VOLUME ONE

ENCYCLOPEDIA OF TOXICOLOGY

SECOND EDITION

EDITOR-IN-CHIEF

PHILIP WEXLER

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Description
The second edition of the **Encyclopedia of Toxicology** continues its comprehensive survey of toxicology. This new edition continues to present entries devoted to key concepts and specific chemicals. There has been an increase in entries devoted to international organizations and well-known toxic-related incidents such as Love Canal and Chernobyl. Along with the traditional

scientifically based entries, new articles focus on the societal implications of toxicological knowledge including environmental crimes, chemical and biological warfare in ancient times, and a history of the U.S. environmental movement. With more than 1150 entries, this second edition has been expanded in length, breadth and depth, and provides an extensive overview of the many facets of toxicology. Also available online via ScienceDirect – featuring extensive browsing, searching, and internal cross-referencing between articles in the work, plus dynamic linking to journal articles and abstract databases, making navigation flexible and easy. For more information, pricing options and availability visit www.info.sciencedirect.com.

Audience
Toxicologists, pharmacologists, drug companies, toxicology testing labs, libraries, poison control centers, physicians, legal and regulatory professionals (EPA, government), and chemists.

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Liothyronine Lipid Peroxidation Lithium (Li) Liver Loperamide Lotronex Loxapine LSD (Lysergic Acid Diethylamide) Lye Lyme Disease Magnesium Malathion Mancozeb Maneb Manganese Margin of Exposure (MOE) Marijuana Marine Organisms Maximum Allowable Concentration (MAC) Maximum Tolerated Dose (MTD) MDMA (Ecstasy) MeCCNU Mechanisms of Toxicity Medical Surveillance Melphalan Meperidine Meprobamate Mercaptans "Mercaptoethanol, 2-" Mercapturic Acid Mercuric Chloride Mercury (Hg) Mescaline Metabonomics Metaldehyde Metallothionein Metals Methadone Methamidophos Methane Methanol Methaqualone Methomyl Methoprene Methoxychlor Methoxyethanol Methoxypsoralen Methyl Acrylate Methyl Bromide Methyl Disulfide Methyl Ether Methyl Ethyl Ketone Methyl Isobutyl Ketone Methyl Parathion Methylamine "Methylcholanthrene, 3-" Methyldichloroarsine Methyldopa Methylene Chloride Methylenedioxymethamphetamine Methylmercury Methylnitrosourea Methyprylon Metronidazole Mevinphos Microarray Analysis Micronucleus Assay Microtox Microtox Minoxidil Mirex Mistletoe Mithramycin Mitomycin C "Mixtures, Toxicology and Risk Assessment" Mode of Action Modifying Factors of Toxicity Mold Molecular Toxicology-Recombinant DNA Technology Molinate Molybdenum Monoamine Oxidase Inhibitors Monosodium Glutamate Monte Carlo Analysis Morning Glory Morphine Mouse Lymphoma Assay Mouthwash Multiple Chemical Sensitivities "Mushrooms, Coprine" "Mushrooms, Cyclopeptide" "Mushrooms, Ibotenic Acid" "Mushrooms, Monomethylhydrazine" "Mushrooms, Muscarine" "Mushrooms, Psilocybin" Mustard Gas Mustard/Lewisite (HL) Genetic Toxicology Mycotoxins N-Nitrosodimethylamine Naled Naphthalene "Naphthylamine, 2-" Naphthylisothiocyanate

National Center for Toxicological Research National Environmental Policy Act National Institute for Occupational Safety and Health National Institute of Environmental Health Sciences National Institutes of Health National Library of Medicine/TEHIP National Toxicology Program Nematocides Neon Neonicotinoids Neurotoxicology Niacin Nickel (Ni) and Nickel Compounds Nickel Chloride Nicotine Nithiazine Nitric Oxide Nitrite Inhalants Nitrites Nitrobenzene Nitrocellulose Nitroethane Nitrogen Mustards Nitrogen Oxides Nitrogen Tetraoxide Nitromethane Nitrosamines Nitrous Oxide Noise: Ototraumatic Effects "Non-Lethal Weapons, Chemical" Nonylphenol Norbormide Nutmeg Occupational Safety and Health Act Occupational Safety and Health Administration Occupational Toxicology Octane Octochlorostyrene "Oil, Crude" "Oil, Lubricating" Oleander Opium Organisation for Economic Cooperation and Development Organochlorine Insecticides "Organophosphate Poisoning, Delayed Neurotoxicity" "Organophosphate Poisoning, Intermediate Syndrome" Organophosphates Organotins Otto Fuel II Oxidative Stress Oxygen Ozone Panomics Paraquat Parathion Paregoric Dosimetry: Adjustments to Applied Dose for Interspecies Extrapola "PBT (Persistent, Bioaccumulative, and Toxic) Chemicals" Pendimethalin Penicillin Pentachlorobenzene Pentachloronitrobenzene Pentachlorophenol Pentane Pentazocine Perchlorate Perchloric Acid Periodic Acid Permethrin Wood Dust Peroxisome Proliferators Pesticides Petroleum Distillates Petroleum Ether Petroleum Hydrocarbons Peyote Pharmacokinetic Models Pharmacokinetics/Toxicokinetics Phenacetin Phenanthrene Phenazopyridine Phencyclidine Phenodichloroarsine Phenol Phenothiazines Phenylmercuric Acetate Phenylpropanolamine Phenytoin Phorbol Esters Phosgene Phosgene Oxime Phosphine

Phosphoric Acid Phosphorus Photoallergens Photochemical Oxidants Phthalate Ester Plasticizers Physical Hazards Picloram Picric Acid Piperazine Piperonyl Butoxide "Plants, Poisonous" Platinum (Pt) Plutonium (Pu) Poinsettia Poisoning Emergencies in Humans Pokeweed Pollutant Release and Transfer Registries (PRTRs) Pollution Prevention Act "Pollution, Air" "Pollution, Air Indoor" "Pollution, Soil" "Pollution, Water" Polybrominated Biphenyls (PBBs) Polybrominated Diphenyl Ethers (PBDEs) Polychlorinated Biphenyls (PCBs) Polycyclic Aromatic Amines Polycyclic Aromatic Hydrocarbons (PAHs) Polyethylene Glycol Polymers Potassium (K) Potassium Iodide Primidone Procainamide Prometryn Propachlor Propane Propanil Propargite Propazine Propene Propionic Acid Proposition 65 Propoxur Propoxyphene Propylene Glycol Propylene Oxide Prostaglandins Proteomics Prunus Species Pseudoephedrine Psychological Indices of Toxicity Public Health Service Puromycin PUVA Pyrene Pyrethrins/Pyrethroids Pyridine Pyridostigmine Pyridoxine Pyriminil Pyrrolizidine Alkaloids QT Interval Quinidine Quinine Quinoline Quinone "Radiation Toxicology, Ionizing and Non-Ionizing" Radium Radon Ranitidine Red Dye No. 2 Red Phosphorous Red Squill Red Tide Reference Concentration (RfC) Reference Dose (RfD) "Reproductive System, Female" "Reproductive System, Male" Research Institute for Fragrance Materials (RIFM) Reserpine Resistance to Toxicants Resource Conservation and Recovery Act Respiratory Tract Rhodium Rhododendron Genus Rhubarb Riboflavin Rifampin "Risk Assessment, Ecological" "Risk Assessment, Human Health" Risk Characterization Risk Communication Risk Management Risk Perception Rotenone Saccharin Safe Drinking Water Act Safety Pharmacology Saint John's Wort Salicylates Salmonella Sarin Saxitoxin Scombroid

Scorpions Selenium (Se) Sensitivity Analysis Sensory Organs Sertraline Hydrochloride Sesqui Mustard Shampoo "Shellfish Poisoning, Paralytic" Shigella Sick Building Syndrome "Silica, Crystalline" Silver (Ag) Sister Chromatid Exchanges Skeletal System Skin "Snake, Crotalidae" "Snake, Elapidae" Snakes Society for Environmental Toxicology and Chemistry Society for Risk Analysis (SRA) Society of Toxicology Sodium (Na) Sodium Fluoroacetate Sodium Sulfite Solanum Genus Soman Soots Speed "Spider, Black Widow" "Spider, Brown Recluse" Spiders SSRIs (Selective Serotonin Uptake Inhibitors) Staphylococcus aureus State Regulation of Consumer Products Statistics Stoddard Solvent Strontium Structure-Activity Relationships Strychnine Styrene Sudan Grass Sulfites Sulfur Dioxide Sulfur Trioxide-Chlorosulfonic Acid Sulfuric Acid "Surfactants, Anionic and Nonionic" "Surfactants, Perfluorinated" Synergism "2,4,5,-T" Tabun Talc Tamoxifen Tannic Acid TCDD (Teflon and perfluroisobutylene) Tear Gases Tellurium Terbutaline Terfenadine Terrestrial Ecotoxicology Tetrabromobisphenol A Tetrachloroethane Tetrachloroethylene Trichlorophenoxyacetic Acid Tetrachlorvinphos Tetrahydrofuran Tetranitromethane Tetrodotoxin Thalidomide Thallium (Tl) Theophylline Thiamine Thiazide Diuretics Thioacetamide Thiomerosal Thiotepa Thioxanthenes Thiram Thorium Dioxide and Thorium Thyroid Extract Tin (Sn) Tissue Repair Titanium Titanium Tetrachloride Tobacco Tobacco Smoke Toluene Toluene Diisocyanate Toluidine Ricin and other Toxalbumins Toxaphene Toxic Substances Control Act Toxic Torts "Toxicity Testing, Alternatives" "Toxicity Testing, Aquatic" "Toxicity Testing, Behavioral" "Toxicity Testing, Carcinogenesis" "Toxicity Testing, Dermal" "Toxicity Testing, Developmental" "Toxicity Testing, Inhalation" "Toxicity Testing, Irritation" "Toxicity Testing, Modeling"

"Toxicity Testing, Mutagenicity" "Toxicity Testing, Reproductive" "Toxicity Testing, Sensitization" "Toxicity, Acute" "Toxicity, Chronic" "Toxicity, Subchronic" Toxicology "Toxicology, Education and Careers" "Toxicology, History of" Trade Associations Transgenic Animals Triadimefon Trichlorfon Trichloroethane Trichloroethylene Tricyclic Antidepressants Trifluralin Trihalomethanes Trinitrotoluenes Tungsten Turpentine Uncertainty Analysis Uncertainty Factors UNEP Chemicals Uranium (U) Urea Urethane United States Pharmacopoeia (USP) V-Gas Valproic Acid Vanadium Vanillin VE Veterinary Toxicology VG Vinyl Acetate Vinyl Bromide Vinyl Chloride Vinylidene Chloride Virtually Safe Dose (VSD) Vitamin A Vitamin D Vitamin E VM Volatile Organic Compounds (VOC) VX Warfarin Wisteria Workplace Environmental Exposure Levels (WEELs) Xenobiotics Xylene Xyrem Yew Yohimbine Zinc (Zn) Zinc Oxide "Safety Testing, Clinical Studies" "Toxicity Testing, Validation" Genetically Engineered Products Global Environmental Change Pharmaceuticals in the Environment Aneuploidy Tacrine Selamectin Minamata Great Smog of London Itai-Itai N-methylpyrrolidone Peptide Coupling Agents DNA Phosphoramidites Occupational Exposure Limits Arts and Crafts Materials and Processes National Center for Environmental Health (NCEH) Curare Department of Defense Diazoaminobenzene Department of Energy (DOE) Drinking Water Criteria Environmental Crimes Grain Incidents Iatrogenic Disease Immediately Dangerous to Life and Health (IDLH) values "Hazardous Chemicals, Import/Export of" Islip Garbage Barge Mad Cow Disease Oxalates Perfluorooctanoic Acid (PFOA) Persisent Organic Pollutants (POPs) Risk Based Corrective Action (RBCA) Recommended Exposure Limits (REL) Sulfates Texas City Disaster United States Department of Agriculture (USDA) Silent

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Editor-in-Chief

Philip Wexler, *National Library of Medicine, Bethesda, MD, USA*

Associate Editors

Dedication

For my son Jake and my parents Yetty and Will, with love, appreciation, and respect.

FOREWORD

It gives me great pleasure to once again have the opportunity to introduce the *Encyclopedia of Toxicology* to its users. The second edition is a worthy successor to the first, expanded and refined, which will serve the toxicology community well. Particularly in these days when specialization tends to narrow the individual focus, it brings a real understanding of the entire scope and function of the science of toxicology.

The changes evident at the publication of the first edition have continued at an accelerated pace. At that time it was clear that toxicology, over a period of four or five decades, had changed from a largely descriptive science based on *in vivo* toxicity to one that included all aspects of modern biology and chemistry, from molecular biology to sophisticated instrumental analysis. The philosophical basis had shifted from routine risk analysis based primarily on pathological or *in vivo* toxicological endpoints to one that emphasized mechanisms of toxic action at the organ, cellular, and molecular levels. All of this brought about an explosion in the toxicological literature.

Since then, the techniques of molecular biology have played an increasing role in the elucidation of toxic mechanisms, in the study of xenobiotic metabolism, in the development of safer and more useful drugs and other chemicals, and in the development of biomarkers of exposure and effect, to mention only a few of the more important aspects impacted by these techniques. Analytical chemistry has continued to develop to the point that vanishing small quantities of xenobiotics can be detected, quantities so small that their toxicological impact is likely to remain unknown for the immediate future. While the application of all of this new science to risk assessment remains problematical, since the latter is still largely based on mathematical models rather than toxicological science, progress in both human health risk assessment and environmental risk assessment is also evident.

