GLOSSARY

acceptable daily intake (ADI) Amount of exposure determined to be "safe"; usually derived from the lowest No Effect Level in an experimental study, divided by a safety factor such as 100. Also known as the Reference Dose (RfD).

acetylation The addition of an acetyl group from acetyl coenzyme A to a xenobiotic or xenobiotic metabolite by the enzyme *N*-acetyltransferase. Polymorphisms in this enzyme can be important in the expression of toxicity in humans.

acetylator phenotype Variation in the expression of *N*-acetyltransferase isoforms in humans gives rise to two subpopulations—fast and slow acetylators. Slow acetylators are more susceptible to the toxic effects of toxicants that are detoxified by acetylation.

acid deposition Wet and dry air pollutants that lower the pH of deposition and subsequently the pH of the environment. Acid rain with a pH of 4 or lower refers to the wet components. Normal rain has a pH of about 5.6. Sulfuric acid from sulfur and nitric acid from nitrogen oxides are the major contributors. In lakes in which the buffering capacity is low, the pH becomes acidic enough to cause fish kills, and the lakes cannot support fish populations. A contributing factor is the fact that acidic conditions concurrently release toxic metals, such as aluminum, into the water.

activation (bioactivation) In toxicology, this term is used to describe metabolic reactions of a xenobiotic in which the product is more toxic than is the substrate. Such reactions are most commonly monooxygenations, the products of which are electrophiles that, if not detoxified by Phase II (conjugation) reactions, may react with nucleophilic groups on cellular macromolecules such as proteins and DNA.

active oxygen Term used to describe various short-lived highly reactive intermediates in the reduction of oxygen. Active oxygen species such as superoxide anion and hydroxyl radical are known or believed to be involved in several toxic actions. Superoxide anion is detoxified by superoxide dismutase.

acute toxicity tests The most common tests for acute toxicity are the LC_{50} and LD_{50} tests, which are designed to measure mortality in response to an acute toxic insult. Other tests for acute toxicity include dermal irritation tests, dermal sensitization tests, eye irritation tests, photoallergy tests, and phototoxicity tests. *See also* eye irritation tests; LC_{50}; and LD_{50}.

acute toxicity Refers to adverse effects on, or mortality of, organisms following soon after a brief exposure to a chemical agent. Either a single exposure or multiple exposures within a short time period may be involved, and an acute

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effect is generally regarded as an effect that occurs within the first few days after exposure, usually less than 2 weeks.

adaptation to toxicants Refers to the ability of an organism to show insensitivity or decreased sensitivity to a chemical that normally causes deleterious effects. The terms resistance and tolerance are closely related and have been used in several different ways. However, a consensus is emerging to use the term *resistance* to mean that situation in which a change in the genetic constitution of a population in response to the stressor chemical enables a greater number of individuals to resist the toxic action than were able to resist it in the previous unexposed population. Thus, an essential feature of resistance is selection and then inheritance by subsequent generations. In microorganisms, this frequently involves mutations and induction of enzymes by the toxicant; in higher organisms, it usually involves selection for genes already present in the population at low frequency. The term *tolerance* is then reserved for situations in which individual organisms acquire the ability to resist the effect of a toxicant, usually as a result of prior exposure.

Ah locus A gene(s) controlling the trait of responsiveness for induction of enzymes by aromatic hydrocarbons. In addition to aromatic hydrocarbons such as the polycyclics, the chlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls, as well as the brominated biphenyls, are also involved. This trait, originally defined by studies of induction of hepatic aryl hydrocarbon hydroxylase activity following 3-methylcholanthrene treatment, is inherited by simple autosomal dominance in crosses and backcrosses between C57BL/6 (Ah-responsive) and DBA/2 (Ah-nonresponsive) mice.

Ah receptor (AhR) A protein coded for by a gene of the Ah locus. The initial location of the Ah receptor is believed to be in the cytosol and, after binding to a ligand such as TCDD, is transported to the nucleus. Binding of aromatic hydrocarbons to the Ah receptor of mice is a prerequisite for the induction of many xenobiotic-metabolizing enzymes, as well as for two responses to TCDD: epidermal hyperplasia and thymic atrophy. Ah responsive mice have a high-affinity receptor, whereas the Ah-nonresponsive mice have a low-affinity receptor.

air pollution In general, the principal air pollutants are carbon monoxide, oxides of nitrogen, oxides of sulfur, hydrocarbons, and particulates. The principal sources are transportation, industrial processes, electric power generation, and the heating of buildings. Hydrocarbons such as benzo(a)pyrene are produced by incomplete combustion and are associated primarily with the automobile. They are usually not present at levels high enough to cause direct toxic effects but are important in the formation of photochemical air pollution, formed as a result of interactions between oxides of nitrogen and hydrocarbons in the presence of ultraviolet light, giving rise to lung irritants such as peroxyacetyl nitrate, acrolein, and formaldehyde. Particulates are a heterogeneous group of particles, often seen as smoke, that are important as carriers of absorbed hydrocarbons and as irritants to the respiratory system.

alkylating agents These are chemicals that can add alkyl groups to DNA, a reaction that can result either in mispairing of bases or in chromosome breaks. The mechanism of the reaction involves the formation of a reactive carbonium ion that combines with electron-rich bases in DNA. Thus, alkylating agents such as dimethylnitrosomine are frequently carcinogens and/or mutagens.

Ames test An *in vitro* test for mutagenicity utilizing mutant strains of the bacterium *Salmonella typhimurium*, which is used as a preliminary screen of chemicals for assessing potential carcinogenicity. Several strains are available that cannot grow in the absence of histidine because of metabolic defects in histidine biosynthesis. Mutagens and presumed carcinogens can cause mutations that enable the strains to regain their ability to grow in a histidine-deficient medium. The test can be performed in the presence of the *S*-9 fraction from rat liver to allow the metabolic activation of promutagens. There is a high correlation between bacterial mutagenicity and carcinogenicity of chemicals.

antagonism In toxicology, antagonism is usually defined as that situation in which the toxicity to two or more compounds administered together is less than that expected from consideration of their toxicities when administered alone. Although this includes lowered toxicity resulting from induction of detoxifying enzymes, this is frequently considered separately because of the time that must elapse between treatment with the inducer and subsequent treatment with the toxicant. Antagonism not involving induction is often at a marginal level of detection and is consequently difficult to explain. Such antagonism may involve competition for receptor sites or nonenzymatic combination of one toxicant with another to reduce the toxic effect. Physiological antagonism, in which two agonists act on the same physiological system but produce opposite effects, may also occur.

