchmark dose
BMDL	Benchmark dose lower bound
BMR	Benchmark response
B[a]P	Benzo[a]pyrene
BPD	Biocidal products directive
BPDE	Benzo[a]pyrene diol epoxides
BrDU	5-Bromo-2-deoxyuridine

b.w.	Body weight
CAA	U.S. Clean Air Act
CAF	Cancer-associated fibroblast
CAG	Carcinogens Assessment Group
CAM	Cellular adhesion molecule
CAR	Constitutive androstane receptor
CCA	Chromated copper arsenate
CCl <sub>4</sub>	Carbon tetrachloride
CD <sub>10</sub>	10% of Cancer dose
CDC	Center for Disease Control
CDC	U.S. Centers for Disease Control and Prevention
CDK	Cyclin-dependent kinase
CEBS	Chemical effects in biological systems
CEO	Chloroethylene oxide
CEO	Cyanoethylene oxide
CEPA	Canadian Environmental Protection Act
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
cGys	Centigrays
ChAMP	Chemical Assessment and Management Program
CHMP	Committee of Human Medicinal Products
CIIT	Chemical Industries Institute of Toxicology
CMRs	Carcinogens, mutagens, or reproductive toxicants
CNDR	Canadian National Dose Registry
CoA	Acyl coenzyme A
COPC	Contaminants of Potential Concern
CPDB	Carcinogenic potency database
CPN	Chronic progressive nephropathy
CPSC	Consumer Product Safety Commission
CPT-I	Carnitine palmitoyl transferase-I
CPUM	Colorado Plateau Uranium Miners
CSA	Chemical Safety Assessment
CSF	Cancer slope factor
CSR	Chemical Safety Report
CTM	Chinese tin miners
Cx	Connexon
CYP	Cytochrome P450
2-D	Two-dimensional
3-D	Three-dimensional
4-DAB	4-Dimethylaminoazobenzene
DAG	Directed acyclic graph
DAPI	4',6-Diamidino-2-phenylindole
4-DAST	4-Dimethylaminostilbene
DB[ <i>a,l</i> ]P	Dibenzo[ <i>a,l</i> ]pyrene
DC	Dendritic cells
DCB	1,4-Dichlorobenzene

DCC	Deleted in colorectal cancer
DCM	Dichloromethane or methylene chloride
1,3-DCP	1,3-Dichloropropene
DDT	Dichlorodiphenyltrichloroethane
DEEM	Dietary Exposure Evaluation Model
DEHA	Di-(2-ethylhexyl)adipate
DEHP	Di-(2-ethylhexyl)phthalate
DEN	<i>N</i> -Nitrosodiethylamine
DEN, DENA	<i>N,N</i> -Diethylnitrosamine
DEPM	Dietary Exposure Potential Model
dGua	Deoxyguanosine
DHEW	U.S. Department of Health Education and Welfare
DINP	Di-(2-isononyl) phthalate
DINP	Diisononyl phthalate
DMA	Dimethylarsenic acid
DMBA	7,12-Dimethylbenz[ <i>a</i> ]anthracene or 9,10-Dimethyl-1,2-benz[ <i>a</i> ]anthracene
DMN	Dimethylnitrosamine
DMN	<i>N</i> -Nitrosodimethylamine
DQA	Data Quality Act
DSS	Dextran sulfate sodium
DSSTox	Distributed structure-searchable toxicity
Dt	Dose metrics
EAF	Enzyme-altered foci
ECHA	European Chemicals Agency
ECM	Extracellular matrix
ECVAM	European Centre for the Validation of Alternative Methods
ED	Effective dose
EFSA	European Food Safety Authority
2-EH	2-Ethylhexanol
EHEN	Ethyl hydroxyethylnitrosamine
ELISA	Enzyme-linked immunosorbant assays
EMSA	Electrophoretic mobility shift assay
ENNG	<i>N</i> -Ethyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine
ENU	Ethylnitrosourea
ENU	<i>N</i> -Nitroso- <i>N</i> -ethylurea
EPA	U.S. Environmental Protection Agency
EPI	Exposure potency index
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinases
ESR	Electron spin resonance
ESTR	Expanded Simple Tandem Repeat
EU	European Union
FDA	U.S. Food and Drug Administration
FDCA	Food, Drug and Cosmetic Act