What has not changed, however, is the need for the toxicological literature to serve many masters. Given the eclectic nature both of the methodological roots and the practical needs served by toxicology, general works are needed more than ever. Works such as the *Encyclopedia of Toxicology* play a critical role at an important intermediate level, more detailed than dictionaries while remaining accessible to the generalist in risk assessment, regulation, teaching, and consultation as well as specialists seeking information beyond the narrow confines of their specialty. It will also serve as an important role for nontoxicologists who need to know more of the philosophy, methods, and uses of this science.

In summary, this is an important and outstanding contribution that no serious toxicologist or library serving toxicologists can afford to be without.

Ernest Hodgson
William Neal Reynolds Professor
Environmental and Molecular Toxicology
North Carolina State University

PREFACE

Time passes, but the need for toxicological understanding persists. As much as we might wish for the end of poverty, ignorance, hunger, and exposure to hazardous chemicals, and as much as we work toward these goals, the challenges are formidable, and the end is not in sight. Chemicals and finished products made from chemicals continue to play an ever-present part in our lives. Although it is not evident that the benefits of chemicals always outweigh their risks, there is little doubt that a wide spectrum of chemicals and drugs has enhanced both the duration and quality of our lives. That said, certain of them, in certain situations, are clearly harmful to certain people. Among the fruits of toxicologists' labors is information on how best to eliminate, reduce, or prevent such harm.

The discipline of toxicology has made considerable strides in the 7 years since the first edition of this encyclopedia was published. The understanding of molecular toxicology continues to advance rapidly. Indeed, it is often much easier to generate the data than to find the time to adequately evaluate it. Genomic, proteomic, and other 'omic' technologies are helping us unravel the complex connection between exposure to environmental chemicals and susceptibility to disease. The US National Center for Toxicogenomics, dedicated to research on informatics and computational toxicology, was established in 2000. As a result of this and other research, much more sophisticated approaches are now available for ascertaining chemical safety, and investigating structure–activity relationships. In addition, analytical instrumentation has become more highly refined and sensitive, making it easier to detect and quantitate even smaller amounts of contaminants in biological systems and the environment.

With greater consumer (especially Western) acceptance of complementary and alternative medicine, more people than ever before are being exposed to a vast array of herbal and other plant-based medicinal products. Although toxicologists have always recognized that 'natural' does not necessarily equate with 'safe', not much has been done to assess the hazards of herbal supplements and their interactions with other chemicals. This is beginning to change.

Chemical, biological, and nuclear warfare have always been subjects of interest, sometimes as practical matters, and more often as academic ones. In the light of the events of September 11, 2001, there has been an increased urgency in learning more about nonconventional warfare and its agents, how they operate, and how to protect ourselves from their effects. Toxicology has found itself broadening its scope to deal with this resurgent type of weaponry.

The scope of what constitutes hazards waste, an ever-present downside of the benefits we derive from the manufacture, processing, and use of chemicals and their products, continues to expand as technology moves forward. In the US two million tons of electronic products, including 50 million computers and 130 million cellphones, are disposed of every year. According to the International Association of Electronic Recylers, this number will more than triple by 2010. With such quantities in landfills and rivers, there are bound to be consequences for our air and water. Potential toxicants include lead, cadmium, and beryllium.

Alternatives to animal studies no longer represent a toxicological sideline. While whole animal testing is unlikely to disappear soon, if ever, other methods of determining hazard and safety are increasingly being embraced by the toxicology community and becoming part of mainstream chemical evaluations. *In vitro* approaches (e.g., using cell culture or skin irritation potential) and *in silico* approaches (i.e., using computer programs to estimate toxic properties based on existing data for similar chemicals with or without supplemental chemical and physical property data) are both generating increasing amounts of toxicity information.

The marketplace is seeing an increase in products utilizing nanotechnologies, and nanotechnology research and development is on the upswing. The United States has had an official National Nanotechnology Initiative since 2001. A start has also been made by federal agencies and universities in assessing the environmental and health effects of nanomaterials.

Greater insight into chemical exposures, both actual and anticipated, is helping to develop a more focused picture of the risks these exposures present to humans and the environment. Growing cooperation between toxicologists and exposure assessors is proving vital to strengthening the scientific basis of risk assessment, thus giving risk assessors and managers more credible tools to address the control of chemical hazards.

At the global level, there have been important strides in the control and management of chemicals. The 10-year followup to the Rio Earth Summit, the World Summit on Sustainable Development, was held in 2002 in Johannesburg, South Africa. Among the targets it set was to use and produce chemicals by 2020 in ways that do not lead to significant adverse effects on human health and the environment.

The Stockholm Convention to protect human health and the environment from persistent organic pollutants (POPs) became binding on May 17, 2004. POPs tend to be toxic, persistent, accumulative, and capable of traveling long distances in the environment. This Convention seeks to eliminate or restrict the production and use of such chemicals. The Kyoto Protocol, designed to decrease greenhouse gas emissions, has now become an international law, despite the resistance of several countries.

The United States hosts a vibrant and growing community of toxicology professionals who perform innovative toxicological research, and scientists in other countries are making their presence felt equally. Global information sharing and collaborations among these investigators are growing, facilitated by the increased accessibility of the Internet and its enhanced technologies. Significant work is proceeding under the auspices of multinational bodies such as Organisation for Economic Co-operation and Development, the European Commission, and the International Program on Chemical Safety.

Efforts to harmonize and link data and information on toxic chemicals throughout the world have been multiplying. The Globally Harmonized System (GHS) of classification and labeling of chemicals has been adopted and is ready for implementation. This will provide a consistent and coherent approach to identifying hazardous chemicals, as well as provide information on such hazards and protective measures to exposed populations. Meanwhile in the European Union, a regulatory framework known as REACH (Registration, Evaluation and Authorization of Chemicals) has been proposed for the registration of chemical substances manufactured or imported in quantities greater than one ton per year.

Last, but not least, the role that poisons played in personal and political intrigues and vendettas, although it may have peaked with Borgias, by no means ended there. A case in point was the 2004 presidential elections in Ukraine. After a bitterly contested battle for the presidency of Ukraine, Viktor Yushchenko emerged victorious and was inaugurated in January 2005, a happy day for democracy, but with a toxic twist. Yushchenko, according to physicians, suffered severe facial disfigurement (chloracne) and other ailments by being poisoned with large dose of dioxins, allegedly mixed in some soup he consumed. Fortunately he is recovering gradually. Although the full story has not yet emerged, political motivations are suspected.

This second edition has grown from 749 entries submitted by 200 authors to 1057 entries contributed by 392 authors. Virtually all the entries from the first edition have been updated and in some cases entirely new versions of these entries have been written. Among the 308 topics appearing for the first time in this edition are avian ecotoxicology, benchmark dose, biocides, computational toxicology, cancer potency factors, metabonomics, chemical accidents, Monte Carlo analysis, nonlethal chemical weapons, invertebrate ecotoxicology, drugs of abuse, cancer chemotherapeutic agents, and consumer products. Many entries devoted to specific chemicals are also brand new to this edition and the international scope of organizations included has been broadened. Entries describing a number of well-known toxin-related incidents, e.g., Love Canal, Times Beach, Chernobyl, and Three-Mile Island, have been added. In addition to the scientific-based entries, others focus on the societal implications of toxicological knowledge. Among them are Toxicology in Culture, Environmental Crimes, Notorious Poisoners and Poisoning Cases Chemical and Biological Warfare in Ancient Times, and a History of the US Environmental Movement. Thus, this new edition has been expanded in length, breadth, and depth and provides an extensive overview of the many facets of toxicology.

Philip Wexler

PREFACE TO THE FIRST EDITION

There are many fine general and specialized monographs on toxicology, most of which are addressed to toxicologists and students in the field and a few to laypeople. This encyclopedia of toxicology does not presume to replace any of them but rather is intended to fulfill the toxicology information needs of new audiences by taking a different organizational approach and assuming a middle ground in the level of presentation by borrowing elements of both primer and treatise.

The encyclopedia is broad-ranging in scope, although it does not aspire to be exhaustive. The idea was to look at basic, critical, and controversial elements in toxicology, which are those elements that are essential to an understanding of the subject's scientific underpinnings and societal ramifications. As such, the encyclopedia had to cover not only key concepts, such as dose response, mechanism of action, testing procedures, endpoint responses, and target sites, but also individual chemicals and classes of chemicals. Despite the strong chemical emphasis of the book, we had to look at concepts such as radiation and noise, and beyond the emphasis on the science of toxicology, we had to look at history, laws, regulation, education, organizations, and databases. The encyclopedia also needed to consider environmental and ecological toxicology to somewhat counterbalance the acknowledged emphasis on laboratory animals and humans because, in the end, all our connections run deep.

In terms of the chemicals, we the editors of this book made a personal selection based on our own knowledge of those with relatively high toxicity, exposure, production, controversy, newsworthiness, or other interest. The chemicals do not represent a merger of regulatory lists or databases of chemicals; they are what we consider to be, for one reason or another, chemicals of concern to toxicology. The book was not intended as a large-scale compendium of toxic chemicals, several of which already exist.

In the tradition of many standard encyclopedias, scientific and otherwise, the encyclopedia is organized entirely alphabetically. Other than in a few useful but smaller scale dictionaries, this style of arrangement has not been done before for toxicology. This organization, along with a detailed index and extensive cross-references, should help the reader quickly arrive at the needed information.

Next, although this book should be of use to the practicing toxicologist, it is geared more to others who, in the course of their work, study, or for general interest, need to know about toxicology. This would include the scientific community in general, physicians, legal and regulatory professionals, and laypeople with some scientific background. Toxicologists needing to brush up on or get a quick review of a subject other than their own specialty would also benefit from it, but toxicologists seeking an in-depth treatment should instead consult a specialized monograph or journal literature.

The encyclopedia is meant to give relatively succinct overviews of sometimes very complex subjects. Formal references and footnotes were dispensed with because these seemed less relevant to the encyclopedia's goals than a simple list of recommended readings designed to lead the reader to more detailed information on a particular subject entry. The entry on Information Resources leads readers to print and electronic sources of information in toxicology.

First and foremost, thanks go to the Associate Editors and contributors, whose efforts are here in print. Yale Altman and Linda Marshall, earlier Acquisitions Editors for the books, were of great assistance in getting the project off the ground. Tari Paschall, the current Acquisitions Editor, and Monique Larson, Senior Production Editor, both of Academic Press, have with great expertise and efficiency brought it to fruition. Organization and formatting of the original entry manuscripts were handled with skill, patience, and poise by Mary Hall with the help of Christen Bosh and Jennifer Brewster.

My work on the *Encyclopedia of Toxicology* was undertaken as a private citizen, not as a government employee. The views expressed are strictly my own. No official support or endorsement by the US National Library of Medicine or any other agency of the US Federal Government was provided or should be inferred.

Philip Wexler

ACKNOWLEDGMENTS

This book, as is all too easy to discern, is not a one-man operation, and doubtlessly could not be one and still encompass the same breadth and depth. Above all, I bow, tip my hat, and throw roses in appreciation, to the nine associate editors Bruce D Anderson, Ann de Peyster, Shayne C Gad, Pertti J Hakkinen, Michael A Kamrin, Betty J Locey, Harihara M Mehendale, Carey N Pope, Lee R Shugart and the authors of this work. There is no exaggerating their importance in this collaboration. We were the prototypical occasionally disputative but affectionate family engaged in a common single-minded goal – self-preservation. Secondarily, we had an encyclopedia to produce cooperatively, and managed to engage in the process with good humor and without punching each other silly. Such are the advantages of online interaction. We survived, relatively intact, in good spirits, and on speaking terms, even after our few in-person meetings. And rest assured, no transfer of funds was involved in Dr Ernie Hodgson's flattering and much appreciated foreword.

On the publisher (Elsevier) end, Tari Paschall, experienced in the production of the first edition, ushered this second edition through its formative stages to the point where we had a stable process and a clear direction. She handed the baton to Judy Meyer, the new Publishing Editor for the encyclopedia, who deftly kept us on course, and hydrated, up to the finish line. Another baton pass shortly before the production process was from Nick Panissidi of Elsevier's San Diego Office to Michael Bevan in Oxford. Nick set up the Encyclopedia Website and initial editorial ground rules. Michael brought the editorial details to fruition and got us into and through production with hardly a scar. I would like to thank the many other unknown to me Elsevier staff who have worked diligently on other aspects of the book, including marketing. I have had great support from many colleagues. Dr Jack Snyder, Associate Director of the Division of Specialized Information Services at the National Library of Medicine, and Jeanne Goshorn, Chief of the Biomedical Information Services Branch of the same division, in particular, have been unflagging boosters of my efforts.

And finally, on the home front, I am certain that my dog, Chi-Chi, barked less than she would have, and my bird, Hercules, moderated his screeching, in consideration of my work on the encyclopedia. As for my teenage son, Jake, he probably bugged me more on account of it, but we are old hands at knowing how to annoy each other with relish.

Notes on the Glossary

Reprinted from the IUPAC 'Glossary for Chemists of Terms used in Toxicology' and the IUPAC 'Glossary of Terms used in Toxicokinetics', with permission from the International Union of Pure and Applied Chemistry.

In order that the *Encyclopedia of Toxicology* may be useful to as wide a readership as possible, a Glossary of key terms has been provided by the publisher. For the purpose of the article text itself, it is important to use the established technical vocabulary of the science of toxicology, in the interest of accuracy, brevity, and consistency.

