MACMILLAN DICTIONARY OF TOXICOLOGY

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Ernest Hodgson
Richard B. Mailman
Janice E. Chambers

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Preface

The first edition of a reference work, especially in a field where no comparable work exists, represents an enormous investment of time, energy and enthusiasm. Despite a desire to continually refine and improve the end product, practical considerations (including the need to conserve the editors' resources) demand a stopping point. Thus, although we hope that this volume is a useful addition to the literature of toxicology, we are aware of its imperfect nature.

In this vein, we welcome both corrections and additions from our readers. This can include completed new entries, suggestions for additional entries, cross-references and corrections or comments about existing entries. The critical input from friends and colleagues will ensure that subsequent editions will be more comprehensive, more accurate and, above all, more useful than the first. Additional or alternative entries should be prepared in the format of the existing ones, and communicated (with the name and affiliation of the preparer) to any of the three editors, whose complete addresses are shown in the list of contributors.

In conclusion, we would like to thank all of our contributors, as well as colleagues who assisted in many different ways. Particular thanks are due to Karen Clark of North Carolina State University, who edited many entries and entered them into the computer data base, and to Theresa Brooks of the University of North Carolina at Chapel Hill, who made many important contributions towards the preparation of the final document. The editors also wish to thank the members of Toxicology Programs at these two universities, who were particularly generous with their time. Besides offering our appreciation to Macmillan Press for bringing this project to fruition, special thanks must be given to Rosemary Foster. Her patience and good humor in the face of several unmet deadlines was as important to us as her skillful guidance.

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August 1987

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Introduction

Entries in a technical directory are neither intended for, nor often used by, specialists needing information related to the research areas in which they are expert. In fact, such scientists are usually quite capable of writing these items or, at the very least, will have no need to read them. However, from time to time, most of us require information that, although within the scope of the science of toxicology, is somewhat removed from our own specialties. An encyclopedia or dictionary (such as this volume) should offer a starting point for such needs. Of greater importance may be the goal of bringing to graduate and undergraduate students, and to scientists in other disciplines, the terms and concepts of toxicology. The entries in this volume, and their cross-references, should form for such individuals a useful starting point, with the list of general references providing further information and serving as a bridge to the research literature. Although many of the entries in this volume are directly related to the broad vista encompassed by toxicology, others (particularly certain anatomical, biochemical, pathological and physiological terms) are provided to give background information that a toxicologist (neophyte or otherwise) might require. Such entries stress the relationship to toxicology, rather than their importance to the discipline from which they are drawn.

To assist in making additions and corrections, the entries in this dictionary were entered into a microcomputer data base, and they then provided to the publisher on magnetic media for computer-based typesetting. The available technology should facilitate revisions, and as noted in the preface, we welcome such input from other toxicologists. It is our intent to update the data continually and to provide revised text for subsequent editions whenever the changes are extensive enough to so justify.

A word about the choice of spelling may be appropriate. Although Macmillan Press is based in the UK, we have resolved the issue of British versus American spelling in favor of the latter. We feel that arguments about this subject generate more heat than light, and we were influenced to use American spelling primarily because of the national origin of the editors. In those cases in which the difference would affect the alphabetized position of the entry (e.g., oestrus versus estrus; haem versus heme), we have included the British spelling as a cross-reference.

Finally, the list of general references is not intended to be exhaustive. The selection is quite arbitrary, the list being intended only as a source of further information on subjects mentioned in the dictionary entries. Other excellent works could be added, and the list will be revised in subsequent editions.

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A

AAALAC. *See* AMERICAN ASSOCIATION FOR ACCREDITATION OF LABORATORY ANIMAL CARE.

AAG. *See* α_1-ACID GLYCOPROTEIN.

AAS. *See* SPECTROMETRY, ATOMIC ABSORPTION.

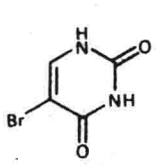
Abakabi disease. *See* TRICOTHECENES.

ABCW extrapolation. A method for extrapolating germ cell mutation tests from species to species. The name is derived from the authors of the initial paper (Abrahamson, Bender, Conger & Wolf *Nature* **245**, 461 (1973)). Based on the results of published studies on the effects of ionizing radiation, the extrapolation is performed by normalizing the mutation rate to the amount of DNA in the haploid genome of the species in question. Attempts to extend the ABCW hypothesis to chemical mutagens have been less successful, and the original hypothesis has been challenged even with regard to ionizing radiation. It appears that this extrapolation is of considerable historical importance and is useful for qualitative assessments, but it is not appropriate for quantitative extrapolations. *See also* EXTRAPOLATION; EXTRAPOLATION, TO MAN; SPECIES EXTRAPOLATION.