antibody A large protein first expressed on the surface of the B cells of the immune system, followed by a series of events resulting in a clone of plasma cells that secrete the antibody into body fluids. Antibodies bind to the substance (generally a protein) that stimulated their production but may cross-react with related proteins. The natural function is to bind foreign substances such as microbes or microbial products but, because of their specificity, antibodies are used extensively in research and in diagnostic and therapeutic procedures.

antidote A compound administered in order to reverse the harmful effect(s) of a toxicant. They may be toxic mechanism specific, as in the case of 2-pyridine aldoxime (2-PAM) and organophosphate poisoning, or nonspecific, as in the case of syrup of ipecac, used to induce vomiting and, thereby, elimination of toxicants from the stomach.

behavioral toxicity Behavior may be defined as an organism's motor or glandular response to changes in its internal or external environment. Such changes may be simple or highly complex, innate or learned, but in any event represent one of the final integrated expressions of nervous system function. Behavioral toxicity is adverse or potentially adverse effects on such expression brought about by exogenous chemicals.

binding, covalent *See* covalent binding.

bioaccumulation The accumulation of a chemical either from the medium (usually water) directly or from consumption of food containing the chemical. Biomagnification is often used as a synonym for bioaccumulation, but is more correctly used to describe an increase in concentration of a chemical as it passes from organisms at one tropic level to organisms at higher tropic levels.

bioactivation *See* activation.

bioassay This term is used in two distinct ways. The first and most appropriate is the use of a living organism to measure the amount of a toxicant present in a

sample or the toxicity of a sample. This is done by comparing the toxic effect of the sample with that of a graded series of concentrations of a known standard. The second and less appropriate meaning is the use of animals to investigate the toxic effects of chemicals as in chronic toxicity tests.

bioinformatics In the narrow and original meaning, bioinformatics was the application of information technology to molecular biology. While this is still the most important aspect of bioinformatics, it is increasingly applied to other fields of biology, including molecular and other aspects of toxicology. It is characterized by computationally intensive methodology and includes the design of large databases and the development of techniques for their manipulation, including data mining.

burden of proof Responsibility for determining whether a substance is safe or hazardous; a range of approaches can be seen when comparing laws. For example, for OSHA, regulators show a substance is hazardous before exposure is restricted, with the government conducting the tests; for FDA, manufacturers must show lack of hazard before marketing.

biomagnification *See* bioaccumulation.

carcinogen Any chemical or process involving chemicals that induces neoplasms that are not usually observed, the earlier induction of neoplasms than are commonly observed, and/or the induction of more neoplasms than are usually found.

carcinogen, epigenetic Cancer-causing agents that exert their carcinogenic effect by mechanisms other than genetic, such as by immunosuppression, hormonal imbalance, or cytotoxicity. They may act as cocarcinogens or promoters. Epigenetic carcinogenesis is not as well understood a phenomenon as is genotoxic carcinogenesis.

carcinogen, genotoxic Cancer-causing agents that exert their carcinogenic effect by a series of events that is initiated by an interaction with DNA, either directly or through an electrophilic metabolite.

carcinogen, proximate *See* carcinogen, ultimate.

carcinogen, ultimate Many, if not most, chemical carcinogens are not intrinsically carcinogenic but require metabolic activation to express their carcinogenic potential. The term procarcinogen describes the initial unreactive compound, the term proximate carcinogen describes its more active products, and the term ultimate carcinogen describes the product that is actually responsible for carcinogenesis by its interaction with DNA.

carcinogenesis This is the process encompassing the conversion of normal cells to neoplastic cells and the further development of these neoplastic cells into a tumor. This process results from the action of specific chemicals, certain viruses, or radiation. Chemical carcinogens have been classified into those that are genotoxic and those that are epigenetic (i.e., not genotoxic).

chronic toxicity This term is used to describe adverse effects manifested after a long time period of uptake of small quantities of the toxicant in question. The dose is small enough that no acute effects are manifested, and the time period is frequently a significant part of the expected normal lifetime of the organism. The most serious manifestation of chronic toxicity is carcinogenesis, but other types of chronic toxicity are also known (e.g., reproductive effects, behavioral effects).

chronic toxicity tests Chronic tests are those conducted over a significant part of the life span of the test species or, in some cases, more than one generation. The most important tests are carcinogenicity tests, and the most common test species are rats and mice.

clinical toxicology Clinical toxicology addresses the diagnosis, treatment, and prevention of chemical poisonings of humans as well as domestic and companion animals, and includes aspects of occupational and emergency medicine, poison control, and public health.

cocarcinogenesis Cocarcinogenesis is the enhancement of the conversion of normal cells to neoplastic cells. This process is manifested by enhancement of carcinogenesis when the agent is administered either before or together with a carcinogen. Cocarcinogenesis should be distinguished from promotion as, in the latter case, the promoter must be administered after the initiating carcinogen.

comparative toxicology The study of the variation in the expression of the toxicity of exogenous chemicals toward organisms of different taxonomic groups or of different genetic strains.

compartment In pharmaco(toxico)kinetics, a compartment is a hypothetical volume of an animal system wherein a chemical acts homogeneously in transport and transformation. These compartments do not correspond to physiological or anatomic areas but are abstract mathematical entities useful for predicting drug or toxicant concentrations. Transport into, out of, or between compartments is described by rate constants, which are used in models of the intact animal.

conjugation reactions *See* Phase II reactions.

covalent binding This involves the covalent bond or "shared electron pair" bond. Each covalent bond consists of a pair of electrons shared between two atoms and occupying two stable orbitals, one of each atom. Although this is distinguished from the ionic bond or ionic valence, in fact, chemical bonds may show both covalent and ionic character. In toxicology, the term covalent binding is used less precisely to refer to the binding of toxicants or their reactive metabolites to endogenous molecules (usually macromolecules) to produce stable adducts resistant to rigorous extraction procedures. A covalent bond between ligand and macromolecule is generally assumed. Many forms of chronic toxicity involve covalent binding of the toxicant to DNA or protein molecules within the cell.

cross-resistance, cross-tolerance These terms describe the situation in which either resistance or tolerance to a particular toxicant (as defined under adaptation to toxicants) is induced by exposure to a different toxicant. This is commonly seen in resistance of insects to insecticides in which selection with one insecticide brings about a broad spectrum of resistance to insecticides of the same or different chemical classes. Such cross-resistance is usually caused by the inheritance of a high level of nonspecific xenobiotic-metabolizing enzymes.

cytotoxicity Cellular injury or death brought about by chemicals external to the cell. Such chemicals may be soluble mediators produced by the immune system, or they may be chemicals (toxicants) to which the organism has been exposed.