However, it is possible that some of these technical terms will not be entirely familiar to the nonprofessional readers of this encyclopedia. Therefore, in the interest of greater understanding for those readers – and also for the possible benefit of professional readers consulting material outside their own area of expertise – the Glossary defines a selected group of several hundred terms. These terms occur frequently within a variety of articles in the encyclopedia and thus can be said to represent a core vocabulary of the field of toxicology. The definitions are presented in a concise, accessible format, based on the use of the term in the context of the encyclopedia.

Notes on the Subject Index

To save in the index, the following abbreviations have been used:

ADI	acceptable daily intake
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CSAF	chemical-specific adjustment factors
DDT	dichloro-diphenyl-trichloro-ethane
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
GCP	good clinical practice
GLP	good laboratory practice
ICH	International Conference on Harmonization
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
OPIDN	organophosphate-induced delayed neurotoxicity
QSARs	quantitative structure-activity relationships
SSRIs	selective serotonin reuptake inhibitors
WHO	World Health Organization

A

Aberrations of Chromosomes *See* Chromosome Aberrations.

Absorption

Jules Brodeur and Robert Tardif

Introduction

Absorption is the process by which a chemical crosses the various membrane barriers of the body before it enters the bloodstream. The main sites of entry are the gastrointestinal tract, the lungs, and the skin. In drug therapy, other convenient, but more rarely used, portals of entry are the intravenous, subcutaneous, and intramuscular routes.

The absorption of a chemical from the site of exposure is regulated by the biologic membrane surrounding the various cells that line the tissue compartments of the body. The membrane is composed principally of phospholipids forming an oriented bilayer, 7–9 nm thick. The more polar hydrophilic (attracted to water) ends of the phospholipids project into the aqueous media on each side of the membrane, and the hydrophobic (repelled by water) fatty acid tails form a barrier to water in the inner space of the membrane. Proteins are embedded throughout the lipid bilayer and have various functions. One of these is to act as active carriers for certain molecules across the membrane. Proteins can also form pathways or small pores through the membrane, serving as aqueous channels and allowing passage of water across them.

Before discussing absorption in more detail, it is important to consider mechanisms by which chemicals cross membranes. These mechanisms are of interest not only for absorption but also for all other processes (distribution, biotransformation, and excretion) involved in the disposition of chemicals because they also require passage through membranes.

Chemicals can cross membranes by one or more of the following mechanisms: passive diffusion, facilitated diffusion, active transport, filtration, and endocytosis.

Passive Diffusion

This is the mechanism by which lipophilic (hydrophobic) uncharged molecules find a passage across the membrane by solubilizing within the lipids of the membrane. The driving force for this process is the concentration gradient of the chemical between each side of the membrane, allowing molecules to be transported from the side with higher concentration to the side with lower concentration. Passive diffusion, therefore, requires no energy expenditure by the cell; it is not saturable or subject to competition between molecules.

Factors that govern passive diffusion are:

1. *The lipid solubility of a chemical*: This is a characteristic that is usually expressed in terms of the ability of the chemical to distribute between separate oil and water phases. The more a chemical dissolves in oil, or its substitute octanol, the more lipid-soluble it is and the more easily it will cross membranes.
2. *The electrical charge (degree of ionization) of a chemical*: As a rule, chemicals that are electrically neutral permeate more easily through the lipid phase of a membrane by virtue of their higher degree of lipid solubility. For several therapeutic agents that are weakly charged molecules, the pH of the aqueous environment will have considerable influence on the degree of ionization of the chemicals and hence on their lipid solubility and membrane permeation.
3. *The molecular size of a chemical*: Passive diffusion is normally limited to molecules whose molecular weight does not exceed 500 Da. However, a small molecule will cross membranes more rapidly than a larger one of equal lipophilicity.

Facilitated Diffusion

Facilitated diffusion is very similar to passive diffusion with the difference that transfer across membranes is assisted by the participation of carrier proteins embedded in the membrane bilayer. Again, the direction of passage will be from the side of the membrane with high concentration of a chemical to the side with low concentration; this also occurs without energy expenditure by the cell. Such a process is somewhat specific in the sense that it applies to molecules that are able to bind to a carrier protein. Absorption of nutrients such as glucose and amino acids across the epithelial membrane of the gastrointestinal tract occurs by facilitated diffusion. Since a finite number of carriers are available for transport, the process is saturable at high concentrations of the transported molecules and competition for transport may occur between molecules of similar structure.

Active Transport

Active transport requires a specialized carrier molecule, a protein, and the expenditure of cellular energy; transfer across membranes can therefore occur against a concentration gradient. The carrier system is selective for certain structural features of chemicals, namely their ionized state, whether anionic, cationic, or neutral. Recent advances in the understanding of active transport have led to the characterization of several families of carriers. Such carrier systems are saturable. In addition, molecules with similar structural features may compete for transport by a given carrier.

Active transport is of limited importance for absorption of chemicals; it plays an important role, however, in the elimination of chemicals by the liver and the kidneys.

Filtration

Small water-soluble and small charged molecules, such as methanol and salts, respectively, may cross the gastrointestinal epithelial membrane through minute pores or water channels (<4 nm) in the membrane. Filtration is also an important function for urinary excretion. Renal glomeruli possess rather large pores (~ 70 nm) that allow passage into the urine of various solutes contained in blood, including small proteins.

Endocytosis

Endocytosis is a specialized form of transport by which very large molecules and insoluble materials are engulfed by invagination of the absorptive cell membrane, forming intracellular vesicles. This process is responsible for the absorption of certain dyes by mucosal cells of the duodenum (pinocytosis). In the lung, alveolar macrophages scavenge insoluble particles, such as asbestos fibers, and may transport them into the lymphatic circulation (phagocytosis).

Absorption by the Gastrointestinal Tract

The major role of the gastrointestinal tract is to provide for efficient absorption of essential nutrients contained in ingested foods and liquids. It is also an important route for absorption of drugs and toxicants. The entire surface of the gastrointestinal tract is very large, being 200 times that of the body surface; the barrier between the contents of the tract and the blood vessels is easily crossed, consisting essentially of an epithelium only one cell thick. The anatomy of the gastrointestinal tract is illustrated in **Figure 1**. Absorption occurs mostly by passive diffusion of lipid-soluble, electrically neutral (nonionized) molecules.

The degree of ionization of many therapeutic drugs, which are usually weak electrolytes, is directly dependent upon the pH of the gastrointestinal content. The pH will therefore have considerable influence on the absorption of such chemicals; absorption will occur at sites where the drugs are present as neutral molecules. At the low acidic pH of the stomach (1–3), most weak organic acids such as

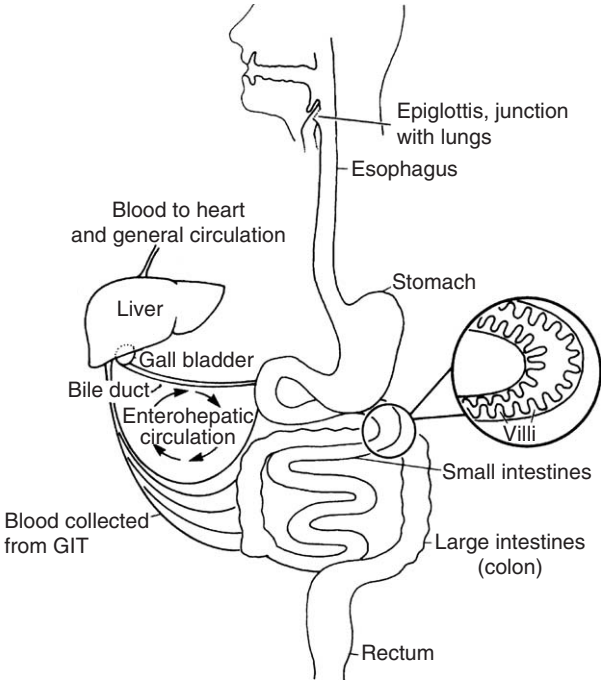

Figure 1 The anatomy of the gastrointestinal tract. (Reproduced from Smith RP (1992) The anatomy of the gastrointestinal tract. *A Primer of Environmental Toxicology*, p. 70. Philadelphia: Lea & Febiger, with permission from Lea & Febiger.)

acetylsalicylic acid will be nonionized and will diffuse passively across the gastric mucosa at a rate that will be proportional to the concentration gradient of the nonionized form. On the other hand, weak organic bases will diffuse more easily through the mucosa of the small intestine in which pH is higher (5–8). However, the bulk of absorption does not necessarily occur at the site where pH is optimal for electrical neutrality of the molecules. The very large surface area of the small intestine, due to the presence of finger-like projections, namely the villi and the microvilli, favors the diffusion of substances even at pH values for which the degree of ionization is not maximal; as a consequence, the small intestine is the region of the gastrointestinal tract that is most effective in the absorption of chemicals.

A small number of chemicals may be absorbed using facilitated diffusion (antimetabolic nucleotides), active transport (lead and 5-fluouracil), or pinocytosis (dyes and bacterial endotoxins).

Chemicals that reach the bloodstream by absorption through the gastrointestinal tract will move, via the portal circulation, directly to the liver, where they will normally undergo metabolic biotransformation to more or less active chemical forms, even before they gain access to the various tissues of the body; this phenomenon is known as the first-pass effect.

Among factors that may modify gastrointestinal absorption of ingested chemicals, the presence of food in the tract is one of the most important. The presence of food in the stomach will delay the absorption of weak organic acids at that site. The presence of lipid-rich food will delay the emptying of the gastric content into the intestine and thus also delay the absorption of chemicals. Conversely, an empty stomach facilitates absorption, a situation that is almost always beneficial in drug therapy.

Chemical interactions in the gastrointestinal tract between nutrients and drugs may considerably reduce the absorption of some drugs: calcium ions from dairy products form insoluble and therefore nonabsorbable complexes with the antibiotic tetracycline. On the other hand, certain drugs are irritants to the gastrointestinal tract (nonsteroidal anti-inflammatory drugs and potassium chloride tablets) and must be ingested with food.

Enterohepatic circulation provides an example of a special case of intestinal absorption. Certain chemicals, like methyl mercury, after undergoing biotransformation in the liver, are excreted into the intestine via the bile. They then can be reabsorbed in the intestine, sometimes after enzymatic modification by intestinal bacteria. This process can markedly prolong the stay of chemicals in the body. It can be interrupted by antibiotics that destroy the intestinal bacterial flora.

Absorption through the Skin

Normal skin represents an effective, but not perfect, barrier against the entry of chemicals present in the environment. There are two major structural components to the skin – the epidermis and the dermis (**Figure 2**).

The epidermis is formed of several layers of cells, with the outermost layers, $\sim 10\,\mu m$ thick, consisting of dried dead cells forming the stratum corneum. The latter, whose cells are rich in a filament-shaped protein called keratin, represents the major structural component of the barrier to passage of chemicals through the skin. Chemicals may move through the various cell layers of the epidermis by passive diffusion, more slowly through the stratum corneum, but more rapidly through the inner layers of live epidermal cells (stratum granulosum, stratum spinosum, and stratum germinativum).

The epidermis rests upon and is anchored onto a much thicker base of connective and fatty tissues, the dermis, whose major structural components are proteins called collagen and elastin; these proteins provide the skin with tensile strength and elasticity. The dermis also contains small blood vessels (capillaries), nerve endings, sebaceous glands, sweat glands, and hair follicles. Small pores in the epidermis that allow passage for sweat and sebum glands, as well as hair shafts, are not an important route of entry for chemicals. Once a chemical has crossed the epidermis by passive diffusion and gained access to the dermis, diffusion into the bloodstream occurs rapidly.

The stratum corneum is much thicker in areas where considerable pressure and repeated friction occur, like palms and soles; absorption is therefore much slower in these areas. Conversely, the stratum corneum is extremely thin on the skin of the scrotum. In general, skin surfaces of the ventral aspect of the body represent barriers that are easier to cross than those of the dorsal aspect.

Mechanical damage to the stratum corneum by cuts or abrasions of the skin or chemical injury by local irritation with acids or alkalis, for example, is likely to facilitate the entry of chemicals through the skin. This may also be the case in subjects suffering from certain skin diseases.

