CALCULATED RISKS

The Toxicity and Human Health Risks of Chemicals in Our Environment

Second Edition, with major revisions and additions

Safeguarding economic prosperity, whilst protecting human health and the environment, is at the forefront of scientific and public interest. This book provides a practical and balanced view on toxicology, control, risk assessment, and risk management, addressing the interplay between science and public health policy. This fully revised and updated new edition provides a detailed analysis on chemical and by-product exposure, how they enter the body and the suitability of imposed safety limits. New chapters on dose, with particular emphasis on children and vulnerable subpopulations, reproductive and developmental toxicants, and toxicity testing are included. With updated and comprehensive coverage of international developments in risk management and safety, this will have broad appeal to researchers and professionals involved in chemical safety and regulation, as well as to the general reader interested in environmental pollution and public health.

Joseph V. Rodricks was a founding principal of ENVIRON International Corporation, a consultancy firm on environmental and health issues. Since 1980 he has consulted for many corporations and institutions, including the World Health Organization, and in 2005 he received the Outstanding Practitioner Award from the Society for Risk Analysis. The first edition of *Calculated Risks* won an "Honourable Mentions" award from the American Medical Writers Association.

Praise for first edition

"Calculated Risks demystifies the science and policies of risk assessment. It has become a staple in risk education, and is essential reading for students and professionals in public health, environmental protection, and public policy." Thomas A. Burke, Professor and Associate Chair, Bloomberg School of Public Health, Johns Hopkins University

". . . Rodricks has made the difficult topic of risk assessment accessible to the regulatory, policy and scientific communities. Calculated Risks focuses on the science of assessing health risks and provides a framework for understanding this complex topic. It should be required reading for those concerned about environmental pollution and protection of health and environment." Carol J. Henry, Vice President Science and Research, American Chemistry Council

". . . presents a practical and balanced clarification of the scientific basis for our concerns and uncertainties. It should serve to refocus the debate." *Biology Digest*

". . . provides access to the science and uncertainty behind the oft-quoted risks of toxic chemicals . . . The reader who completes the book is likely to know much more about the limitations of all assessments of risk." *BioScience*

"Rather than attempting to expose governmental and corporate ignorance, negligence or corruption, this book explores the underlying scientific issues. It presents a clarification of the scientific basis for our concerns and uncertainties." *The Bulletin of Science, Technology and Society*

". . . a well-organized and readable text . . . The book should be recommended reading for those interested in obtaining an understanding of risk assessment." *Canadian Field Naturalist*

"It is difficult to praise this book enough. An evenhanded text that emphasizes complexity and reveals the gaps in our knowledge rather than oversimplifying the science of toxicology, *Calculated Risks*: *The Toxicity and Human Health Hazards of Chemicals in Our Environment* belongs on the shelves of every environmental organization. Writing in a manner that neither condescends nor baffles his readers, Joseph V. Rodricks has produced a text that if used as a point of departure in discussing siting, pollution, and similar disputes could save time and effort . . . This book is the basic text we all should read." *Environment*

". . . the best book we have yet seen on the theory of risk assessment – lucidly written, and evenhanded . . . If you want to understand the theory of risk assessment from the viewpoint of a successful risk assessor, this is the book for you." *Rachel's Hazardous Waste News*

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Preface to the first edition

Think how many carcinogens are household names: asbestos, cigarette smoke (a mixture of several thousand chemical compounds), DES, dioxin, saccharin, arsenic, PCBs, radon, EDB, Alar. Hundreds more of these substances, some very obscure, are known to the scientific and medical community, and many of these are scattered throughout the land at thousands of hazardous waste sites similar to Love Canal. People are exposed to these dreadful substances through the air they breathe, the water they drink and bathe in, and the foods they eat. Chemicals can also produce many other types of health damage, some very serious, such as birth defects and damage to our nervous and immune systems.

The chemical accident at Bhopal, India, in late 1984, is only the worst example of events that take place almost daily, on a smaller scale, throughout the world. Human beings are not the only potential victims of chemical toxicity – all of life on earth can be affected. Chemicals are ravaging human health and the environment, and conditions are worsening.