Delaney Amendment *See* Food, Drug and Cosmetics Act.

detoxication A metabolic reaction or sequence of reactions that reduces the potential for adverse effect of a xenobiotic. Such sequences normally involve an increase in water solubility that facilitates excretion and/or the reaction of a reactive product with an endogenous substrate (conjugation), thereby not only increasing water solubility but also reducing the possibility of interaction with cellular macromolecules. Not to be confused with detoxification. *See also* detoxification.

detoxification Treatment by which toxicants are removed from intoxicated patients or a course of treatment during which dependence on alcohol or other drugs of abuse is reduced or eliminated. Not to be confused with detoxication. *See also* detoxication.

distribution The term distribution refers both to the movement of a toxicant from the portal of entry to the tissue and also to the description of the different concentrations reached in different locations. The first involves the study of transport mechanisms primarily in the blood, and both are subject to mathematical analysis in toxicokinetic studies.

dosage The amount of a toxicant, drug, or other chemical administered or taken expressed as some function of the organism (e.g., mg/kg body weight/day).

dose The total amount of a toxicant, drug, or other chemical administered to or taken in by the organism.

dose–response relationship In toxicology, the quantitative relationship between the amount of a toxicant administered or taken and the incidence or extent of the adverse effect.

dose–response assessment A step in the risk-assessment process to characterize the relationship between the dose of a chemical administered to a population of test animals and the incidence of a given adverse effect. It involves mathematical modeling techniques to extrapolate from the high dose effects observed in test animals to estimate the effects expected from exposure to the typically low doses that may be encountered by humans.

Draize Test *See* eye irritation test.

drugs of abuse Although all drugs may have deleterious effects on humans, drugs of abuse either have no medicinal function or are taken at higher than therapeutic doses. Some drugs of abuse may affect only higher nervous functions (i.e., mood, reaction time, and coordination), but many produce physical dependence and have serious physical effects, with fatal overdose being a common occurrence. The drugs of abuse include central nervous system (CNS) depressants such as ethanol, methaqualone (Quaalude), and secobarbital; CNS stimulants such as cocaine, methamphetamine (speed), caffeine, and nicotine; opioids such as heroin and morphine; hallucinogens such as lysergic acid diethylamide (LSD), phencyclidine (PCP), and tetrahydrocannabinol (THC), the most important active principle of marijuana.

drugs, therapeutic All therapeutic drugs can be toxic at some dose. The danger to the patient is dependent on the nature of the toxic response, the dose necessary to produce the toxic response, and the relationship between the therapeutic and the toxic dose. Drug toxicity is affected by all of those factors that affect the toxicity of xenobiotics, including (genetic) variation, diet, age, and the presence

of other exogenous chemicals. The risk of toxic side effects from a particular drug must be weighed against the expected benefits; the use of a quite dangerous drug with only a narrow tolerance between the therapeutic and toxic doses might be justified if it is the sole treatment for an otherwise fatal disease. For example, cytotoxic agents used in the treatment of cancer are known carcinogens.

ecotoxicology *See* environmental toxicology.

electron transport system (ETS) This term is often restricted to the mitochondrial system, although it applies equally well to other systems, including that of microsomes and chloroplasts. The mitochondrial ETS (also termed respiratory chain or cytochrome chain) consists of a series of cytochromes and other electron carriers arranged in the inner mitochondrial membrane. These components transfer the electrons from NADH or $FADH_2$ generated in metabolic oxidations to oxygen, the final electron acceptor, through a series of alternate oxidations and reductions. The energy that these electrons lose during these transfers is used to pump H^+ from the matrix into the intermembrane space, creating an electrochemical proton gradient that drives oxidative phosphorylation. The energy is conserved as adenosine triphosphate (ATP).

electron transport system (ETS) inhibitors The three major respiratory enzyme complexes of the mitochondrial electron transport system can all be blocked by inhibitors. For example, rotenone inhibits the NADH dehydrogenase complex, antimycin A inhibits the b-c complex, and cyanide and carbon monoxide inhibits the cytochrome oxidase complex. Although oxidative phosphorylation inhibitors prevent phosphorylation while allowing electron transfers to proceed, ETS inhibitors prevent both electron transport and ATP production.

electrophilic Electrophiles are chemicals that are attracted to and react with electron-rich centers in other molecules in reactions known as electrophilic reactions. Many activation reactions produce electrophilic intermediates such as epoxides, which exert their toxic action by forming covalent bonds with nucleophilic centers in cellular macromolecules such as DNA or proteins.

endocrine disruptors An endocrine disruptor is an exogenous chemical that interacts with the endocrine system of an organism to produce one or more deleterious effects. These effects may be brought about in a number of ways including serving as ligands for hormone receptors and inhibition or induction of hormone-metabolizing enzymes.

endoplasmic reticulum The endoplasmic reticulum (ER) is an extensive branching and anastomosing double membrane distributed in the cytoplasm of eukaryotic cells. The ER is of two types: rough ER (RER) contains attached ribosomes on the cytosolic surface and smooth ER (SER) is devoid of ribosomes. Ribosomes are involved in protein biosynthesis, and RER is abundant in cells specialized for protein synthesis. Many xenobiotic-metabolizing enzymes are integral components of both SER and RER, such as the cytochrome P450-dependent monooxygenase system and the flavin-containing monooxygenase, although the specific content is usually higher in SER. When tissue or cells are disrupted by homogenization, the ER is fragmented into many smaller (c. 100 nm diameter) closed vesicles called microsomes, which can be isolated by differential centrifugation.

enterohepatic circulation This term describes the excretion of a compound into the bile and its subsequent reabsorption from the small intestine and transport back to the liver, where it is available again for biliary excretion. The most important mechanism is conjugation in the liver, followed by excretion into the bile. In the small intestine, the conjugation product is hydrolyzed, either nonenzymatically or by the microflora, and the compound is reabsorbed to become a substrate for conjugation and re-excretion into the bile.