Lipid-soluble chemicals like organophosphate insecticides, tetraethyl lead, certain organic solvents, and certain dyes like aniline are relatively well absorbed through the skin. Percutaneous absorption is facilitated by increasing peripheral dermal blood

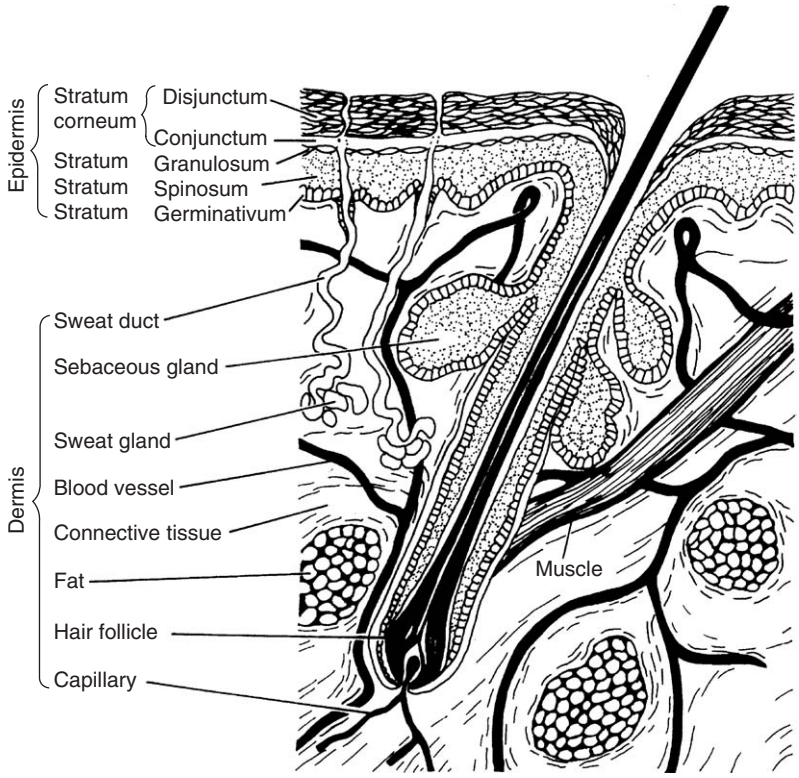

Figure 2 The organization of the skin as a biologic barrier. (Reproduced from Smith RP (1992) The organization of the skin as a biological barrier. *A Primer of Environmental Toxicology*, p. 73. Philadelphia: Lea & Febiger, with permission from Lea & Febiger.)

flow, as might occur when the ambient temperature is elevated. Under the same conditions, and in the presence of elevated sweating, the degree of hydration of the skin will increase considerably, enhancing the permeability of the stratum corneum to foreign chemicals; this observation is of special interest to workers in occupational settings.

Absorption by the Lung

The fundamental physiologic role of the lung is to allow gas exchange, extracting oxygen from the ambient air and eliminating carbon dioxide as a catabolic waste. When performing this function, the human adult lung is exposed each day to $\sim 10\,000$ l of more or less contaminated air. The lung can therefore become an important portal of entry for airborne chemicals present in the environment.

Extraneous substances are presented to the lung as gases or vapors or as liquid or solid particles; following inhalation, they may reach various regions of the respiratory tract, where some fraction of them will undergo absorption into the bloodstream; the remaining part will be either deposited locally or eliminated by exhalation even before being absorbed.

In terms of its anatomical and functional relationship with the contaminated atmospheric environment, the respiratory tract can be divided into three regions: the nasopharyngeal, the tracheobronchiolar, and the alveolar regions (**Figure 3**). The major part of the absorptive process takes place in the alveolar region, due principally to its large surface area ($80\,m^2$ in an adult human) and the extreme thinness of the cellular barrier ($<1\,\mu m$) between the air-side of the alveolar sac (lined with epithelial cells) and the lumen of the lung capillaries (lined with endothelial cells).

When discussing absorption of chemicals through the respiratory tract, it is practical to consider separately gases and vapors, on the one hand, and particles on the other hand.

Gases and Vapors

How much and at what location a contaminant gas or vapor will be absorbed in the respiratory tract is determined primarily by the solubility of the contaminant. The more water-soluble agents (sulfur dioxide and ketonic solvents) may dissolve in the aqueous fluid lining the cells of the more proximal region of the respiratory tree, even before they reach the alveolar region. They may then undergo absorption by passive diffusion or passage through membrane pores. When, in addition, water-soluble contaminants

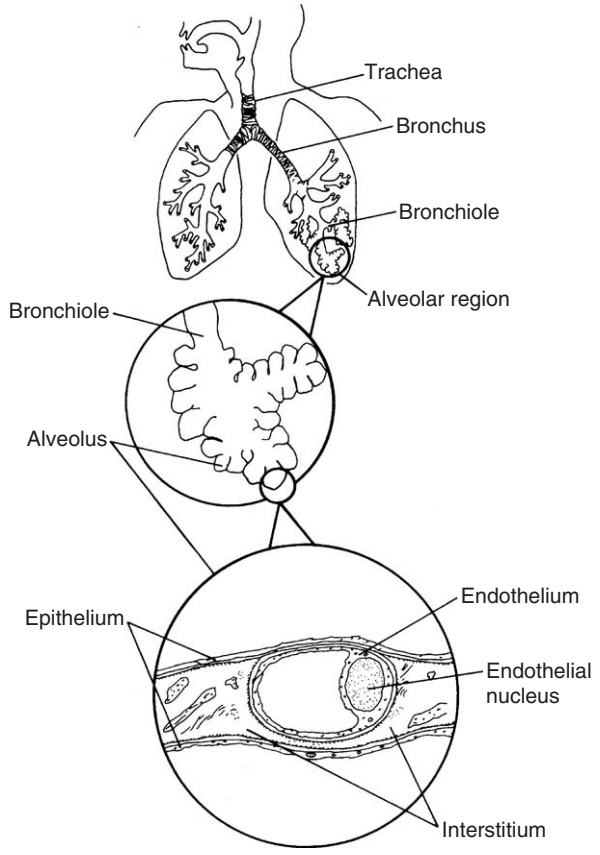

Figure 3 The anatomy of the respiratory tract from trachea to alveolus. (Reproduced from Smith RP (1992) The anatomy of the respiratory tract from trachea to alveolus. *A Primer of Environmental Toxicology*, p. 67. Philadelphia: Lea & Febiger, with permission from Lea & Febiger.)

are very reactive substances, like formaldehyde, they may form stable molecular complexes with cell components as proximally as the nasopharyngeal region. By virtue of these mechanisms, the alveolar region of the lung is partially protected against potential injury by certain gases and vapors.

Lipid-soluble contaminants diffuse passively through the thin alveolar–vascular cell barrier of the alveolar sac and then dissolve into the blood according to the ability of the contaminant to partition between alveolar air and circulating blood. Substances that are very soluble in blood are rapidly transported into the bloodstream. For these substances, like styrene and xylene, the amount absorbed will be greatly enhanced by increasing the rate and the depth of respiration, as is likely to happen when doing strenuous physical work. On the other hand, substances that are poorly soluble in blood have limited capacity for absorption due to rapid saturation of blood. For these substances, like the solvents cyclohexane and methyl chloroform, the amount absorbed may be increased only by increasing the blood perfusion rate in the lung; that is, by enhancing the replacement of saturated blood circulating in the lung capillaries. This can be achieved, for example, when doing work requiring heavy muscular activity.

Particles

Liquid (sulfuric acid and cutting fluids) and solid (silica dusts, asbestos fibers, and microorganisms) particles may become airborne and form respirable aerosols. According to their size and diameter, inhaled particles may be deposited in different anatomical regions of the respiratory system. Once deposited, particles may dissolve locally or may undergo removal to other regions of the respiratory tree.

The surface of the cells lining the tracheobronchial tree and the surface of most of the cells lining the nasopharyngeal region are covered with a layer of relatively thick mucous material; in the alveolar region, cells are lined with a thin film of fluid. The aqueous environment provided by these surface liquids favors at least partial dissolution and eventually absorption of water-soluble particles, especially those present as liquid droplets. Various defense mechanisms may help to remove less soluble particles from their site of deposition.

Particles larger than 5 μm in diameter are usually deposited by inertial impaction on the surface of the nasopharyngeal airways. They may be removed by coughing, sneezing, or nose wiping.

Particles with diameters between 1 and 5 μm are deposited in the tracheobronchial region as a result of either inertial impaction at airway bifurcations or gravitational sedimentation onto other airway surfaces. Undissolved particles may then be removed by the action of the mucociliary defense system working as an escalator; particles trapped in the mucus are propelled toward the pharynx by the action of thin cilia located on the surface membrane of specialized cells. Once in the pharynx, the particles may be swallowed. The efficiency of the escalator defense system may be greatly impaired by various environmental contaminants, like sulfur dioxide, ozone, and cigarette smoke that are known to paralyze the activity of the ciliated cells and consequently the upward movement of the mucus.

Particles ranging between 0.1 and 1.0 μm in diameter reach the alveolar region, where they finally hit cellular walls as a result of their random movement within minute air sacs. Removal of particles in this region of the lung is much less efficient. Some of the particles may eventually reach the tracheobronchiolar escalator system, either as engulfed

material within alveolar macrophages or as naked particles transported by the slow movement of the fluid lining the alveoli. Other possible mechanisms involve transport of the particles into the lymphatic system, either within macrophages or by direct diffusion through the intercellular space of the alveolar wall.

Particles smaller than 0.1 μm are not usually deposited in the lung, entering and exiting the airways together with inhaled and exhaled air.

Often, particulate matter acts as a carrier for gases, vapors, and fumes adsorbed onto their surface (solid particles) or dissolved within them (liquid particles); this increases the residence time of such pollutants in specific areas of the lung and imposes an additional task on the pulmonary defense mechanisms.

The most striking example of this synergistic effect is the one observed between sulfur dioxide, a respiratory tract irritant, and suspended particles, both being typical components of urban air pollution. This explains why current guideline values for exposure to sulfur dioxide in the presence of particulate matter are lower than those for exposure to sulfur dioxide alone. Similar concerns can be expressed for combinations comprising exhaust particles from diesel engines and certain carcinogens like polycyclic aromatic hydrocarbons, as well as cigarette smoke and certain other carcinogens like aromatic amines.

Chemicals absorbed by the lung reach the systemic circulation directly and are therefore immediately available for distribution to the various tissues of the body – brain, kidneys, liver, muscles, skin, bones, and others.

See also: Biotransformation; Distribution; Excretion; Exposure; Gastrointestinal System; Modifying Factors of Toxicity; Pharmacokinetics/Toxicokinetics; Respiratory Tract; Skin; Toxicity Testing, Dermal; Toxicity Testing, Inhalation.

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Acceptable Daily Intake (ADI)

Jaya Chilakapati and Harihara M Mehendale

The acceptable daily intake (ADI) is commonly defined as the amount of a chemical to which a person can be exposed, on a daily basis over an extended period of time, usually a lifetime without suffering a deleterious effect. It represents a daily intake level of a chemical in humans that is associated with minimal or no risk of adverse effects. It is a numerical estimate of daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime. The ADI is expressed in milligrams of the chemical, as it appears in the food, per kilogram of body weight per day ($mg\,kg^{-1}\,day^{-1}$). The Environmental Protection Agency (EPA) refers to such an exposure level as the risk reference dose (RfD) in order to avoid any implication that any exposure to a toxic material is 'acceptable'. RfDs are generally used for health effects that are thought to have a threshold or low dose limit for producing effects. The ADI concept has often been used as a tool in reaching risk management decisions such as establishing allowable levels of contaminants in foodstuffs and water.

ADI is derived from an experimentally determined 'no-observed-adverse-effect level (NOAEL)'. An NOAEL is an experimentally determined dose at which there is no statistically or biologically significant indication of the toxic effect of concern. In an experiment with several NOAELs, the regulatory focus is normally on the highest one, leading to the common usage of the term NOAEL as the highest experimentally determined dose without a statistically or biologically significant adverse effect. In cases in which a NOAEL has not been demonstrated experimentally, the term 'lowest-observed-adverse-effect level (LOAEL)' is used.

ADI values are typically calculated from NOAEL values by dividing by uncertainty (UF) and/or modifying factors (MFs):

$$\text{ADI (human dose)} = \text{NOAEL (experimental dose)}/(\text{UF} \times \text{MF})$$

In principle, these safety factors (SFs) allow for intraspecies and interspecies (animal to human) variation with default values of 10. An additional uncertainty factor can be used to account for experimental inadequacies; for example, to extrapolate

from short-exposure-duration studies to a situation more relevant for chronic study or to account for inadequate numbers of animals or other experimental limitations. Traditionally, a safety factor of 100 would be used for RfD calculations to extrapolate from a well-conducted animal bioassay (10-fold factor for animal to human) and to account for human variability in response (10-fold factor human-to-human variability).

Modifying factors can be used to adjust the uncertainty factors if data on mechanisms, pharmacokinetics, and the relevance of the animal response to human risk justify such modifications. For example, if there is kinetic information suggesting that rat and human metabolisms are very similar for a particular compound, producing the same active target metabolite, then, rather than using a 10-fold uncertainty factor to divide the NOAEL from the animal toxicity study to obtain a human relevant RfD, a factor of 3 for that uncertainty factor might be used. Of particular interest is the new extra 10-fold Food Quality and Protection Act (FQPA) factor, added to ensure protection of infants and children.

For other chemicals, with databases that are less complete (for example, those for which only the results of subchronic studies are available), an additional factor of 10 might be judged to be more appropriate leading to an SF of 1000. For certain other chemicals, based on well-characterized responses in sensitive humans, an SF as small as 1 might be selected, as in the case of the effect of fluoride on human teeth.

Some scientists interpret the absence of widespread effects in the exposed human populations as evidence of the adequacy of the SFs traditionally employed.

The RfD approach represents a generally accepted (Food and Drug Administration, National Academy of Sciences (NAS), and EPA) method for setting lifetime exposure limits for humans, and the use of 10-fold uncertainty factors has some experimental support.

Limitations of RfD

However, there are several limitations in the RfD approach, the net result of which is that exposures resulting in the same RfD do not imply the same level of risk for all chemicals. In addition, the RfD approach does not make use of dose–response information. There are also difficulties in the implications of specific UFs. The default value of 10 for the interspecies UF is a reasonable assumption in some cases, but in other cases may not be appropriate. Too narrow a focus on the NOAEL means that information on the shape of the dose–response curve is ignored. Such data could be important in estimating levels of concern for public safety. Guidelines have not been developed to take into account the fact that some studies have used larger (smaller) numbers of animals and, hence, are generally more (less) reliable than other studies.