FFDCA	Federal Food, Drug and Cosmetic Act
FGF	Fibroblast growth factor
FGFR3	Fibroblast growth factor receptor 3
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FISH	Fluorescent <i>in situ</i> hybridization
FPG	Formamido pyrimidine glycosylase
FQPA	Food Quality Protection Act
GAC	Genetic alterations in cancer
$\gamma$ -GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GJIC	Gap junction intercellular communication
GJs	Gap junction connections
GLP	Good laboratory practice
G6PD	Glucose-6-phosphate dehydrogenase
GSSG	Glutathione disulfide
GSH	Glutathione
GST	Glutathione <i>S</i> -transferases
GST-P	Glutathione <i>S</i> -transferase placental form
Gua	Guanine
HaSDR	Health and Safety Data Reporting
HCA	Hydrocyanic acid
HCA	High content analysis
HC	Health Canada
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HEAA	$\beta$ -Hydroxyacetic acid
HGP	Human Genome Project
HIV	Human immunodeficiency virus
HMG-CoA	3-Hydroxy-3-methylglutaryl-CoA
Hmgcr	Hydroxymethylglutaryl-CoA reductase
hPPAR $\alpha$	Human PPAR $\alpha$
HPLC	High-performance liquid chromatography
<i>hprt</i>	Hypoxanthine-guanine phosphoribosyl transferase
HPV	Human papilloma viruses
HPV	High production volume
HPVIS	High Production Volume Information System
HRF	Human relevance framework
HSC	Hemocytoblasts
HTLV	Human T-cell lymphotropic virus
HTS	High-throughput screening
IAEMS	International Association of Environmental Mutagen Societies
IARC	International Agency for Research on Cancer
ICEM	International Conferences on Environmental Mutagens
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICH	International Conference on Harmonisation

IDS	Immunodefense system
IKK	I $\kappa$ B kinase
IL1 $\alpha$	Interleukin-1alpha
IL1 $\beta$	Interleukin-1beta
ILSI	International Life Science Institute
ILSI RSI	International Life Sciences Risk Sciences Institute
IND	Exploratory investigational new drug applications
IPCS	International Programme on Chemical Safety
IR	Ionizing radiation
IRIS	Integrated Risk Information System
IRIS	U.S. EPA Integrated Risk Information System
ITER	International Toxicity Estimates for Risk
ITC	TSCA Interagency Testing Committee
IUR	Inhalation unit risk
IUR	Inventory update reporting
IWGT	International Workshop(s) on Genotoxicity Tests
IWR	Interaction weighting ratio
JaCVAM	Japanese Center for the Validation of Alternative Methods
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JEM	Job exposure matrix
JNK	c-Jun N-terminal kinases
$K_{dis}$	Dissolution rate constants
LBD	Ligand binding domains
LED <sub>01</sub>	Lower limit on effective dose <sub>01</sub>
LED <sub>10</sub>	Lower 95% confidence limit for the dose giving the animals an increased tumor incidence of 10%
LET	Linear-energy-transfer
LFC	Lowest feasible concentration
LMS	Linearized multistage
LMW	Low-molecular-weight protein
ln(GSD)	Logarithm of the geometric standard deviation
LNT	Linear no-threshold
LOAEL	Lowest observed adverse effect level
LSC	Lymphoblast
LSS	Life-stage study
LTA	Local tissue array
MAC	Apoptosis-induced channel
MACT	Maximum achievable control technology
MAP	Mitogen-activated protein
MC	Mast cell
MCL	Maximum contaminant level
MCMC	Markov chain Monte Carlo
MDA	Malondialdehyde
MEHP	Mono-2-ethylhexyl phthalate
MeIQx	2-Amino-3,8-Dimethylimidazo[4,5-f] quinoxaline
MIBK	Methyl isobutyl ketone