environmental toxicology This is concerned with the movement of toxicants and their metabolites in the environment and in food chains and the effect of such toxicants on populations of organisms.

epigenetic carcinogen *See* carcinogen, epigenetic.

exposure assessment A component of risk assessment. The number of individuals likely to be exposed to a chemical in the environment or in the workplace is assessed, and the intensity, frequency, and duration of human exposure are estimated.

eye irritation test (Draize Test) Eye irritation tests measure irritancy of compounds applied topically to the eye. These tests are variations of the Draize test, and the experimental animal used is the albino rabbit. The test consists of adding the material to be tested directly into the conjunctival sac of one eye of each of several albino rabbits, the other eye serving as the control. This test is probably the most controversial of all toxicity tests, being criticized primarily on the grounds that it is inhumane. Moreover, because both concentrations and volumes used are high and show high variability, it has been suggested that these tests cannot be extrapolated to humans. However, because visual impairment is a critical toxic end point, tests for ocular toxicity are essential. Attempts to solve the dilemma have taken two forms: to find substitute *in vitro* tests and to modify the Draize test so that it becomes not only more humane, but also more predictive for humans.

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) This law is the basic U.S. law under which pesticides and other agricultural chemicals distributed in interstate commerce are registered and regulated. First enacted in 1947, FIFRA placed the regulation of agrochemicals under the control of the U.S. Department of Agriculture. In 1970, this responsibility was transferred to the newly created Environmental Protection Agency (EPA). Subsequently, FIFRA has been revised extensively by the Federal Environmental Pesticide Control Act (FEPCA) of 1972 and by the FIFRA amendments of 1975, 1978, and 1980. Under FIFRA, all new pesticide products used in the United States must be registered with the EPA. This requires the registrant to submit information on the composition, intended use, and efficacy of the product, along with a comprehensive database establishing that the material can be used without causing unreasonable adverse effects on humans or on the environment. The Food Quality Protection Act of 1996 is an amendment to FIFRA.

fetal alcohol syndrome (FAS) FAS refers to a pattern of defects in children born to alcoholic mothers. Three criteria for FAS are prenatal or postnatal growth retardation; characteristic facial anomalies such as microcephaly, small eye opening, and thinned upper lip; and central nervous system dysfunction, such as mental retardation and developmental delays.

food additives Chemicals may be added to food as preservatives (either antibacterial or antifungal compounds or antioxidants) to change the physical characteristics, for processing, or to change the taste or odor. Although most food additives are safe and are without chronic toxicity, many were introduced when toxicity testing was relatively unsophisticated and some have been shown subsequently to be toxic. The most important inorganic additives are nitrate and nitrite. Well-known examples of food additives include the antioxidant butylatedhydroxyanisole (BHA), fungistatic agents such as methyl *p*-benzoic acid, the emulsifier propylene glycol, sweeteners such as saccharin and aspartame, and dyes such as tartrazine and Sunset Yellow.

food contaminants (food pollutants) Food contaminants, as opposed to food additives, are those compounds included inadvertently in foods that are raw, cooked, or processed. They include bacterial toxins such as the exotoxin of *Clostridium botulinum*, mycotoxins such as aflatoxins from *Aspergillus flavus*, plant alkaloids, animal toxins, pesticide residues, residues of animal food additives such as diethylstilbestrol (DES) and antibiotics, and a variety of industrial chemicals such as polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs).

Food, Drug and Cosmetics Act The Federal Food, Drug and Cosmetic Act is administered by the Food and Drug Administration (FDA). It establishes limits for food additives, sets criteria for drug safety for both human and animal use, and requires proof of both safety and efficacy. This act contains the Delaney Amendment, which states that food additives that cause cancer in humans or animals at any level shall not be considered safe and are, therefore, prohibited. The Delaney Amendment has been modified to permit more flexible use of mechanistic and cost–benefit data. This law also empowers the FDA to establish and modify the "Generally Recognized as Safe" (GRAS) list and to establish Good Laboratory Practice (GLP) rules. As a result of the Food Quality Protection Act (1996), the Delaney amendment no longer applies to chemicals regulated under FIFRA.

forensic toxicology Forensic toxicology is concerned with the medicolegal aspects of the adverse effects of chemicals on humans and animals. Although primarily devoted to the identification of the cause and circumstances of death and the legal issues arising therefrom, forensic toxicologists also deal with sublethal poisoning cases.

free radicals Molecules that have unpaired electrons. Free radicals may be produced metabolically from xenobiotics and, because they are extremely reactive, may be involved in interactions with cellular macromolecules, giving rise to adverse effects. Examples include the trichloromethyl radical produced from carbon tetrachloride or the carbene radical produced by oxidation of the acetal carbon of methylenedioxyphenyl synergists.

genomics The sometimes stated distinction that genomics deals with genomes while molecular biology deals with single genes is unrealistic and unnecessary; it is more appropriate to regard genomics as an aspect of molecular biology that deals not only with genomes and gene expression but also such important aspects as genetic polymorphisms, particularly single nucleotide polymorphisms (SNPs). Techniques, such as microarrays, are now available to examine simultaneously the expression of very large numbers of genes.

genotoxic carcinogen *See* carcinogen, genotoxic.

genotoxicity Genotoxicity is an adverse effect on the genetic material (DNA) of living cells that, on the replication of the cells, is expressed as a mutagenic or a carcinogenic event. Genotoxicity results from a reaction with DNA that can be measured either biochemically or in short-term tests with end points that reflect DNA damage.

Good Laboratory Practice (GLS) In the United States, this is a code of laboratory procedures laid down under federal law and to be followed by laboratories undertaking toxicity tests, the results of which will be used for regulatory or legal purposes.