But wait. Let's remember that chemicals have virtually transformed the modern world in extraordinarily beneficial ways. During the past 100 years the chemical industry has offered up, and we have eagerly consumed, thousands of highly useful materials and products. Among these products are many that have had profoundly beneficial effects on human health – antibiotics and other remarkable medicinal agents to prevent and cure diseases, pesticides to protect crops, preservatives to protect the food supply, plastics, fibers, metals and hundreds of other materials that have enhanced the safety and pleasures of modern

life. Perhaps the misuse of certain chemicals has caused some small degree of harm, but on balance the huge benefits of modern chemical society clearly outweigh the exceedingly small risks these products may carry. Moreover, we have made and are continuing to make progress in controlling the risks of chemical technology.

Somewhere between these two views sits a somewhat befuddled scientific and medical community, attempting to sort the true from the false, and not quite sure how it should respond to the public while this sorting takes place. What science can now say with reasonably high certainty about the risks of chemical technology falls far short of the knowledge about those risks that our citizens are seeking. And, although substantial progress in scientific understanding has been made during the past three to four decades, it will probably be another several decades before the questions about chemical risks facing us today can be answered with the degree of certainty normally sought by scientists.

It is not at all surprising that confusion and controversy should arise when knowledge is absent or weak. When, as in the case of the risks of the products and byproducts of chemical technology, scientists know just enough to raise fearful suspicions, but do not always know enough to separate the true fears from the false, other social forces take command. Among the most important of these forces are the environmental laws that sometimes require regulatory authorities to act even before scientific understanding is firm. When the consequences of these actions cause economic harm, combat begins. Depending on which side of the battle one sits, fears about chemical risks are emphasized or downplayed. The form of the battle that will occur following what have become routine announcements about carcinogens in pancakes or apples, or nervous system poisons in drinking water or soft drinks, is now highly predictable. Except for a few brave (or foolish?) souls, the scientific community tends to remain relatively impassive in such circumstances, at most calling for "more research." Those scientists who are sufficiently intrepid to offer opinions tend to be scorned either as environmentalist quacks or industry hacks, who have departed from the traditional, scientifically acceptable standards of proof. Perhaps they have, but as we shall see, there is certainly an argument to be made on their behalf.

The question of whether and to what degree chemicals present in air, food, drinking water, medicinal agents, consumer products, and in the work place pose a threat to human health is obviously of enormous social and medical importance. This book is an attempt to answer

this question with as much certainty as science can currently offer. It is in part a book of popular science – that is, it attempts to provide for the layman a view of the sciences of toxicology and chemical carcinogenesis (considered by some a branch of toxicology). It describes how the toxic properties of chemicals are identified, and how scientists make judgments about chemical risks. What is known with reasonable certainty is separated from the speculative; the large gray areas of science falling between these extremes are also sketched out. Toxicology, the science of poisons, is such a rich and fascinating subject, that it deserves more widespread recognition on purely intellectual grounds. Because it is now such an important tool in public health and regulatory decision-making, it is essential that its elements be widely understood.

The focus of this book is on the methods and principles of toxicology and risk assessment, and not on particular toxic agents or on the scientists who have built the discipline. To emphasize specific agents and scientists would have resulted in too great a departure from the book's second aim – to cast a little light upon the difficult interaction between science and the development of public health and regulatory policies. What is of interest here is not the administrative detail of policy implementation, which can be a rather unlively topic, but the principles that have come to govern the interaction of a highly uncertain scientific enterprise with the social demand for definitive actions regarding matters of public health.

The purpose of this book is, then, to describe and to clarify the scientific reasons for our present concerns about chemicals in the environment; the strengths and weaknesses of our scientific understanding; and the interplay between science and public policy. Unlike most other works related to these subjects, it is not an attempt to expose governmental and corporate ignorance, negligence or corruption. There is no end to literature on this subject, much of it presenting an incomplete or biased view of current scientific understanding of the effects of chemicals on human health and the environment. Perhaps a little clarification of the scientific bases for our concerns and the uncertainties that accompany them, and of the dilemmas facing decision-makers, will serve to refocus and advance the debate.

A word about organization of topics is in order. First, it is important to understand what we mean when we talk about "chemicals." Many people think the term refers only to generally noxious materials that are manufactured in industrial swamps, frequently for no good purpose. The existence of such an image impedes understanding of

toxicology and needs to be corrected. Moreover, because the molecular architecture of chemicals is a determinant of their behavior in biological systems, it is important to create a little understanding of the principles of chemical structure and behavior. For these reasons, we begin with a brief review of some fundamentals of chemistry.