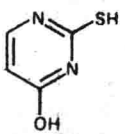
EH

abnormal base analogs. Exogenous (xenobiotic) analogs of the bases normally found in DNA. They are potent mutagens and many were originally developed as drugs for cancer therapy. As anticancer drugs their effectiveness is due to their ability to produce lethal mutations in rapidly dividing cancer cells. 5-Bromouracil, 5-fluorouridine, 2-aminopurine and 6-mercaptopurine are examples of mutagenic base analogs. Incorporation into DNA results in mispairing during the next replication cycle, giving rise to altered (mutant) DNA. Since these chemicals are mutagens and carcinogens, the toxic hazard attendant upon their use is high; however, the life-threatening nature of the disease justifies the use of drugs with a small therapeutic index. *See also* CARCINOGENESIS; DNA; 6-MERCAPTOPURINE; MUTATION; THERAPEUTIC INDEX.

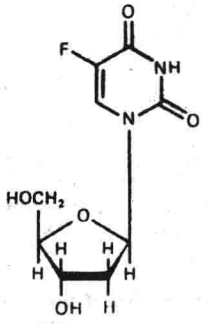
EH



bromouracil



2-thiouracil



5-fluorodeoxyuridine (floxuridine)

abnormal development, consequences. Death, malformation, growth retardation or functional disorder can occur. The embryo is not usually damaged by most agents, prior to differentiation; however, a sufficiently high dose may result in death of the embryo. The time of organogenesis is the most sensitive time for induction of specific malformations, whereas structural defects at the tissue level, growth retardation or functional deficits are most likely to occur after damage during the fetal period. Structural defects are the main criterion used in estimating teratological risks since they are more obvious. However, functional disorders may be as incapacitating and result in as great a mortality rate among offspring as morphological abnormalities. *See also* TERATOGENESIS, CRITICAL PERIOD.

PEL

ABP. *See* ANDROGEN-BINDING PROTEIN.

ABPI. *See* ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY.

abrin (toxalbumin). A lectin composed of two polypeptide chains connected by a disulfide bridge. It is nearly identical to the toxin produced by the castor bean (*Ricinus communis*). Abrin is found in the seed of the rosary pea (*Abrus precatorius*). It is a common vine of the tropics, including central and southern Florida. The LD_{50} in mice is 0.02 mg/kg, i.p. Ingestion of one chewed or broken seed can cause fatal poisoning. It is a gastrointestinal toxin; one of the polypeptide chains binds to the intestinal cell membrane, allowing the other chain to enter the cytoplasm. Ribosomal protein synthesis is inhibited, resulting in cell death. Diarrhea associated with bloody mucus may begin as late as three days following ingestion of seeds with broken seed coats. Death may occur due to loss of intestinal function and consequent alterations in plasma composition leading to secondary cerebral edema and cardiac arrhythmia. Therapy for acute poisoning is to correct hypovolemia and electrolyte balance. *See also* CASTOR BEAN; LECTINS; RICIN.

BEM

absorption of toxicants. The processes involved in the movement of the toxicant from the exterior or the lumen of the portal of entry (i.e. skin, respiratory system or gastrointestinal tract) to the circulatory system (generally the blood, but not excluding the lymphatic system). Absorption of toxicants is generally a passive process, dependent upon the lipophilicity of the toxicant, but, in some cases, it involves active or facilitated transport. *See also* ACTIVE TRANSPORT; ENTRY MECHANISMS, ENDOCYTOSIS; ENTRY MECHANISMS, FILTRATION; ENTRY MECHANISMS, PASSIVE TRANSPORT; ENTRY MECHANISMS, SPECIAL TRANSPORT; FACILITATED TRANSPORT; PENETRATION; PENETRATION ROUTES, DERMAL; PENETRATION ROUTES, GASTROINTESTINAL; PENETRATION ROUTES, PULMONARY; PERCUTANEOUS ABSORPTION.

EH

acaricides. Pesticides with specificity for mites, typically phytophagous mites in contrast to parasitic mites. A number of insecticides also display acaricidal activity. The acaricides include a diverse array of chemical structures. Common examples are dicofol and chlorobenzilate. *See also* DICOFOL.

HC

Acarin. *See* DICOFOL.

acceptable daily intake (ADI). The amount of a chemical (usually restricted to pesticides and food additives) that can be ingested daily, by humans, for an entire life-time without causing appreciable adverse effects; it is expressed in mg/kg body weight/day. The ADI is obtained by dividing the no observed effect level (NOEL) by a safety factor (e.g., 10, 100 or 1000) that is intended to make allowance for possible differences in sensitivity between the animal test species and humans, as well as for interindividual variations within the human population. The term ADI was first used by the Joint FAO/WHO Expert Committee on Food Additives in 1961 and subsequently was adopted by the Joint FAO/WHO Expert Committee on Pesticide Residues (1962). The ADI constitutes a useful regulatory bench-mark that is employed by international (e.g., FAO/WHO) and national (e.g., EPA, UK Advisory Committee on Pesticides and Other Toxic Chemicals) agencies for establishing tolerances for pesticide residues in raw agricultural and other commodities and for developing health advisory guidelines for such residues in potable water. *See also* NO OBSERVED EFFECT LEVEL; SAFETY FACTOR.