Generally Regarded as Safe (GRAS) list *See* Food, Drug and Cosmetics Act.

hazard identification Considered the first step in risk assessment, hazard identification involves the qualitative determination of whether exposure to a chemical causes an increased incidence of an adverse effect, such as cancer or birth defects, in a population of test animals and an evaluation of the relevance of this information to the potential for causing similar effects in humans.

hepatotoxicity Hepatotoxicants are those chemicals causing adverse effects on the liver. The liver may be particularly susceptible to chemical injury because of its anatomic relationship to the most important portal of entry, the gastrointestinal (GI) tract, and its high concentration of xenobiotic-metabolizing enzymes. Many of these enzymes, particularly cytochrome P450, metabolize xenobiotics to produce reactive intermediates that can react with endogenous macromolecules such as proteins and DNA to produce adverse effects.

immunotoxicity This term can be used in either of two ways. The first refers to toxic effects mediated by the immune system, such as dermal sensitivity reactions to compounds like 2,4-dinitrochlorobenzene. The second and currently most acceptable definition refers to toxic effects that impair the functioning of the immune system—for example, the ability of a toxicant to impair resistance to infection.

in vitro tests Literally, these are tests conducted outside of the body of the organism. In toxicity testing, they would include studies using isolated enzymes, subcellular organelles, or cultured cells. Although technically the term would not include tests involving intact eukaryotes (e.g., the Ames test), it frequently is used by toxicologists to include all short-term tests for mutagenicity that are normally used as indictors of potential carcinogenicity.

***in vivo* tests** Tests carried out on the intact organism, although the evaluation of the toxic end point almost always requires pathological or biochemical examination of the test organism's tissues. They may be acute, subchronic, or chronic. The best known are the lifetime carcinogenesis tests carried out on rodents.

induction The process of causing a quantitative increase in an enzyme as a result of de novo protein synthesis following exposure to an inducing agent. This can occur either by a decrease in the degradation rate or an increase in the synthesis rate or both. Increasing the synthesis rate is the most common mechanism for induction by xenobiotics. Coordinate (pleiotypic) induction is the induction of multiple enzymes by a single-inducing agent. For example, phenobarbital can induce isoforms of both cytochrome P450 and glutathione *S*-transferase.

industrial toxicology A specific area of environmental toxicology dealing with the work environment; it includes risk assessment, establishment of permissible levels of exposure, and worker protection.

inhibition In its most general sense, inhibition means a restraining or a holding back. In biochemistry and biochemical toxicology, inhibition is a reduction in the rate of an enzymatic reaction, and an inhibitor is any compound causing such a reduction. Inhibition of enzymes important in normal metabolism is a significant mechanism of toxic action of xenobiotics, whereas inhibition of xenobiotic-metabolizing enzymes can have important consequences in the ultimate toxicity of their substrates. Inhibition is sometimes used in toxicology in a more general and rather ill-defined way to refer to the reduction of an overall process of toxicity, as in the inhibition of carcinogenesis by a particular chemical.

initiation The initial step in the carcinogenic process involving the conversion of a normal cell to a neoplastic cell. Initiation is considered to be a rapid and essentially irreversible change involving the interaction of the ultimate carcinogen with DNA; this change primes the cell for subsequent neoplastic development via the promotion process.

intoxication In the general sense, this term refers primarily to inebriation with ethyl alcohol, secondarily to excitement or delirium caused by other means, including other chemicals. In the clinical sense, it refers to poisoning or becoming poisoned. In toxicology, it is sometimes used as a synonym for activation—that is, the production of a more toxic metabolite from a less toxic parent compound. This latter use of intoxication is ambiguous and should be abandoned in favor of the aforementioned general meanings, and activation or bioactivation used instead.

isozymes (isoenzymes) Isozymes, also known as isoforms, are multiple forms of a given enzyme that occur within a single species or even a single cell and that catalyze the same general reaction but are coded for by different genes. Different isozymes may occur at different life stages and/or in different organs and tissues, or they may coexist within the same cell. The first well-characterized isozymes were those of lactic dehydrogenase. Most xenobiotic-metabolizing enzymes exist in multiple isozymes, including cytochrome P450 and glucuronosyltransferase.

LC_{50} (median lethal concentration) The concentration of a test chemical that, when a population of test organisms is exposed to it, is estimated to be fatal to 50% of the organisms under the stated conditions of the test. Normally used in lieu of the LD_{50} test in aquatic toxicology and inhalation toxicology.

LD_{50} (median lethal dose) The quantity of a chemical compound that, when applied directly to test organisms, is estimated to be fatal to 50% of those organisms under the stated conditions of the test. The LD_{50} value is the standard for comparison of acute toxicity between toxicants and between species. Because the results of LD_{50} determinations may vary widely, it is important that both biological and physical conditions be narrowly defined (e.g., strain, gender, and age of test organism; time and route of exposure; environmental conditions). The value may be determined graphically from a plot of log dose against mortality expressed in probability units (probits) or, more recently, by using one of several computer programs available.

lethal synthesis This term is used to describe the process by which a toxicant, similar in structure to an endogenous substrate, is incorporated into the same metabolic pathway as the endogenous substrate, ultimately being transformed into a toxic or lethal product. For example, fluoroacetate simulates acetate in intermediary metabolism, being transformed via the tricarboxylic acid cycle to fluorocitrate, which then inhibits aconitase, resulting in disruption of the TCA cycle and energy metabolism.

lipophilic The physical property of chemical compounds that causes them to be soluble in nonpolar solvents (e.g., chloroform and benzene) and, generally, relatively insoluble in polar solvents such as water. This property is important toxicologically because lipophilic compounds tend to enter the body easily and to be excretable only when they have been rendered less lipophilic by metabolic action.

maximum tolerated dose (MTD) The MTD has been defined for testing purposes by the U.S. environmental Protection Agency as the highest dose that causes no more than a 10% weight decrement, as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animals' natural life span. It is an important concept in chronic toxicity testing; however, the relevance of results produced by such large doses has become a matter of controversy.

mechanism of action *See* mode of action.

membranes Membranes of tissues, cells, and cell organelles are all basically similar in structure. They appear to be bimolecular lipid leaflets with proteins embedded in the matrix and also arranged on the outer polar surfaces. This basic plan is present in spite of many variations, and it is important in toxicological studies of uptake of toxicants by passive diffusion and active transport.

metabolomics Metabolomics is concerned with the profile of small molecules produced by the metabolic processes of an organism. Changes in the profile in response to chemical stress are of importance to both fundamental and applied toxicology.

microarray Microarrays are based on the principle that any gene being expressed at any point in time is giving rise to a specific, corresponding mRNA. The microarray itself consists of spots of DNA (c. 200 μ) bound to a suitable matrix. The mRNAs in the biological sample in question bind to the corresponding DNA and can be visualized by techniques involving dyes. Given the complexity of the data obtained (often thousands of genes are evaluated on a single microarray), special techniques have been developed for array scanning, data extraction, and statistical analysis.