The ADI is generally viewed by risk assessors as a 'soft' estimate, whose bounds of uncertainty can span an order of magnitude. That is, within reasonable limits, while exposures somewhat higher than the ADI are associated with increased probability of adverse effects, that probability is not a certainty. Similarly, while the ADI is seen as a level at which the probability of adverse effects is low, the absence of all risk to all people cannot be assured at this level.

See also: Benchmark Dose.

Further Reading

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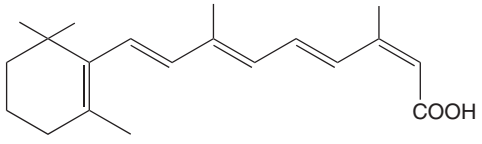
Accutane

Russell Barbare

- Chemical Abstracts Service Registry Number: CAS 4759-48-2
- Synonyms: Isotretinoin; 13-*cis*-Retinoic acid; 2-*cis*-Vitamin A acid; Ro-4-3780; Isotrex
- Chemical Formula: $C_{20}H_{28}O_2$
- Chemical Structure:



Uses

Isotretinoin is approved for use in the treatment of severe recalcitrant nodular acne and psoriasis, and is also used to treat keratinization disorders and some skin cancers.

Background Information

Isotretinoin is a retinoid, the class of natural and synthetic compounds that exhibit vitamin A activity. It is a naturally occurring metabolite of vitamin A that inhibits sebum production. The US Food and Drug Administration classifies it as Pregnancy Risk Category X.

Exposure Routes and Pathways

Ingestion is the most common route of exposure, and capsules are the only form currently produced.

Toxicokinetics

The apparent time lag between oral administration and appearance in systemic circulation is 30 min to 2 h. Absorption is approximately three times greater when taken with a high-fat meal as opposed to fasting, although the half-life is $\sim$21 h either way. Once in the body, isotretinoin binds to plasma proteins, especially albumin, at a rate greater than 99.9%. In humans, it readily undergoes reversible isomerization and irreversible oxidation; the exposure to these metabolites is more than three times greater than to the parent form. *In vitro* studies have indicated that the converted forms may have higher retinoid activity, but the clinical significance of this is unknown. ^{14}C studies have indicated that the half-life of the all drug activity in blood is $\sim$90 h. There was no statistically significant difference in exposure to any of the compounds between adults and patients 12–15 years of age. Excretion occurs in both feces and urine in approximately equal amounts, and overdosage in men can result in trace amounts in their semen. It is unknown whether it is excreted in human breast milk. It is metabolized by the liver, with the parent form having a terminal elimination half-life of 10–20 h.

Mechanism of Toxicity

Retinoids increase cellular mitotic activity, DNA and RNA synthesis, and protein synthesis. The primary toxicity of concern is female-mediated teratogenesis. Isotretinoin alters cell differentiation and placement in developing fetuses that are exposed to it in the first 3 weeks. Any exposed fetus has an increased change of spontaneously aborting or dying and may develop external or internal abnormalities. Cases of IQ less than 85 have been reported without other noted abnormalities. There is no accurate way to determine if a fetus has been exposed, so the safety recommendations are for potentially fertile females to not be pregnant or get pregnant within 30 days before or after exposure or at any time during exposure. External abnormalities have included skull, ear, and eye abnormalities such as cleft palate, absent external auditory canals, or microphthalmia. Noted internal changes have included abnormalities in the central nervous system such as hydrocephalus and microcephaly, abnormalities in the cardiovascular system or thymus gland, and parathyroid hormone deficiency. Even though it is unknown whether isotretinoin is excreted in human breast milk, breastfeeding should be avoided for the same period as pregnancy.

Acute and Short-Term Toxicity (or Exposure)

Animal

In rats and mice the oral LD_{50} of isotretinoin is $>4000\,mg\,kg^{-1}$; in rabbits it is $\sim1960\,mg\,kg^{-1}$.

Human

Overdosage can produce headache or abdominal pain, vomiting, dizziness, irregular muscular coordination, facial flushing, or drying and cracking of the lips, but all symptoms pass quickly and with no known long-term effects. An acute toxic dose has not been established – doses up to 1600 mg in an adult and 63 mg kg^{-1} in a child have resulted in only mild toxicity.

Chronic Toxicity (or Exposure)

Animal

Accutane is a potent rat and rabbit developmental toxin (teratogen). Testicular atrophy and evidence of lower spermatogenesis was noted in dogs given isotretinoin for 30 weeks at 20 or 60 $mg\,kg^{-1}\,day^{-1}$. Fischer 344 rats dosed at 8 or 32 $mg\,kg^{-1}\,day^{-1}$ for over 18 months had a dose-related raised incidence of pheochromocytoma, an adrenal gland tumor. The relevance in man is unknown since this animal develops spontaneous pheochromocytoma at a significant rate.

Human

Any level of exposure may be teratogenic, so potentially fertile females must not be pregnant or get

pregnant within 30 days before, during, and after exposure (see Mechanism of Toxicity). Other effects that often require monitoring are psychiatric disorders, including depression and suicidal thoughts, and benign intercranial hypotension, which can lead to headache, visual disturbances, or nausea and vomiting. These disorders may not stop upon discontinuation and should be evaluated by a professional. Dose-dependent adverse effects on the skin and mucous membranes may include inflammation or cracking of the lips, dry eyes, nosebleeding, irritation of the palpebral conjunctiva, and redness or dryness of the skin. Less common effects on the same organ systems include hair loss, photosensitivity, formation of granular tissue, or dark adaptation dysfunction. Colonization and, rarely, infection by *Staphylococcus aureus* can also occur. Hyperlipidemia is reported in 25% of treated patients during therapeutic courses of treatment on a systemic level, with the most common effect being increased triglyceride levels. There may also be increased cholesterol levels, raising of low-density lipoprotein levels, or lowering of high-density lipoprotein levels. Long-term treatments can generate several skeletal side effects including joint or lower back pain, bone hypertrophy, ossification at tendinous insertions, and lowered bone density. Children may experience premature closure of the epiphyseals. Tests of sperm count and motility in man have shown no significant changes.

Clinical Management

Roche Pharmaceuticals has produced the System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™) and the Accutane Pregnancy Prevention Protocol (PPP) to be used in conjunction with the prescription of Accutane. Management of toxic effects involves monitoring by the appropriate specialist and discontinuation of the exposure where indicated. Isotretinoin-related depression may require long-term monitoring.

Exposure Standards and Guidelines

The recommended therapeutic dosage is 0.5–1.0 $mg\,kg^{-1}\,day^{-1}$ in two doses per day taken with food for 15–20 weeks.

See also: Developmental Toxicology; Photoallergens; Vitamin A.

Further Reading

Ellis CN and Krach KJ (2001) Uses and complications of isotretinoin therapy. *Journal of the American Academy of Dermatology* 45: S150–S157.

Goldsmith LA, *et al.* (2004) American Academy of Dermatology Consensus Conference on the safe and optimal use of isotretinoin: Summary and recommendations. *Journal of the American Academy of Dermatology* 50: 900–906.

Relevant Website

http://www.rocheusa.com – Roche Pharmaceuticals, Accutane® Website for the United States.

ACE Inhibitors

Henry A Spiller

This article is a revision of the previous print edition article by Daniel J Cobaugh, volume 1, pp. 7–9, © 1998, Elsevier Inc.

- Representative Chemicals: Benazepril, Lotensin®; Capropril, Capoten®; Enalapril, Vasotec®; Enalaprilat, Vasotec IV®; Fosinopril, Monopril®; Lisinopril, Prinivil®; Zestril®; Quinapril, Accupril®; Ramipril, Altace®
- Chemical Abstracts Service Registry Numbers: CAS 86541-75-5; CAS 62571-86-2; CAS 75847-73-3; CAS 84680-54-6; CAS 888 89-14-9; CAS 76547-98-3; CAS 85441-61-8; CAS 87333-19-5
- Chemical/Pharmaceutical/Other Class: Angiotensin-converting enzyme (ACE) inhibitors
- Chemical Formulas: Benazepril, $C_{24}H_{28}N_2O_5$; Captopril, $C_9H_{15}NO_3S$; Enalapril, $C_{20}H_{28}N_20_5$; Enalaprilat, $C_{18}H_{24}N_2O_5 \cdot 2H_2O$; Fosinopril, $C_{30}H_{46}NO_7P$; Lisinopril, $C_{21}H_{31}N_3O_5 \cdot 2H_2O$; Quinapril, $C_{25}H_{30}N_2O_5$; Ramipril, $C_{23}H_{32}N_2O_5$

Uses

Angiotensin-converting enzyme (ACE) inhibitors are used in the management of hypertension and congestive heart failure.

Exposure Routes and Pathways

Ingestion is the most common route for both accidental and intentional exposures. Enalaprilat is

available for parenteral administration and toxicity could occur via this route.

Toxicokinetics

The extent of oral absorption varies from 25% (lisinopril) to 75% (captopril). The rate of absorption also varies from 0.5 h (captopril and enalopril) to 7 h (lisinopril). Reported volumes of distribution range from $0.7\,l\,kg^{-1}$ (captopril) to $1.8\,l\,kg^{-1}$ (lisinopril). All of the ACE inhibitors, except for captopril and lisinopril, are metabolized in the liver to active metabolites. Excretion is via both the urine and the feces. The half-life ranges from 1.3 h (enalapril) to 17 h (ramipril).

Mechanism of Toxicity

The ACE inhibitors affect the rennin–angiotensin system. This system has effects on blood pressure as well as fluids and electrolyte balance. Renin modulates the formation of angiotensin I from angiotensinogen. Angiotensin I is then converted via angiotensin-converting enzyme to angiotensin II. Angiotensin II is a potent vasoconstrictor that also causes increased aldosterone secretion. Aldosterone is responsible for sodium and water retention. The ACE inhibitors interfere with the conversion of angiotensin I to angiotensin II and, therefore, cause vasodilation as well as loss of sodium and water. Literature supporting a relationship between angiotensin and the beta endorphins exists. Angiotensin II is thought to be inhibited by endogenous beta endorphin. *In vitro* studies have demonstrated that captopril can inhibit encephalinase, the enzyme that degrades endorphins. Interference with endorphin metabolism may result in prolonged effects from these opiate-like neurotransmitters. Also, the opiate antagonist naloxone is thought to interfere with beta-endorphin inhibition of angiotensin II. An interaction between angiotensin and bradykinin may also exist. ACE is identical to kinase IT, which is responsible for inactivation of bradykinins. Accumulation of bradykinins may cause a decrease in blood pressure by a direct vasodilatory mechanism or through stimulation of prostaglandin release and/or synthesis.

Acute and Short-Term Toxicity (or Exposure)

Animal

There are limited data, but accidental ingestion of small amount of ACE inhibitors by companion animals would not expected to be a problem.

Human

The clinical effects observed following ACE inhibitor poisoning or overdose are a direct extension of their therapeutic effects and would be expected to manifest in 1–2 h postingestion. Ingestions involving small amounts of ACE inhibitors may result in limited or no toxic effects. Clinical effects that may occur include hypotension with or without a reflex tachycardia and changes in level of consciousness that are directly related to vascular changes. Only a few cases of profound hypotension have been reported. In each of these cases, blood pressure returned to normal within 24 h of ingestion. One death has been attributed to an ACE inhibitor. This was in a 75-year-old male who ingested captopril and the calcium channel blocker diltiazem. Because this was a coingestion, it is not certain that captopril was the primary cause of death.

Chronic Toxicity (or Exposure)

Animal

Carcinogenicity studies carried out over years have not demonstrated any increased tumor incidence. No teratogenic effects have been documented in mice despite large chronic doses (e.g., 625 times the maximum daily dose of lisinopril on days 6–15 of gestation).

Human

Adverse effects observed at therapeutic doses include cough, dermal reactions, blood dyscrasias, bronchospasm, and hypogeusia. Angioedema has been reported, but does not appear to be an IgG related immune response. Reversible renal failure has been reported with chronic therapy. Clinical effects that may occur include hypotension with or without a reflex tachycardia, changes in level of consciousness that are directly related to vascular changes, and hyperkalemia. Hyperkalemia can occur as a response to sodium loss. Delayed hypotension, at 19 and 25 h, has been observed following ingestion of captopril.

In Vitro Toxicity Data

Lisinopril, captopril, quinapril, and benazepril have been studied for mutagenicity using a variety of methods and none have documented evidence of mutagenicity.

Clinical Management

Supportive care, including airway management as well as cardiac and blood pressure monitoring,

should be provided to unstable patients. Ingestion of small amounts of an ACE inhibitor in children can be managed with observation at home. Following ingestion of a toxic amount of these agents or recent ingestions involving toxic coingestants, activated charcoal can be utilized to decontaminate the stomach. Hypotension following ACE inhibitor ingestion has been managed with fluids alone or in combination with vasopressors such as dopamine. A limited number of case reports exist that describe a need for dopamine to treat hypotension. If profound hypotension resistant to dopamine were to occur, other vasopressors, such as epinephrine and norepinephrine, can be used. Laboratory analysis should be used to monitor electrolytes, especially sodium and potassium. ACE inhibitor serum concentrations are not readily available and have little if any clinical utility. Because ACE inhibitors may potentiate the effects of the opiate-like beta endorphins, some authors have suggested the use of naloxone to reverse their toxicities. Successes and failures with naloxone have been described in case reports. Because naloxone has limited adverse effects, its use could be considered in the management of serious ACE inhibitor toxicity. One case report describes the use of the experimental exogenous angiotensin II to counter severe ACE inhibitor toxicity. The pharmacokinetic characteristics of the ACE inhibitors, limited protein binding, and small volume of distribution make them amenable to hemodialysis. Because major morbidity is rare with these agents, the need for dialysis is questionable.