CW

accessory cells of immune system. *See* IMMUNE SYSTEM; MACROPHAGES/MONOCYTES.

accessory cells of testis. *See* SERTOLI CELLS.

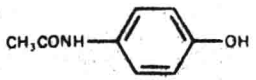
acetaldehyde (ethanal; ethylaldehyde; acetic aldehyde). An organic compound used in the manufacture of paraldehyde, acetic acid, butanol, aniline dyes, synthetic rubber and in the silvering of mirrors. It is also used in trace quantities in artificial flavors. It is produced physiologically in individuals taking disulfiram who have also ingested ethanol. The oral LD_{50} in rats is 1930 mg/kg and the inhalatory LD_{50} in rats is 4000 ppm/4 hr. The primary toxic action is as an irritant. Acetaldehyde interferes with mitochondrial oxygen consumption and energy production in rat liver. After inhalation, it causes irritation, nausea and vomiting. Skin and eye

contact results in a burning sensation and severe irritation. The therapy after inhalation is to remove the victim to fresh air and give artificial respiration if breathing has stopped. Following eye contact, the eyes should be flushed with water; following skin contact, the skin should be washed with soap and water. *See also* DISULFIRAM. BM

CH_3CHO

acetaldehyde

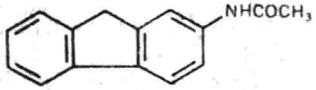
acetaminophen (*N*-(4-hydroxyphenyl)acetamide; paracetamol; Datril; Panadol; Tylenol). An analgesic and antipyretic drug. It is also used in the manufacture of azo dyes and photographic chemicals. The oral LD_{50} in mice is 338 mg/kg and the i.p. LD_{50} is 500 mg/kg. Acetaminophen is an hepatotoxicant at high doses due to its metabolism to a toxic intermediate by cytochrome P-450. The proposed toxic metabolite is acetimidoquinone. Following an overdose, detoxification by glutathione conjugation is saturated, leading to an increase in the concentration of the toxic metabolite which, in turn, binds to various hepatocellular constituents. Within hours sweating, anorexia, nausea and vomiting develop. In three to five days, jaundice, coagulation defects, hypoglycemia, renal failure and myocardiopathy may occur. If given within 12 hours of ingestion of an acetaminophen overdose, *N*-acetylcysteine appears to be effective in blocking the covalent binding of the toxic metabolite and the prevention of hepatotoxicity. Hinson, J.A. *Rev. Biochem. Toxicol.* **2**, 103–129 (1980). SC



acetaminophen

acetonylacetone. *See* 2,5-HEXANEDIONE.

***N*-2-acetylaminofluorene.** Originally developed as an insecticide. Due to its effect as a potent bladder carcinogen, it is of importance as a model compound that has been studied intensively with regard to metabolic activation as a carcinogen and hepatotoxicant and the role of its metabolites in the subsequent processes of carcinogenesis. The primary metabolism of *N*-2-acetylaminofluorene is monooxygenation catalyzed by cytochrome P-450. The reactions involved are either aromatic hydroxylation (a detoxication reaction) or *N*-hydroxylation (an activation). Interspecies variations in the cytochrome P-450 isozymes catalyzing these reactions are held to explain interspecies differences in carcinogenic susceptibility. Subsequent phase II reactions, sulfate ester formation, acetylation and glucuronidation, yield reactive metabolites that can react with nucleophilic substitutents on nucleic acids and proteins. Adducts of *N*-2-acetylaminofluorene with DNA bases (particularly the C-8 of guanine) have been identified. *See also* PHASE I REACTIONS; PHASE II REACTIONS. EH



N-2- acetylaminofluorene

acetylation. Acetylated derivatives of foreign exogenous amines are formed by *N*-acetyltransferase, an enzyme that utilizes acetyl CoA as the acetyl donor. This cytosolic enzyme has been purified from rat liver, but is known to occur in several organs, probably in multiple isozymic forms. Although a variety of groups on endogenous substrates may be acetylated, in xenobiotics only amino groups appear to function as acetyl group acceptors. Newborn mammals generally have low levels of the transferase activity, whereas genetically determined fast and slow acetylators occur in both rabbit and human populations. Slow acetylators are more susceptible to the effects of compounds detoxified by acetylation. The *N*-acetyltransferase(s) responsible for the acetylation of *S*-substituted cysteines, the last step in mercapturic acid formation, is found in the microsomes of kidney and liver. It is specific for acetyl CoA as the acetyl donor and is distinguished from other *N*-acetyltransferases by substrate specificity and subcellular location. *See also* ACYLATION; FAST AND SLOW ACETYLATORS. EH

acetylcholine (ACh). The choline ester of acetic acid. ACh is released in vertebrates as the neurotransmitter for cholinergic neurons