microsomes Microsomes are small closed vesicles (c.110 nm diameter) that represent membrane fragments formed form the endoplasmic reticulum when cells are disrupted by homogenization. Microsomes are separated from other cell organelles by differential centrifugation. The cell homogenate contains rough microsomes that are studded with ribosomes and are derived from rough endoplasmic reticulum, and smooth microsomes that are devoid of ribosomes and are derived from smooth endoplasmic reticulum. Microsomes are important preparations for studying the many processes carried out by the endoplasmic reticulum, such as protein biosynthesis and xenobiotic metabolism.

mode of action (mode of toxic action) Terms used to describe the mechanism(s) that enables a toxicant to exert its toxic effect. The term(s) may be narrowly used to describe only those events at the site of action (perhaps better referred to as mechanism of action) or more broadly, to describe the sequence of events from uptake from the environment, through metabolism, distribution, and so on, up to and including events at the site of action.

monooxygenase (mixed-function oxidase) An enzyme for which the cosubstrates are an organic compound and molecular oxygen. In reactions catalyzed by these enzymes, one atom of a molecule of oxygen is incorporated into the substrate whereas the other atom is reduced to water. Monooxygenases of importance in toxicology include cytochrome P450 and the flavin-containing monooxygenase, both of which initiate the metabolism of lipophilic xenobiotics by the introduction of a reactive polar group into the molecule. Such reactions may represent detoxication or may generate reactive intermediates of importance in toxic action. The term mixed-function oxidase is now considered obsolete and should not be used. The term multifunction oxidase was never widely adopted and also should not be used.

mutagenicity Mutations are heritable changes produced in the genetic information stored in the DNA of living cells. Chemicals capable of causing such changes are known as mutagens and the process is known as mutagenesis.

mycotoxins Toxins produced by fungi. Many, such as aflatoxins, are particularly important in toxicology.

nephrotoxicity A pathologic state that can be induced by chemicals (nephrotoxicants) and in which the normal homeostatic functioning of the kidney is impaired. It is often associated with necrosis of the proximal tubule.

neurotoxicity This is a general term referring to all toxic effects on the nervous system, including toxic effects measured as behavioral abnormalities. Because the nervous system is complex, both structurally and functionally, and has considerable functional reserve, the study of neurotoxicity is a many-faceted branch of toxicology. It involves electrophysiology, receptor function, pathology, behavior, and other aspects.

No Observed Effect Level (NOEL) This is the highest dose level of a chemical that, in a given toxicity test, causes no observable effect in the test animals. The NOEL for a given chemical varies with the route and duration of exposure and the nature of the adverse effect (i.e., the indicator of toxicity). The NOEL for the most sensitive test species and the most sensitive indicator of toxicity is usually employed for regulatory purposes. Effects considered are usually adverse effects, and this value may be called the No Observed Adverse Effects level (NOAEL).

nuclear receptors These are cellular proteins that bind steroid and other hormones as well as some toxicants. As part of a process involving other proteins as well as migration into the nucleus of the cell, nuclear receptors regulate gene expression. These genes may be involved in development, metabolism, or toxicity. The role of nuclear receptors in the induction of xenobiotic-metabolizing enzymes is of particular importance in metabolic interactions of toxicants.

Occupational Safety and Health Administration (OSHA) In the United States, OSHA is the government agency concerned with health and safety in the workplace. Through the administration of the Occupational Safety and Health Act, OSHA sets the standards for worker exposure to specific chemicals, for air concentration values, and for monitoring procedures. OSHA is also concerned with research (through the National Institute for Occupational Safety and Health [NIOSH]), information, education, and training in occupational safety and health.

oncogenes Oncogenes are genes that, when activated in cells, can transform the cells from normal to neoplastic. Sometimes, oncogenes are carried into normal cells by infecting viruses, particularly RNA viruses or retroviruses. In some cases, however, the oncogene is already present in the normal human cell, and it needs only a mutation or other activating event to change it from a harmless and possible essential gene, called *proto-oncogene*, into a cancer-producing gene. More than 30 oncogenes have been identified in humans.

oxidative phosphorylation The conservation of chemical energy extracted from fuel oxidations by the phosphorylation of adenosine diphosphate (ADP) by inorganic phosphate to form adenosine triphosphate (ATP) is accomplished in several ways. The majority of ATP is formed by respiratory chain-linked oxidative phosphorylation associated with the electron transport system in the mitochondrial inner membrane. The oxidations are tightly coupled to phosphorylations through a chemiosmotic mechanism in which H^+ are pumped across the inner mitochondrial membrane. Uncouplers of oxidative phosphorylation serve as H^+ ionophores to dissipate the H^+ gradient, and thus uncouple the phosphorylations from the oxidations.

oxidative stress Damage to cells and cellular constituents and processes by reactive oxygen species generated *in situ*. Oxidative stress may be involved in such toxic interactions as DNA damage, lipid peroxidation, and pulmonary and cardiac toxicity. Because of the transitory nature of most reactive oxygen species, although oxidative stress is often invoked as a mechanism of toxicity, rigorous proof may be lacking. (See also reactive oxygen species.)

partition coefficient This is a measure of the relative lipid solubility of a chemical and is determined by measuring the partitioning of the compound between an organic phase and an aqueous phase (e.g., octanol and water). The partition coefficient is important in studies of the uptake of toxicants because compounds with high coefficients (lipophilic compounds) are usually taken up more readily by organisms and tissues.

pharmacokinetics The study of the quantitative relationship between absorption, distribution, and excretion of chemicals and their metabolites. It involves derivation of rate constants for each of these processes and their integration into mathematical models that can predict the distribution of the chemical throughout the body compartments at any point in time after administration. Pharmacokinetic studies have been carried out most extensively in the case of clinical drugs. When applied specifically to toxicants, the term *toxicokinetics* is often used.

Phase I reactions These reactions introduce a reactive polar group into lipophilic xenobiotics. In most cases, this group becomes the site for conjugation during Phase II reactions. Such reactions include microsomal monooxygenations, cytosolic and mitochondrial oxidations, co-oxidations in the prostaglandin

synthetase reaction, reductions, hydrolyses, and epoxide hydrolases. The products of Phase I reactions may be potent electrophiles that can be conjugated and detoxified in Phase II reactions or that may react with nucleophilic groups on cellular constituents, thereby causing toxicity.