Angioedema with potential for airway obstruction may not respond to epinephrine and antihistamines. Rapid intubation to protect the airway may be necessary.

Environmental Fate

No information is currently available on breakdown in soil, groundwater, or surface water. ACE inhibitors are excreted into breast milk in trace amounts. Captopril is distributed into milk in concentrations of ~1% of those in maternal blood.

See also: Charcoal; Prostaglandins.

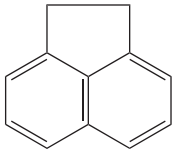
Further Reading

Augenstein WL, Kulig KW, and Rumack BH (1988) Captopril overdose resulting in hypotension. *Journal of the American Medical Association* 259: 3302–3305.

Acenaphthene

Sanjay Chanda and Harihara M Mehendale

- Chemical Abstracts Service Registry Number: CAS 83-32-9
- Synonyms: 1,2-Dihydroacenaphthylene; 1,8-Dihydroacenaphthalene; 1,8-Ethylenenaphthalene; Acenaphthylene; Naphthyleneethylene; Periethylenenaphthalene; Ethylenenaphthylene
- Chemical/Pharmaceutical/Other Class: Arene belonging to the class of polycyclic aromatic hydrocarbons
- Chemical Structure:



Uses

Acenaphthene is a chemical intermediate used to produce naphthalimide dyes, which are used as fluorescent whitening agents, and used in manufacturing plastics, insecticides, and fungicides.

Background Information

Acenaphthene is a component of crude oil and a product of combustion, which may be produced and released to the environment during natural fires. Emissions from petroleum refining, coal tar distillation, coal combustion, and diesel fueled engines are the major contributors of acenaphthene to the environment. Acenaphthene is used as a chemical intermediate and may be released to the environment via manufacturing effluents and the disposal of manufacturing waste by-products. Because of the widespread use of acenaphthene in a variety of products, acenaphthene may also be released to the environment through landfills, municipal waste

water treatment facilities, and waste incinerators. Acenaphthene should biodegrade rapidly in the environment. The reported biodegradation half-lives for acenaphthene in aerobic soil and surface waters range from 10 to 60 and from 1 to 25 days, respectively. However, acenaphthene may persist under anaerobic conditions or at high concentration due to toxicity to microorganisms. Acenaphthene is not expected to hydrolyze or bioconcentrate in the environment; yet, it should undergo direct photolysis in sunlight environmental media. Acenaphthene is expected to exist entirely in the vapor phase in ambient air.

Exposure Routes and Pathways

Skin contact is the most common accidental exposure pathway. Acenaphthene may irritate or burn skin. Exposure can also be through ingestion or inhalation. Its vapor can be poisonous if inhaled.

Toxicokinetics

The half-life of acenaphthene in the bluegill fish is less than 1 day. A *Beijerinckia* species and a mutant strain, *Beijerinckia* species strain B8/36, were shown to oxidize acenaphthene. Both organisms oxidize acenaphthene to the same spectrum of metabolites, which included 1-acenaphthenol, 1-acenaphthenone, 1,2-acenaphthenediol, acenaphthenequinone, and a compound that was tentatively identified as 1,2-dihydroxyacenaphthylene.

Mechanism of Toxicity

5-Nitroacenaphthene causes toxicity by the reduction of the nitro function to the corresponding hydroxylamine. These arylhydroxylamines may be either direct-acting mutagens or may become so following nonenzymic conversion to aryl nitronium ions or they may be esterified to the corresponding electrophilic hydroxamic acid esters. Acenaphthene can bind to hemoglobin to cause methemoglobinemia.

Acute and Short-Term Toxicity (or Exposure)

Animal

Acenaphthene can cause hepatotoxicity in rats and mice. Little information is available regarding acute exposure to acenaphthene. It is biotransformed in the liver. On the basis of a mouse oral subchronic study in which hepatotoxicity was seen as the major effect, the no-observed-adverse-effect level and the lowest-observed-adverse-effect level were 175 and $350\,mg\,kg^{-1}\,day^{-1}$, respectively.

Human

Acenaphthene can be irritating to eyes, skin, and mucous membrane. Acenaphthene may be poisonous if inhaled or absorbed through skin. The vapor may cause dizziness or suffocation. Acenaphthene may cause vomiting if swallowed in large quantity. It can cause methemoglobinemia.

Chronic Toxicity (or Exposure)

Animal

Rats exposed to acenaphthene at a level of $12 \pm 1.5\,mg\,m^{-3}$ for 4 h a day, 6 days per week for 5 months showed toxic effects on the blood, lung, and glandular constituents. The bronchial epithelium showed hyperplasia and metaplasia, which may have been symptoms of the pneumonia that killed a large number of rats during the study. No signs of malignancy appeared during the 8 month postexposure observation period.

Human

Chronic human exposure data are not available. Currently, acenaphthene is under review by US Environmental Protection Agency for evidence of human carcinogenic potential. This does not imply that this agent is necessarily a carcinogen. The nitroderivative of acenaphthene (5-nitroacenaphthene) is a possible carcinogen to humans.

In Vitro Toxicity Data

Acenaphthene is devoid of any mutagenic activity in *Salmonella typhimurium* (TA 98) assay. The nitroderivatives of acenaphthene have tumorigenic potential.

Clinical Management

The victim should be moved to fresh air and emergency medical care should be provided. If the victim is not breathing, artificial respiration should be provided; if breathing is difficult, oxygen should be administered. In case of contact with the eyes, the eyes should be flushed immediately with running water for at least 15 min. Affected skin should be washed with soap and water. Contaminated clothing and shoes should be removed and isolated at the site. If methemoglobinemia occurs and is severe, treatment with methylene blue and oxygen is recommended.

Environmental Fate

The reported biodegradation half-lives for acenaphthene in aerobic soil and surface waters range from 10 to 60 and from 1 to 25 days, respectively. However, acenaphthene may persist under anaerobic conditions or at high concentrations due to toxicity to microorganisms. Acenaphthene is not expected to hydrolyze or bioconcentrate in the environment; yet, it should undergo direct photolysis in sunlit environmental media. A calculated K_{oc} range of 2065–3230 indicates acenaphthene will be slightly mobile in soil. In aquatic systems, acenaphthene can partition from the water column to organic matter contained in sediments and suspended solids. A Henry's law constant of 1.55×10^{-4} atm m^3 mol^{-1} at 25°C suggests volatilization of acenaphthene from environmental waters may be important. The volatilization half-lives from a model river and a model pond, the latter considers the effect of adsorption, have been estimated to be 11 h and 39 days, respectively. Acenaphthene is expected to exist entirely in the vapor phase in ambient air. In the atmosphere, the reaction with photochemically produced hydroxyl radicals (half-life of 7.2 h) is likely to be an important fate process. The most probable human exposure would be occupational exposure, which may occur through dermal contact or inhalation at places where acenaphthene is produced or used. Atmospheric workplace exposures have been documented. Nonoccupational exposures would most likely occur via urban atmospheres, contaminated drinking water supplies, and recreational contaminated waterways.

Ecotoxicology

Treatment of cherry-mazzard hybrid seeds with acenaphthene powder for 10 h inhibited the seed germination and seedling growth. Treatment of *Allium cepa* root meristem cells with acenaphthene vapor for 12–96 h caused anomalies leading to random development of cells. Acute toxicity value for bluegill fish was 1700 UG l^{-1} in freshwater and the toxicity to sheepshed minnow was 2230 UG l^{-1} in saltwater.

Exposure Standards and Guidelines

CERCLA reportable quantities: Persons in charge of vessels or facilities are required to notify the National Response Center (NRC) immediately, when there is a release of this designated hazardous substance, in an amount equal to or greater than its reportable quantity of 100 lb or 45.4 kg. State drinking water guidelines: Minnesota 400 µg l^{-1} and Florida 20 µg l^{-1}.

See also: Polycyclic Aromatic Hydrocarbons (PAHs).

Further Reading

Byrne M *et al.* (1985) Government Reports, Announcements & Index, Issue 21. *Exposure and Risk Assessment for Benzo(a)pyrene and Other Polycyclic Aromatic Hydrocarbons*, vol. 3.

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Health & Welfare Canada (1979) *Polycyclic Aromatic Hydrocarbons*, Report No. 80-EHD-50.

Staples CA and Werner AF (1985) Priority pollutant assessment in the USA: Scientific and regulatory implications. *Toxic Substances* 6(4): 186–200.

US Department of Health & Human Services/Agency for Toxic Substances Disease Registry (1995) *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Update), NTIS# PB/95/264370.

USEPA (1979) *Health Assessment Document: Polycyclic Organic Matter*, EPA-600/9-79-008.

USEPA (1980a) *Ambient Water Quality Criteria Doc: Acenaphthene* (Draft).

USEPA (1980b) *Ambient Water Quality Criteria Doc: Polynuclear Aromatic Hydrocarbons* (Draft).

Wilkins ES and Wilkins MG (1985.) Review of toxicity of gases emitted from combustion pyrolysis of municipal and industrial wastes. *Journal of Environmental Science and Health – Part A* 20(2).

Relevant Website

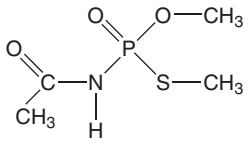
http://www.atsdr.cdc.gov – Agency for Toxic Substances and Disease Registry. Toxicological Profile for Acenaphthene.

Acephate

Subramanya Karanth

- Chemical Abstracts Service Registry Number: CAS 30560-19-1
- Synonyms: Asataf; Aimthane; Chrevron RE 12420; Kitron; Orthene; Ortril; Pillarthene
- Chemical/Pharmaceutical/Other Class: Organophosphorus insecticide
- Chemical Formula: $C_4H_{10}NO_3PS$

- Chemical Structure:



Uses

Acephate is registered for use on a variety of field, fruit, and vegetable crops (e.g., cotton, tobacco, cranberries, mint). It is also used commonly in food handling establishments, on ornamental plants (cut flowers), and in and around residential and commercial buildings for the control of roaches and fire ants. It is effective against a wide range of biting and sucking insects, especially aphids.

Exposure Routes and Pathways

Common routes of acephate exposure include ingestion and inhalation.

Toxicokinetics

Acephate is converted to another organophosphorus compound, methamidophos, in the body. Studies with ^{14}C-acephate in mammals have shown 75% of the parent compound eliminated in the urine. Other major metabolites include *O*,*S*-dimethyl phosphorothioate (DMPT, 5%) and *S*-methyl acetyl phosphoramidothioate (5%).

Mechanism of Toxicity

Acephate exerts its toxicity by inhibiting the enzyme acetylcholinesterase in the synapse and neuromuscular junctions, which leads to accumulation of the neurotransmitter acetylcholine and overstimulation of postsynaptic receptors.

Acute and Short-Term Toxicity (or Exposure)

Animal

Acephate is moderately toxic to mammals with an acute oral LD_{50} of 850–950 mg kg^{-1} in rats, whereas its metabolite methamidophos is highly toxic to mammals. The common symptoms of acephate poisoning include salivation, nasal discharge, vomiting, diarrhea, nausea, blurred vision, difficulty in breathing, headache, and muscle weakness. Convulsions, coma, and death may occur in cases of severe acute poisoning.

Human

Acephate exposure can result in cholinesterase inhibition, which causes overstimulation of the nervous system. Acephate is nonirritating to skin and slightly irritating to the eyes but is not a skin sensitizer.

Chronic Toxicity (or Exposure)

Animal

Chronic studies in rats and dogs have shown cholinesterase inhibition. No pathological changes were observed in rats following 3 month exposure to 30 mg kg^{-1} dosage of acephate.

Human

Acephate is classified as a possible human carcinogen. Since acephate is used both on food crops and other common residential areas, risks of human exposures through multiple routes are high. Based on cholinesterase inhibition studies in rats, the no-observed-adverse-effect level for chronic dietary exposure is 0.12 mg kg^{-1} day^{-1}. Agricultural workers who are involved in mixing, formulation, and application may be at higher risk of exposure.

Clinical Management

In case of dermal exposure, the contaminated area should be washed with plenty of water or showered using soap and shampoo. Eyes should be flushed with water repeatedly for several minutes. Contaminated clothing should be removed and the airway cleared. In case of ingestion, vomiting should be induced. Atropine treatment should be initiated immediately to counteract muscarinic effects. Atropine (adults and children >12 years: 2–4 mg; children <12 years: 0.05–0.1 mg) treatment should be repeated every 15 min until oral and bronchial secretions are controlled and atropinization is achieved. The duration and dosage of atropine treatment should be slowly reduced as the condition of the patient improves. Pralidoxime should be administered slowly at the recommended dosage (adults and children >12 years: 1–2 g; children <12 years: 20–50 mg by IV infusion in 100 ml saline at $\sim$0.2 g min^{-1}). This dosage can be repeated at every 1–2 h intervals initially and at 10–12 h intervals later depending on the condition of the patient. Periodic medical examination and care is required depending on the degree of exposure.

Environmental Fate

Acephate is readily degraded in soil by microorganisms and in water it undergoes rapid hydrolysis.

Its half-life is less than 3 and 6 days under aerobic and anaerobic conditions, respectively. CO_2 is the major metabolite following microbial degradation in soil.