miRNA	MicroRNAs
MLA	Mouse lymphoma tk+/- assay
MLE	Maximum likelihood estimate
MMP	Matrix metalloprotease
MMS	Methyl methanesulfonate
MN	Micronuclei
MNU	Methylnitrosourea
MOA	Mode of action
MOE	Margin of exposure
MPV	Medium-production volume
MS	Mass spectrometric
MSCE	Multistage clonal expansion
MTBE	Methyl- <i>tert</i> -butyl ether
MTD	Maximum tolerable dose
MUP	Mouse urinary protein
MVK	Moolgavkar–Venzon–Knudson
NAS	National Academy of Sciences
NAS	U.S. National Academies of Science
NBR	NCI Black–Reiter
NCEA	U.S. EPA National Center for Environmental Assessment
NCEs	Normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCOR	Nuclear receptor corepressor
NDI	National death index
NF-kB	Nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NIOSH	U.S. National Institute for Occupational Safety and Health
NIOSH-IREP	Interactive RadioEpidemiological Program
NNG	Net nuclear grain
NNM	<i>N</i> -Nitrosomorpholine
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NPCs	Nonparenchymal cells
NRC	National Research Council
NRC	U.S. National Research Council
NSRLs	No significant risk levels
NTP	National Toxicology Program
NTP	U.S. National Toxicology Program
$C_{\max}$	Maximum or peak concentration
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment, California EPA
8-OH-dG	8-Hydroxy-2'-deoxyguanosine
2-OH-TMP	2,2,4-Trimethyl 2-pentanol
OMB	U.S. Office of Management and Budget
OPP	U.S. EPA Office of Pesticide Programs



OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORD	U.S. EPA Office of Research and Development
OSHA	U.S. Occupational Safety and Health Administration
OSH Act	U.S. Occupational Safety and Health Act of 1970
OSOR	One substance, one registration
OSTP	U.S. Office of Science and Technology Policy
OSWER	U.S. EPA Office of Solid Waste and Emergency Response
PAHs	Polycyclic aromatic hydrocarbons
PAIR	Preliminary assessment and information reporting
PAPS	3'-Phosphoadenosine 5'-phosphosulfate
PBBs	Polybrominated biphenyls
PBPK	Physiologically based pharmacokinetic
PBTs	Persistent, bioaccumulative, and toxic substances
PCBs	Polychlorinated biphenyls
PCDD	Polychlorinated dibenzo dioxin
PCE	Polychromatic erythrocyte
pCi	Picocuries
PCNA	Proliferating cell nuclear antigen
PD	Cell population growth over time
PDF	Probability density function
PDGF	Platelet-derived growth factor
PEI	Polyethyleneimine
PELs	Permissible exposure limits
PFAA	Perfluoroalkyl acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
PGMBE	Propylene glycol monobutyl ether
Pgp	P-glycoprotein
PHGs	Public health goals
PhIP	2-Amino-1-methyl- 6-phenylimidazo[4,5- <i>b</i> ] pyridine
PIR	Proportionate incidence ratio
PMR	Proportionate mortality ratio
POD	Point of departure
PPAR	Peroxisome proliferator-activated receptor
PPAR- $\alpha$	Peroxisome proliferation activating receptor-alpha
PPL	<sup>32</sup> P-Postlabeling
PPREs	PPAR $\alpha$ responsive elements
pRb	Inactivated retinoblastoma gene product
PRGs	Preliminary remediation goals
PSP	Poorly soluble particles
PTEN	Phosphatase and tension
PTL	Priority testing list
PXR	Pregnane X receptor
q1*	Upper 95% confidence limit on the cancer potency slope
qPCR	Quantitative polymerase chain reaction
(Q)SAR	Quantitative structure-activity relationships