The two ultimate sources of chemicals – nature and industrial and laboratory synthesis – are then briefly described. This review sets the stage for a discussion of how human beings become exposed to chemicals. The conditions of human exposure are a critical determinant of whether and how a chemical will produce injury or disease, so the discussion of chemical sources and exposures naturally leads to the major subject of the book – the science of toxicology.

The major subjects of the last third of this volume are risk assessment – the process of determining the likelihood that chemical exposures have or will produce toxicity – and risk control, or management, and the associated topic of public perceptions of risk in relation to the judgments of experts. It is particularly in these areas that the scientific uncertainties become most visible and the public debate begins to heat up. The final chapter contains some suggestions for improving the current state-of-affairs and also sets out some new challenges. Risks to human health are the subject of this book; risks to the rest of the living and non-living environment are not covered. The absence of this topic from the present volume has only to do with the author's interests and knowledge and says nothing about its relative importance.

Much of the discussion of risk assessment turns on the activities of regulatory agencies responsible for enforcing the two dozen or so federal laws calling for restrictions of one sort or another on human exposures to environmental chemicals. The Environmental Protection Agency (EPA) has responsibilities for air and water pollutants, pesticides, hazardous wastes, and industrial chemicals not covered by other statutes. The Food and Drug Administration (FDA), part of the Department of Health and Human Services, manages risks from foods and substances added thereto, drugs for both human and veterinary uses (some of the latter can reach people through animal products such as meat, milk and eggs), cosmetics, and constituents of medical devices. The Occupational Safety and Health Administration (OSHA), a unit of the Labor Department, handles chemical exposures in the workplace. Consumer products not covered by other agencies fall to the Consumer Product Safety Commission (CPSC). Other agencies with similar, though somewhat narrower responsibilities, include the

Food Safety and Inspection Service of the Department of Agriculture (for meat, poultry, and eggs) and the Department of Transportation. Although laws and regulatory programs vary, most countries have agencies with similar sets of responsibilities.

The use of the phrase "regulatory risk assessments" throughout this book may seem odd, because risk assessment is a scientific activity and its conduct, it would seem, should be independent of where it is undertaken. But we shall see that a scientific consensus on the proper conduct of risk assessment does not exist, and regulatory agencies have had to adopt, as a matter of policy, certain assumptions that do not have universal acceptance in the scientific community. The agencies do this to allow them to operate in accordance with their legal mandates, and one of the purposes of this book is to create understanding of (but not necessarily to urge agreement with) these regulatory policies.

Before embarking on what is perhaps an overly systematic approach to our subject, we should attempt to develop a bird's-eye view of the entire landscape. We shall use a specific example – the case of a group of chemicals called aflatoxins – to illustrate the type of problem this book is designed to explore.

Preface to the second edition

The central topics of this book have, since its publication in 1992, become permanent occupants of the public health agendas of governments everywhere. The imposition of controls on the production, uses, and environmental releases of chemical products, by-products, and environmental pollutants, whatever their sources, has become the ambition of most societies, and many now claim to rely upon risk assessments to guide their decisions about the necessity for, and extent of, such controls. Indeed, the risk assessment framework sketched out in the first edition, and given far more extensive treatment in this one, has come to be seen as a most powerful tool for evaluating and putting into useful form the complex, diverse, often inconsistent, and always incomplete scientific information and knowledge we have been able to accumulate about the health hazards and risks all chemicals pose if exposures become excessive. So in this edition the reader will be provided with a broader and deeper look at risk assessment as it continues to evolve as a scientific enterprise, and in its role as the bridge between basic and applied research and the many forms of decision-making aimed at risk reduction. Chapters dealing with the early evolution of the risk assessment framework and the several principles and concepts that gave rise to its structure, the ways in which relevant scientific data and knowledge are put to use within that framework, and some of the new challenges risk assessment faces, are almost wholly new in this edition. This much expanded look at the many dimensions and evolving uses of the risk assessment framework was driven in part by the comments I received from students and many other readers that the first edition had been too limited

on these topics. So I hope I have now delivered something more satisfying.