Ecotoxicology

Both acephate and its metabolite, methamidophos, pose a high acute and chronic risk to birds. Studies in insects have shown that acephate is highly toxic to honey bees and other beneficial insects. Methamidophos is also very highly toxic to freshwater invertebrates.

Exposure Standards and Guidelines

The chronic reference dose for acephate is $0.0012\,mg\,kg^{-1}\,day^{-1}$ while the accepted daily intake is $0.03\,mg\,kg^{-1}\,day^{-1}$.

See also: Acetylcholine; Methamidophos; Neurotoxicity; Organophosphates; Pesticides.

Relevant Websites

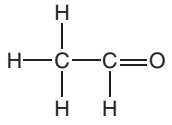
http://extoxnet.orst.edu – Extension Toxicology Network, Oregon State University.
http://www.epa.gov – US Environmental Protection Agency.

Acetaldehyde

John Sanseverino

This article is a revision of the previous print edition article by Edward Kerfoot, volume 1, pp. 10–11, © 1998, Elsevier Inc.

- Chemical Abstracts Service Registry Number: CAS 75-07-0
- Synonyms: Acetic aldehyde; Acetylaldehyde; Ethylaldehyde; Ethanal
- Chemical/Pharmaceutical/Other Class: Aldehydes
- Chemical Formula: C_2H_4O
- Chemical Structure:



Uses

Acetaldehyde is used in the manufacturing of various chemicals such as acetic acid, pyridine, peracetic acid, pentaerythritol, 1,3-butylene glycol, and chloral. It is also used in the silvering of mirrors, leather tanning, fuel compositions, preservatives, paper processing, glues, cosmetics, dyes, plastics, and rubber. Natural sources of acetaldehyde include metabolic intermediate in higher plants, alcohol fermentation, and sugar decomposition in the body. Anthropogenic sources include vehicle exhaust, fuel oil and coal, organic chemical manufacturing.

Exposure Routes and Pathways

Industrial exposures to acetaldehyde are most likely to occur by inhalation with potential for skin and eye contact. Accidental ingestion is also possible. Acetaldehyde is produced from the metabolism of ethanol in the body.

Toxicokinetics

Following inhalation exposure, acetaldehyde is deposited in the nasal cavity and upper respiratory tract, and eventually some traces can be absorbed into the blood and be distributed throughout the body. The uptake of acetaldehyde in the nasal cavity is influenced by its solubility and inspiratory flow rate. Perhaps acetaldehyde uptake in the nasal tissue is dependent on its reaction with tissue substrates that become depleted at high exposure concentrations. Acetaldehyde vapor can be metabolized in the nasal cavity by the mixed-function oxidase and carboxylesterase systems. The first metabolite of ethanol metabolism is acetaldehyde. Metabolism takes place in the liver to a number of metabolites and some unchanged acetaldehyde that can be excreted in the urine. Most of the free acetaldehyde is excreted in the exhaled breath.

Mechanism of Toxicity

Acetaldehyde is soluble in the mucous membranes of the upper respiratory tract causing irritation of the sensory nerve endings. There is also depression of the mucociliary defense system. The direct action of acetaldehyde in the skin and eyes is the result of irritation to these tissues.

Acute and Short-Term Toxicity (or Exposure)

Animal

The oral LD_{50} for acetaldehyde in rats has been reported to be $1930\,mg\,kg^{-1}$ and the 4 h LC_{50} is

approximately 13 300 ppm. Acetaldehyde is a severe eye irritant to rabbits at 40 mg and mildly irritating to rabbit skin at 500 mg. Rats were exposed to acetaldehyde concentrations ranging from 400 to 5000 ppm in a 4 week subchronic inhalation study at 6 h day^{-1}, 5 day week^{-1}. At 1000 and 2200 ppm, the rats exhibited growth retardation, polyuria, and nasal epithelial degeneration. At 400 ppm, there was slight degeneration of the olfactory epithelium.

Human

Inhalation exposures to acetaldehyde can result in irritation of the upper respiratory tract. Inhalation at concentrations ranging from 100 to 200 ppm can cause irritation to the mucous membranes. Skin and eye contact with liquid acetaldehyde can produce a burning sensation, lacrimation, and blurred vision. Unacclimated subjects experienced eye irritation at 50 ppm after a 15 min exposure. Some more sensitive persons exhibited eye irritation at 25 ppm for a 15 min exposure.

Chronic Toxicity (or Exposure)

Animal

A 52 week chronic inhalation study in hamsters exposed to 1500 ppm acetaldehyde produced growth retardation, slight anemia, increased enzyme and protein content in the urine, and increased kidney weight. There were distinct histopathological changes in the nasal mucosa and trachea, including hyperplasia, squamous cell metaplasia, and inflammation.

Inhalation exposure to acetaldehyde has produced nasal tumors in rats and laryngeal tumors in hamsters. Male and female rats were exposed to acetaldehyde 6 h day^{-1}, 5 day week^{-1} for 28 months at concentrations of 0, 750, 1500, or 3000 ppm. A concentration-related incidence of squamous cell carcinomas of the respiratory epithelium was observed in both male and female rats. A statistically significant number of adenocarcinomas occurred in the olfactory epithelium of both sexes of rats exposed at all three acetaldehyde concentrations. Male and female hamsters were exposed to acetaldehyde 7 h day^{-1}, 5 day week^{-1} at concentrations gradually reduced from 2500 to 1650 ppm for 52 weeks. Both sexes of acetaldehyde-exposed hamsters developed laryngeal tumors consisting of squamous cell carcinomas and adenosquamous cell carcinomas.

Data from studies with rats suggest that acetaldehyde is teratogenic. Fetuses from dams injected intraperitoneally with acetaldehyde concentrations ranging from 50 to 100 mg kg^{-1} on day 10, 11, or 12 of gestation produced a significant increase in fetal resorptions, growth retardation, and an increase in malformations, including digital anomalies, cranial and facial malformations, and delayed skeletogenesis. It was concluded that acetaldehyde interfered with placental function via the maternal–placental nutrient exchange, resulting in retarded growth.

Data from some animal studies suggest that acetaldehyde is teratogenic. According to the American Conference of Governmental Industrial Hygienists (ACGIH), the recent identification of nasal and laryngeal carcinomas indicated that acetaldehyde should be considered an A3 animal carcinogen.

Human

Acetaldehyde, produced from the metabolism of ethanol, may also be responsible for localized cancers, brain damage in prenatal infants, and growth suppression (in chicken embryos). Acetaldehyde, as a direct result of ethanol metabolism in the body, has been implicated in alcoholic cardiomyopathy and cancer of the digestive tract. The levels of acetaldehyde in blood are directly correlated with ethanol consumption.

In Vitro Toxicity Data

Acetaldehyde has been shown to induce mutagenic changes in many assays. In mammalian *in vitro* assays, acetaldehyde produced sister chromatid exchanges and chromosomal breaks and aberrations in mammalian *in vitro* assays.

Clinical Management

Exposures by inhalation should be monitored for respiratory tract irritation, bronchitis, or pneumonitis. Humidified supplemental 100% oxygen should be administered. Gastric lavage may be indicated soon after ingestion of acetaldehyde followed by administration of activated charcoal slurry mixed with a saline cathartic or sorbitol. Exposed eyes should be irrigated with copious amounts of tepid water for at least 15 min. If eye irritation, pain, swelling, lacrimation, or photophobia persists, the patient should be seen in a health care facility.

Exposure Standards and Guidelines

A short-term exposure limit ceiling of 25 ppm for acetaldehyde was recommended to prevent excessive eye irritation, lacrimation, and potential injury to the respiratory tract.

See also: Respiratory Tract.

Further Reading

Eriksson C and Peter J (2001) The role of acetaldehyde in the actions of alcohol (Update 2000). *Alcoholism: Clinical and Experimental Research* 25(5, Suppl.): 15S–32S.

Verschueren K (2000) *Handbook of Environmental Data on Organic Chemicals*, 3rd edn. New York: Wiley.

World Health Organization (1995) *Acetaldehyde*. Geneva: World Health Organization.

Acetamide

Gerald L Kennedy

- Chemical Abstracts Service Registry Number: CAS 60-35-5
- Synonyms: Acetic acid amide; Ethanamide; Methane-carboxamide
- Chemical/Pharmaceutical/Other Class: Amide, aliphatic; Organic solvent; Volatile organic compound
- Chemical Formula: CH_3CONH_2

Uses

As a dipolar solvent, acetamide finds many uses as a solvent for both inorganic and organic compounds. The solvency has led to widespread uses in industry including applications in cryoscopy, soldering, and the textile industry. The neutral and amphoteric characteristics allow its use as an antacid in the lacquer, explosives, and cosmetics industries. Its hygroscopic properties make it useful as a plasticizer in coatings, fixtures, cloth, and leather, and as a humectant for paper. It is also a raw material in organic synthesis of methylamine and thioacetamide and as an intermediate in preparation of medicines, insecticides, and plastics.

Exposure Routes and Pathways

Acetamide may be inhaled, swallowed, or absorbed through the skin. The chemical is considered to be mildly irritating to the skin and eyes. In its usual application, inhalation is the most common route of exposure, although dermal contact is always possible.

Toxicokinetics

Oral administration of acetamide in the rat is followed by absorption and 62% is excreted into the urine unchanged in 24 h. Likewise, a large proportion of an oral dose is excreted in the urine unchanged by the dog and cat. In sheep, absorption of an oral dose is followed by metabolism to CO_2 within 7–12 h. Sequential demethylation of methylacetamide results in acetamide production by rat liver but it is not clear whether this occurs in man. Acetamide is a metabolite of the antiprotozoal drugs metronidazole and ornidazole.

Mechanism of Toxicity

The mechanism of toxicity of acetamide is not known; the response profile is quite different from the better studied dimethyl derivative.

Acute and Short-Term Toxicity (or Exposure)

Animal

The oral LD_{50} in rodents ranges from 1 to 7 g kg^{-1} and intravenous LD_{50} in mice and rats is 10 g kg^{-1}. No acute lethality information is available following either dermal or inhalation exposures. Acetamide is not a developmental toxicant and is generally inactive in genetic toxicity tests.

Human

No reports could be found in the literature concerning acute toxicity of acetamide in humans.

Chronic Toxicity (or Exposure)

Animal

Liver cancers were produced in rats following oral administration of relatively large amounts of acetamide. The liver appears to be the target of acetamide toxicity although the animal experiments have been limited in the range of endpoints studied.

Human

No reports could be found in the literature concerning the potential human health effects of chronic acetamide exposure.

Clinical Management

Exposed persons should be removed to fresh air and medical attention sought as needed for any breathing difficulty. If swallowed, several glasses of water should be given to dilute the chemical; medical attention is needed if large amounts are ingested. For skin contact, the exposed area should be washed with soap and water; medical attention should be sought if irritation develops. For eye contact, water should be used to flush for at least 15 min while lifting the lower and upper eyelids occasionally; immediate medical attention should be sought.

Environmental Fate

Acetamide will exist as a vapor in the ambient atmosphere. Atmospheric degradation occurs by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 7.6 days. If released to soil, acetamide is expected to have very high mobility and is not expected to adsorb to suspended solids and sediment. Experiments suggest that this chemical may break down in the environment through biodegradation and not through hydrolysis. Volatilization from water surfaces is not expected to be an important fate process based on this compound's estimated Henry's law constant. The potential for bioconcentration in aquatic organisms is low.

Exposure Standards and Guidelines

US Environmental Protection Agency: Listed as a hazardous air pollutant under the Clean Air Act of 1990.

Occupational Safety and Health Administration: No permissible exposure limit (as of October 2003).

International Agency for Research on Cancer: Classified as a 2B carcinogen (probable human carcinogen with sufficient evidence in laboratory animals).

See also: Clean Air Act (CAA), US; Methylamine; Metronidazole; Thioacetamide.

Further Reading

Kennedy GL Jr. (1986) Biological effects of acetamide, formamide, and their monomethyl and dimethyl derivatives. *Critical Reviews in Toxicology* 17: 129–182.

Kennedy GL Jr. (2001) Biological effects of acetamide, formamide, and their monomethyl and dimethyl derivatives: An update. *Critical Reviews in Toxicology* 31: 139–222.

Relevant Website

http://toxnet.nlm.nih.gov – TOXNET, Specialized Information Services, National Library of Medicine. Search for Acetamide.

Acetaminophen

Kartik Shankar and Harihara M Mehendale

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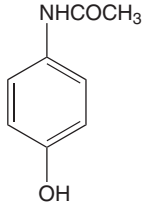
- Chemical Abstracts Service Registry Number: CAS 103-90-2
- Synonyms: APAP; 4′-Hydroxyacetanilide; *p*-Hydroxyacetanilide; Acetamide *N*-(4-hydroxyphenyl); *N*-Acetyl-*p*-aminophenol; *N*-Acetyl-*p*-aminophenol; *p*-Acetamidophenol; 4-Acetamidophenol; 4-Acetaminophenol; Paracetamol; Tylenol
- Chemical/Pharmaceutical/Other Class: Acetaminophen is a synthetic nonopioid congener of acetanilide in the *p*-aminophenol class
- Chemical Formula: $C_8H_9NO_2$
- Chemical Structure:



Uses

Acetaminophen is a nonnarcotic analgesic and antipyretic drug. It is used to relieve pain of moderate intensity, such as usually occurs in headache and in many muscle, joint, and peripheral nerve disorders. Headaches are one of the most common indications for the use of acetaminophen. Acetaminophen is used to treat acute tension-headaches and mild to moderate

migraine, especially in combination with caffeine and aspirin. Acetaminophen is indicated in chronic pain associated with rheumatoid arthritis, back or hip pain, osteoarthritis, dental pain, or acute pain due to soft-tissue injury. Acetaminophen is a suitable substitute for aspirin for its analgesic or antipyretic uses in cases where aspirin is contraindicated (gastric bleeding) or when the prolongation of bleeding time caused by aspirin would be a disadvantage. Acetaminophen has been used in studies of pain relief following obstetric and gynecological procedures including Caesarean section, hysterectomy, tubal ligation, primary dysmenorrhoea, and termination of pregnancy. Acetaminophen is also used to manage chronic pain of cancer, postpartum and postoperative pain after minor surgery. In a double blind crossover study, the analgesic oral butorphanol and acetaminophen in combination, showed additive analgesic effects against moderate to severe pain due to metastatic carcinoma over that of individual drug. Acetaminophen is also widely used as an antipyretic drug to reduce fever.