Phase II reactions Reactions involving the conjugation with endogenous substrates of Phase I products and other xenobiotics that contain functional groups such as hydroxyl, amino, carboxyl, epoxide, or halogen. The endogenous metabolites include sugars, amino acids, glutathione, and sulfate. The conjugation products, with rare exceptions, are more polar, less toxic, and more readily excreted than are their parent compounds. There are two general types of conjugations: type I (e.g., glycoside and sulfate formation), in which an activated conjugating agent combines with substrate to yield the conjugated product; and type II (e.g., amino acid conjugation), in which the substrate is activated and then combines with an amino acid to yield a conjugated product.

poison (toxicant) A poison (toxicant) is any substance that causes a harmful effect when administered to a living organism. Due to a popular connotation that poisons are, by definition, fatal in their effects and that their administration is usually involved with attempted homicide or suicide, most toxicologists prefer the less prejudicial term toxicant. Poison is a quantitative concept. Almost any substance is harmful at some dose and, at the same time, is harmless at a very low dose. There is a range of possible effects, from subtle long-term chronic toxicity to immediate lethality.

pollution This is contamination of soil, water, food, or the atmosphere by the discharge or admixture of noxious materials. A pollutant is any chemical or substance contaminating the environment and contributing to pollution.

portals of entry The sites at which xenobiotics enter the body. They include the skin, the gastrointestinal (GI) tract, and the respiratory system.

potentiation *See* synergism and potentiation.

procarcinogen *See* carcinogen, ultimate.

promotion The facilitation of the growth and development of neoplastic cells into a tumor. This process is manifested by enhancement of carcinogenesis when the agent is given after a carcinogen.

proteomics Deals with the protein complement of organisms, the entire complement being known as the proteome. Thus, while genomics is concerned with gene expression, proteomics examines the products of the expressed genes.

pulmonary toxicity This term refers to the effects of compounds that exert their toxic effects on the respiratory system, primarily the lungs.

quantitative structure activity relationships (QSAR) The relationship between the physical and/or chemical properties of chemicals and their ability to cause a particular effect, enter into particular reactions, and so on. The goal of QSAR studies in toxicology is to develop procedures whereby the toxicity of a compound can be predicted from its chemical structure by analogy with the properties of other toxicants of known structure and toxic properties.

reactive intermediates (reactive metabolites) Chemical compounds, produced during the metabolism of xenobiotics that are more chemically reactive than is the parent compound. Although they are susceptible to detoxication by

conjugation reactions, these metabolites, as a consequence of their increased reactivity, have a greater potential for adverse effects than does the parent compound. A well-known example is the metabolism of benzo(a)pyrene to its carcinogenic dihydrodiol epoxide derivative as a result of metabolism by cytochrome P450 and epoxide hydrolase. Reactive intermediates involved in toxic effects include epoxides, quinones, free radicals, reactive oxygen species, and a small number of unstable conjugation products.

reactive oxygen species Molecular oxygen normally exists in a relatively unreactive triplet state ($3O_2$). However, reactive species such as superoxide anion, hydrogen peroxide, singlet oxygen, and the highly reactive hydroxyl radical are also known. Reactive oxygen species are formed *in vivo*, either during, or as a consequence of, aerobic metabolism. There is a great deal of evidence that these reactive oxygen species are linked to a number of toxic end points, and this phenomenon is known as oxidative stress.

Reference Dose (RfD) See Acceptable Daily Intake (ADI).

resistance See adaptation to toxicants.

Resource Conservation and Recovery Act (RCRA) Administered by the EPA, the RCRA is the most important act governing the disposal of hazardous wastes in the United States; it promulgates standards for identification of hazardous wastes, their transportation, and their disposal. Included in the last are siting and construction criteria for landfills and other disposal facilities as well as the regulation of owners and operators of such facilities.

risk analysis This term includes risk assessment (below) together with consideration of risk communication and risk management.

risk assessment The process by which the potential adverse health effects of human exposure to chemicals are characterized; it includes the development of both qualitative and quantitative expression of risk. The process of risk assessment may be divided into four major components: hazard identification, dose–response assessment (high-dose to low-dose extrapolation), exposure assessment, and risk characterization.

risk, toxicologic The probability that some adverse effect will result from a given exposure to a chemical is known as the risk. It is the estimated frequency of occurrence of an event in a population and may be expressed in absolute terms (e.g., 1 in 1 million) or in terms of relative risk (i.e., the ratio of the risk in question to that in an equivalent unexposed population).

safety factor (uncertainty factor) A number by which the no observed effect level (NOEL) is divided to derive the reference dose (RfD), the reference concentration (RfC), or minimum risk level (MRL) of a chemical from experimental data. The safety factor is intended to account for the uncertainties inherent in estimating the potential effects of a chemical on humans from results obtained with test species. The safety factor allows for possible differences in sensitivity between the test species and humans, as well as for variations in the sensitivity within the human population. The size of safety factor (e.g., 100–1000) varies with confidence in the database and the nature of the adverse effects. Small safety factors indicate a high degree of confidence in the data, an extensive database, and/or the availability of human data. Large safety factors are indicative of an inadequate and uncertain database and/or the severity of the unexpected toxic effect.

selectivity (selective toxicity) A characteristic of the relationship between toxic chemicals and living organisms whereby a particular chemical may be highly toxic to one species but relatively innocuous to another. The search for and study of selective toxicants is an important aspect of comparative toxicology because chemicals toxic to target species but innocuous to nontarget species are extremely valuable in agriculture and medicine. The mechanisms involved vary from differential penetration rates through different metabolic pathways to differences in receptor molecules at the site of toxic action.

solvents In toxicology, this term usually refers to industrial solvents. These belong to many different chemical classes, and a number of these are known to cause problems of toxicity to humans. They include aliphatic hydrocarbons (e.g., hexane), halogenated aliphatic hydrogens (e.g., methylene chloride), aliphatic alcohols (e.g., methanol), glycols and glycol ethers (e.g., propylene and propylene glycol), and aromatic hydrocarbons (e.g., toluene).

subchronic toxicity Toxicity due to chronic exposure to quantities of a toxicant that do not cause any evident acute toxicity for a time period that is extended but is not so long as to constitute a significant part of the life span or the species in question. In subchronic toxicity tests using mammals, a 30–90 day period is considered appropriate.