The new edition is otherwise arranged much like the first, beginning as it does with a discussion of the world of chemicals and moving systematically to the subjects of human exposures to these substances and the various ways in which they can cause harm if those exposures somehow become excessive. Just how we come to know how much is excessive for an individual substance is given much discussion. The sciences of toxicology and epidemiology, their methods and applications, are extensively treated, in updated and almost wholly rewritten chapters. All the major types of toxic harm, including cancer, are reviewed. New issues – everything from chemicals commonly released during industrial accidents, some used for terrorist purposes, and some of the recently uncovered sources of chronic toxicity can be found throughout the new edition. New thinking on mechanisms of toxic action and the use of mechanistic information in risk assessment comes up time and again. Persistent chemicals, chemicals found in the human body, endocrine-disrupting substances, and products of the hottest new technology – that carried out at the nano scale – are here. Expanding uses of the risk assessment framework include the problems of nutrient deficiency and excess. Microbial pathogens that cause food poisoning are given some space in the risk assessment chapter dealing with new challenges.

I have attempted to hold to a writing style that is accessible to the non-professional and that is at the same time at least moderately interesting to professionals. The problem of keeping professionals interested is eased a little by the fact that so many different areas of the health sciences, both basic and applied, medicine, and the environmental sciences are drawn into the subjects I cover; and I hope a reading of this book provides a satisfyingly broad perspective.

At the beginning of this preface I described an expanding web of risk assessment practitioners and users; this description, while accurate, may create a false impression. It is true that the subjects of this book and the ways in which they are brought together within the risk assessment framework are increasingly discussed and advocated, by governments and by many non-governmental organizations and corporations. Almost everywhere risk assessment is promoted as the guide to a safer environment. The subject is increasingly taught in formal and informal settings all over the world. This is admirable.

What is not so admirable is that in so many of these institutions there is a lack of commitment to turning discussion and advocacy

into action. Lack of resources to develop and implement risk-based health protection programs explains much but not all of the inaction. In fact, once it is recognized that the practice of risk assessment does not generate new information and knowledge – that can only come from research – but that it serves rather to organize and tell us what we know and do not know about threats to our health, then it becomes clear that support for risk assessment-based decision-making requires that we support the scientific research, epidemiology investigations, and toxicity testing upon which it depends. Supporting risk assessment without at the same time providing the much more substantial resources needed to support research and testing becomes something of an empty gesture.

Even when resources are available to produce reliable assessments, inaction may result when the results of these assessments put risk managers into politically awkward positions. And, of course, many risk assessments are produced by well-meaning but inexperienced, inadequately trained individuals, and one would hope risk managers would have mechanisms in place to eliminate incompetent work.

Even admitting these various impediments to the broader use of risk-based decisions to protect the public health, much progress has been made, and there is no reason to believe this trend will not continue. I hope this new edition contributes in some way to this trend.

I am grateful beyond words to the technical guidance provided by my long-term associate, Duncan Turnbull, and to all manner of assistance provided by Gail Livingston. My dear wife Karen Hulebak, herself a public health scientist, kept me from veering off-track at many points; any such veering that remains in the book is due to my own lack of control. The Second Edition is dedicated to my daughter, Elizabeth.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry (DHHS)
CDC	Centers for Disease Control (DHHS)
CPSC	Consumer Product Safety Commission
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization (UN)
FDA	Food and Drug Administration (DHHS)
FSIS	Food Safety and Inspection Service (USDA)
IARC	International Agency for Research on Cancer (WHO)
NCI	National Cancer Institute (DHHS)
NIEHS	National Institutes of Environmental Health Sciences
NIH	National Institutes of Health (DHHS)
NIOSH	National Institute of Occupational Safety and Health (DHHS)
NTP	National Toxicology Program (DHHS)
OSHA	Occupational Safety and Health Administration (DOL)
WHO	World Health Organization (UN)
DHHS	Department of Health and Human Services
DOL	Department of Labor
UN	United Nations
USDA	United States Department of Agriculture
ADI	allowable daily intake
ADME	absorption, distribution, metabolism, elimination

AEGL	acute exposure guideline
BMD	benchmark dose
CI	confidence interval
LOAEL	lowest observed adverse effect level
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MRL	minimum risk level
NOAEL	no observed adverse effect level
OR	odds-ratio
PD	pharmacodynamics
PEL	permissible exposure level
PK	pharmacokinetics
POD	point-of-departure
RfC	toxicity reference concentration
RfD	toxicity reference dose
RR	relative risk
TDI	tolerable daily intake
TLV	threshold limit value[1]
UF	uncertainty factor
UL	upper level

[1] Registered Trademark of the American Conference of Governmental Industrial Hygienists (ACGIH).