Background Information

Acetaminophen can be found as the active ingredient in more than 100 over-the-counter products and a number of prescription drugs, alone or in combination with other drugs. The pharmacology and toxicology of this drug has been extensively studied and reviewed. Acetaminophen has been the subject of more than 30 000 articles in medical literature since 1966. The first clinical use of acetaminophen dates back to 1893 by von Mering (and subsequently by Hinsberg and Treupel, 1894) as an effective antipyretic with comparable pharmacological effects to antipyrine and phenacetin. However, after a hiatus of almost half a century, acetaminophen was rediscovered as the major metabolite of phenacetin and acetanilide in man and was marketed in the United States as a combination with aspirin and caffeine in 1950. In the 1960s and 1970s concerns about gastrointestinal adverse effects of aspirin and methemoglobinemia of acetanilide only led to increased popularity of acetaminophen as a generally safe antipyretic analgesic. Hepatotoxicity of acetaminophen began to be reported in the late 1960s and has been a topic of intense scientific evaluation to this day. The impact of acetaminophen-induced liver toxicity, accidental or otherwise, will be taken up in later sections.

Exposure Routes and Pathways

Acetaminophen is available in several dosage forms including tablets, capsules, syrups, elixirs, and suppositories. Oral ingestion is the most common route for both accidental and intentional exposure to acetaminophen.

Toxicokinetics

Absorption of acetaminophen occurs in the gastrointestinal tract primarily by passive nonionic diffusion and is highly dependent on the several factors including dose, presence of food and other chemicals, mucosal blood flow, age, body weight, time of day, and coexisting disease conditions. At pharmacological doses acetaminophen is absorbed rapidly with $\sim$75–95% of the therapeutic oral dose being recovered in the urine by 12–24 h as unchanged acetaminophen or metabolite. A large number of studies have evaluated the pharmacokinetic parameters of acetaminophen in man after oral or intravenous dosing. Most studies consistently report volume of distribution to be between 0.8 and 1 l kg^{-1}. Total clearance and plasma half-life with therapeutic doses in healthy subjects were usually 3–5 ml min kg^{-1} and 1–3 h, respectively. After suprapharmacological or toxic doses absorption may be delayed after producing peak blood concentrations at $\sim$4 h postingestion. In man, the majority of acetaminophen is metabolized in the liver to glucuronide and sulfate conjugates that are eliminated in the urine. Estimates in man from urinary metabolites report 50–60% as glucuronide conjugate, 25–35% as sulfate conjugate, and between 2% and 5% of cysteine and mercapturate conjugates each. In young children, the sulfate conjugate predominates. The water-soluble glucuronide and sulfate conjugates are eliminated via the kidneys. Approximately 2–5% is eliminated in the urine as unchanged acetaminophen. The half-life of therapeutic dose is 1–3 h. In overdose patients, this may be increased to more than 4 h and may even exceed 12 h in patients with severe acetaminophen-induced liver toxicity.

Mechanism of Toxicity

Although major part of the ingested dose of acetaminophen is detoxified, a very small proportion of acetaminophen is metabolized via the cytochrome P450-mixed function oxidase pathway to a highly reactive *N*-acetyl-*p*-benzoquinoneimine (NAPQI). The toxic intermediate NAPQI is normally detoxified by endogenous glutathione to cysteine and mercapturic acid conjugates and excreted in the urine. Recent studies have shown that hepatic P450 s, CYP2E1 and, to a lesser extent CYP1A2 are responsible for conversion of acetaminophen to NAPQI. In acetaminophen overdosage, the amount of NAPQI

increases and depletes endogenous glutathione stores. Time course studies have shown that covalent binding of reactive NAPQI and subsequent toxicity occurs only after cellular glutathione stores are reduced by 70% or more of normal. Mitochondrial dysfunction and damage can be seen as early as 15 min after a toxic dose in mice, suggesting that this may be a critical to cellular necrosis. The NAPQI is then thought to covalently bind to critical cellular macromolecules in hepatocytes and cause cell death. Recent proteomic studies have identified at least 20 known proteins that are covalently modified by the reactive acetaminophen metabolite. Hepatic necrosis as a consequence of hepatocellular death then results in development of clinical and laboratory findings consistent with liver failure. A similar mechanism is postulated for the renal damage that occurs in some patients who suffer from acetaminophen toxicity.

Acute and Short-Term Toxicity (or Exposure)

Animal

A large body of evidence is available examining the acute toxicity of acetaminophen in animal models. Mice and rats have been widely used to study the toxic effects of acetaminophen. Since the rat is relatively resistant, the mouse has been the most widely used species to study both the mechanisms of acetaminophen toxicity and to examine chemicals that potentiate or protect from the toxicity. Hepatotoxicity and nephrotoxicity are the two main effects associated with acute overdose of acetaminophen. Of these, death in most species is due to acute hepatic failure. LD_{50} values range from 350 to 4500 mg kg^{-1} depending on the species and the route of acetaminophen administration, mice (LD_{50} 350–600 mg kg^{-1}) being more far more sensitive than rats, guinea pigs, and rabbits ($LD_{50} > 3$ g kg^{-1}). Death occurs within 12 h after acetaminophen exposure. In mice after a toxic dose, general findings in addition to the severe hepatic necrosis, include necrotic changes in the kidney, bronchiolar epithelium, testes, lymphoid follicles of the spleen, and small intestine. Cats are particularly susceptible to acetaminophen intoxication because of their impaired glucuronic acid conjugation mechanism and saturation of their sulfate conjugation pathway. The clinical signs associated with experimental acetaminophen administration to cats included cyanosis followed by anemic hemoglobinuria, icterus, and facial edema. Laboratory findings in acetaminophen poisoned cats include methemoglobinemia and an elevated serum alanine aminotransferase activity.

Human

Hepatotoxicity is the primary toxic insult from acute acetaminophen overdose. Acetaminophen overdose accounts for more than 56 000 emergency room visits and is implicated in ~50% of all acute liver failure in the United States (US Acute Liver Failure (ALF) Study Group). Exposure to toxic doses of acetaminophen may be intentional (suicidal) or unintentional (accidental). Recent data from Parkland Hospital suggests that greater percentages of unintentional overdose victims suffer from fatal consequences compared to persons attempting suicide (with acetaminophen) primarily due to their characteristic late presentation. Data from the US ALF Study Group shows that unintentional overdoses (which are more frequent in liver failure cases) were also larger (median dose of 34 g) compared to suicidal doses, being consumed over several preceding days. There is no clear agreement on a maximum tolerated dose of acetaminophen. Most people tolerate 4–8 g day^{-1} of acetaminophen without any hepatotoxic incidence. However, the risk of severe liver injury may be quite high above the 4 g day^{-1} dose, especially in a group of individuals due to indeterminate idiosyncratic reasons.

The typical clinical manifestations are secondary to hepatic damage. Plasma concentrations should be obtained to determine the probability of acetaminophen-induced hepatotoxicity. The Rumack–Matthews nomogram is used to assess the risk of hepatotoxicity. Levels in excess of 200 μg ml^{-1} of acetaminophen at 4 h postingestion are associated with high probability of development of hepatotoxicity. A second treatment line 25% lower than the original '200' line was added at the request of the Food and Drug Administration (FDA) in 1976. The clinical presentation follows four distinct phases. Gastrointestinal irritation, nausea and vomiting are present in the first 24 h postingestion. The second stage (24–48 h) postingestion is characterized by the resolution of the initial symptoms, accompanied by elevations of hepatic transaminases. Cases that progress to stage three develop hypoglycemia, coagulopathies, jaundice, and symptoms consistent with hepatic failure. Surviving patients go through a fourth stage of recovery. As toxicity develops half-life becomes prolonged and transaminases rise and fall. In instances where reliable history of time of ingestion is not available calculations of body burden may be useful in deciding treatment.

Chronic Toxicity (or Exposure)

Animal

In a 2 year feed study, there was no evidence of carcinogenic activity of acetaminophen in male F344/N

rats that received 600, 3000, or 6000 ppm acetaminophen for 104 weeks. There was equivocal evidence of carcinogenic activity in female F344/N rats based on increased incidences of mononuclear cell leukemia. Overall, there is inadequate evidence in experimental animals for the carcinogenicity of acetaminophen and is not classifiable as to its carcinogenicity. Acetaminophen was nonmutagenic in the *Salmonella*/mammalian microsome assay at concentrations ranging from 0.1 to 50 mg per plate. In a study to examine effect of acetaminophen on reproduction and fertility, no changes in the number of pups/litter, viability, or in adjusted pup weight were found. Acetaminophen in the diet of Swiss mice reduced weight gain during nursing. Fertility endpoints (ability to bear normal numbers of normal-weight young) were generally not affected.

Human

There is inadequate evidence in humans for the carcinogenicity of acetaminophen and is therefore not classifiable. The chronic ingestion of excessive amounts of acetaminophen may produce similar toxicity as a large acute dose but in a more insidious fashion. Age, chronic alcohol abuse, and preexisting disease may be contributing factors. The American Academy of Pediatrics considers use of acetaminophen safe during breast-feeding and is classified as a category B chemical by the FDA (studies in laboratory animals have not demonstrated a fetal risk, but there are no controlled studies in pregnant women). Acetaminophen should be given with care to patients with impaired kidney or liver function. Care should also be taken when giving acetaminophen to patients taking other drugs that affect the liver.

In Vitro Toxicity Data

Acetaminophen causes cytotoxicity in several cell types; however, the most widely studied cytotoxicity of acetaminophen is in primary hepatocytes or hepatocyte cell lines.

Cytotoxicity in Hepatic Cells

Primary hepatocytes from rats, mice, hamsters, rabbits, dogs, pigs, monkeys, and humans have been shown to be susceptible to acetaminophen *in vitro*. The cytotoxicity of acetaminophen varies considerably depending on species, presumably due to differences in bioactivation and glutathione status. The most obvious morphological effect of acetaminophen in isolated primary hepatocytes is blebbing of the cell membrane. However, electron microscopy has shown that toxicity is associated with progressive loss of microvilli, mitochondrial abnormalities and appearance of myeloid bodies. Exposure of primary mouse hepatocytes to concentrations of acetaminophen above 1 mmol l^{-1}, led to significant lactate dehydrogenase leakage as early as 3 h. Cytotoxicity of acetaminophen has also been examined using standard liver cell lines including, PC12 cells, HepG2 cells, H4IIEC3G$^-$ cells, among other cell lines. Immortalized hepatocyte cultures, in many cases, lose their ability to bioactivate acetaminophen and hence are resistant to toxicity. Transient or consistent overexpression of P450 enzymes (CYP2E1 and/or CYP1A2) leads to increased cytotoxicity of acetaminophen. Acetaminophen is also cytotoxic in cultures of rat liver sinusoidal endothelial cells, Kupffer cells and mouse fibroblasts.

Cytotoxicity in Other Cells

The cytotoxicity of acetaminophen has been demonstrated in cultures of HeLa cells, L929 and 3T3 murine fibroblasts, chick embryo neurons, rat embryonic and skeletal muscle, peripheral blood lymphocytes, and lung and dermal cells. In addition cytotoxicity of acetaminophen has been evaluated in BF-2 fish cell line (see section on 'Ecotoxicology').

Clinical Management

Activated charcoal or other gastrointestinal decontamination procedures can be utilized when deemed necessary. Induction of emesis is not recommended as prolonged emesis may interfere with *N*-acetyl cysteine (NAC) therapy. The Rumack–Matthews nomogram is utilized to identify proper course of treatment. Blood acetaminophen concentrations of 200 mg l^{-1} (or higher) at 4 h postingestion indicate severe risk of hepatic failure and are treated with standard NAC treatment regimen. NAC is a glutathione substitute and prevents hepatic damage by quenching the reactive NAPQI. An oral loading dose of 140 mg kg^{-1} (as a 5% solution in soft drink or juice) is followed by 70 mg kg^{-1} given orally as a (5% solution in soft drink or juice) every 4 h for an additional 17 doses. An alternative intravenous dosing protocol (20 h regimen) for NAC (Acetadote) can also be used in patients where oral NAC administration is not possible. A loading dose of 150 mg kg^{-1} NAC (in 200 ml of 5% dextrose in water) is administered over 15 min, followed by 50 mg kg^{-1} NAC (in 500 ml of 5% dextrose) over the next 4 h. A final dose of 100 mg kg^{-1} NAC is administered in 1000 ml of 5% dextrose over a 16 h period. A longer 72 h treatment regimen with intravenous NAC is recommended in the United States.