synergism and potentiation The terms synergism and potentiation have been variously used and defined but in any case involve a toxicity that is greater when two compounds are given simultaneously or sequentially than would be expected from a consideration of the toxicities of the compounds given alone. In an attempt to make the use of these terms uniform, it is a suggested that, insofar as toxic effects are concerned, they be used as defined as follows: both involve toxicity greater than would be expected from the toxicities of the compounds administered separately, but in the case of synergism, one compound has little or no intrinsic toxicity administered alone, whereas in the case of potentiation, both compounds have appreciable toxicity when administered alone.

systems biology Although systems biology has been defined in a number of ways, some involving quite simple approaches to limited problems, in the currently most commonly accepted sense, it is an integrative approach to biological structure and function. In large part, biology has been reductionist throughout its history, studying organs as components of organisms, cells as components of organs, enzymes, nucleic acids, and so on, as components of cells, with the goal of describing function at the molecular level. Systems biology, on the other hand, is holistic and has the objective of discerning interactions between components of biological systems and describing these interactions in rigorous mathematical models. Furthermore, the proponents of systems biology aim to integrate these models at higher and higher levels or organization in order to develop an integrated model of the entire organism.

teratogenesis This term refers to the production of defects in the reproduction process resulting in either reduced productivity due to fetal or embryonic mortality or the birth of offspring with physical, mental, behavioral, or developmental defects. Compounds causing such defects are known as teratogens.

therapy Poisoning therapy may be nonspecific or specific. Nonspecific therapy is treatment for poisoning that is not related to the mode of action of the particular

toxicant. It is designed to prevent further uptake of the toxicant and to maintain vital signs. Specific therapy, however, is therapy related to the mode of action of the toxicant and not simply to the maintenance of vital signs by treatment of symptoms. Specific therapy may be based on activation and detoxication reactions, on mode of action, or on elimination of the toxicant. In some cases, more than one antidote, with different modes of action, are available for the same toxicant.

threshold dose The dose of a toxicant below which no adverse effect occurs. The existence of such a threshold is based on the fundamental tenet of toxicology that, for any chemical, there exists a range of doses over which the severity of the observed effect is directly related to the dose, the threshold level representing the lower limit of this dose range. Although practical thresholds are considered to exist for most adverse effects, for regulatory purposes it is assumed that there is no threshold dose for carcinogens.

threshold limit value (TLV) Upper permissive limit of airborne concentrations of substances. They represent conditions under which it is believed that nearly all workers may be exposed repeatedly, day after day, without adverse effect. Threshold limits are based on the best available information from industrial experience, from experimental human and animal studies, and when possible, from a combination of the three.

threshold limit value–ceiling (TLV-C) This is the concentration that should not be exceeded even momentarily. For some substances (e.g., irritant gases), only one TLV category, the TLV-C, may be relevant. For other substances, two or three TLV categories may need to be considered.

threshold limit value–short-term exposure limit (TLV-STEL) This is the maximal concentration to which workers can be exposed for a period up to 15 min. continuously without suffering from (1) irritation, (2) chronic or irreversible tissue change, or (3) narcosis of sufficient degree to increase accident proneness.

threshold limit value–time-weighted average (TLV-TWA) This is the TWA concentration for a normal 8-hr workday or 40-hr workweek to which nearly all workers may be exposed repeatedly day after day, without adverse effect. Time-weighted averages allow certain permissible excursions above the limit, provided they are compensated by equivalent excursions below the limit during the workday. In some instances, the average concentration is calculated for a workweek rather than for a workday.

tolerance *See* adaptation to toxicants.

Toxic Substances Control Act (TSCA) Enacted in 1976, the TSCA provides the EPA with the authority to require testing and to regulate chemicals, both old and new, entering the environment. It was intended to supplement sections of the Clean Air Act, the Clean Water Act, and the Occupational Safety and Health Act that already provide for regulation of chemicals. Manufacturers are required to submit information to allow the EPA to identify and evaluate the potential hazards of a chemical prior to its introduction into commerce. The act also provides for the regulation of production, use, distribution, and disposal of chemicals.

toxicant *See* poison.

toxicogenomics Those aspects of genomics of relevance to toxicology (see genomics).

toxicokinetics *See* pharmacokinetics.

toxicology Toxicology is defined as that branch of science that deals with poisons (toxicants) and their effects; a poison is defined as any substance that causes a harmful effect when administered, either by accident or design, to a living organism. There are difficulties in bringing a more precise definition to the meaning of poison and in the definition and measurement of toxic effect. The range of deleterious effects is wide and varies with species, gender, developmental stage, and so on, while the effects of toxicants are always dose dependent.

toxin A *toxin* is a toxicant produced by a living organism. Toxin should never be used as a synonym for toxicant.

transport In toxicology, this term refers to the mechanisms that bring about movement of toxicants and their metabolites from one site in the organism to another. *Transport* usually involves binding to either blood albumins or blood lipoproteins.

ultimate carcinogen *See* carcinogen, ultimate.

venom A venom is a toxin produced by an animal specifically for the poisoning of other species via a mechanism designed to deliver the toxin to its prey. Examples include the venom of bees and wasps, delivered by a sting, and the venom of snakes, delivered by fangs.

water pollution Water pollution is of concern in both industrialized and nonindustrialized nations. Chemical contamination is more common in industrialized nations, whereas microbial contamination is more important in nonindustrialized areas. Surface water contamination has been the primary cause for concern but, since the discovery of agricultural and industrial chemicals in groundwater, contamination of water from this source is also a problem. Water pollution may arise from runoff of agricultural chemicals, from sewage or from specific industrial sources. Agricultural chemicals found in water include insecticides, herbicides, fungicides, and nematocides; fertilizers, although less of a toxic hazard, contribute to such environmental problems as eutrophication. Other chemicals of concern include low molecular-weight halogenated hydrocarbons such as chloroform, dichloroethane, and carbon tetrachloride; polychlorinated biphenyls (PCBs); chlorophenols; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD); phthalate ester plasticizers; detergents; and a number of toxic inorganics.

xenobiotic A general term used to describe any chemical interacting with an organism that does not occur in the normal metabolic pathways of that organism. The use of this term in lieu of "foreign compound," among others, has gained wide acceptance.

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A Textbook of Modern Toxicology, *Fourth Edition*. Edited by Ernest Hodgson