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Nota di contenuto

Reactive Drug Metabolites; Contents; Preface; A Personal Foreword; 1 Origin and Historical Perspective on Reactive Metabolites; Abbreviations; 1.1 Mutagenesis and Carcinogenesis; 1.2 Detection of Reactive Metabolites; 1.3 Induction and Inhibition: Early Probes for Reactive Metabolites and Hepatotoxicants; 1.4 Covalent Binding and Oxidative Stress: Possible Mechanisms of Reactive Metabolite Cytotoxicity; 1.5 Activation and Deactivation: Intoxication and Detoxification; 1.6 Genetic Influences on Reactive Metabolite Formation 1.7 Halothane: the Role of Reactive Metabolites in Immune-Mediated Toxicity1.8 Formation of Reactive Metabolites, Amount Formed, and Removal of Liability; 1.9 Antibodies: Possible Clues but Inconclusive; 1.10 Parent Drug and Not Reactive Metabolites, Complications in Immune-Mediated Toxicity; 1.11 Reversible Pharmacology Should not be Ignored as a Primary Cause of Side Effects; 1.12 Conclusions: Key Points in the Introduction; References; 2 Role of Reactive Metabolites in Genotoxicity; Abbreviations; 2.1 Introduction; 2.2 Carcinogenicity of Aromatic and Heteroaromatic Amines 2.3 Carcinogenicity of Nitrosamines2.4 Carcinogenicity of Quinones and Related Compounds; 2.5 Carcinogenicity of Furan; 2.6 Carcinogenicity of Vinyl Halides; 2.7 Carcinogenicity of Ethyl Carbamate; 2.8 Carcinogenicity of Dihaloalkanes; 2.9 Assays to Detect Metabolism-Dependent Genotoxicity in Drug Discovery; 2.10 Case Studies in Eliminating Metabolism-Based Mutagenicity in Drug Discovery Programs; References; 3 Bioactivation and Inactivation of Cytochrome P450 and Other Drug-Metabolizing Enzymes; Abbreviations; 3.1 Introduction 3.2 Pharmacokinetic and Enzyme Kinetic Principles Underlying Mechanism-Based Inactivation and Drug-Drug Interactions3.2.1 Enzyme Kinetic Principles of Mechanism-Based Inactivation; 3.2.2 Pharmacokinetic Principles Underlying DDIs Caused by Mechanism-Based Inactivation; 3.3 Mechanisms of Inactivation of Cytochrome P450 Enzymes; 3.3.1 Quasi-Irreversible Inactivation; 3.3.2 Heme Adducts; 3.3.3 Protein Adducts; 3.4 Examples of Drugs and Other Compounds that are Mechanism-Based Inactivators of Cytochrome P450 Enzymes; 3.4.1 Amines; 3.4.2 Methylenedioxophenyl Compounds 3.4.3 Quinones, Quinone Imines, and Quinone Methides3.4.4 Thiophenes; 3.4.5 Furans; 3.4.6 Alkynes; 3.4.7 2-Alkylimidazoles; 3.4.8 Other Noteworthy Cytochrome P450 Inactivators; 3.5 Mechanism-Based Inactivation of Other Drug-Metabolizing Enzymes; 3.5.1 Aldehyde Oxidase; 3.5.2 Monoamine Oxidases; 3.6 Concluding Remarks; References; 4 Role of Reactive Metabolites in Drug-Induced Toxicity - The Tale of Acetaminophen, Halothane, Hydralazine, and Tienilic Acid; Abbreviations; 4.1 Introduction; 4.2 Acetaminophen; 4.2.1 Metabolism of Acetaminophen; 4.2.2 Metabolic Activation of Acetaminophen 4.3 Halothane

Sommario/riassunto

Closing a gap in the scientific literature, this first comprehensive introduction to the topic is based on current best practice in one of the largest pharmaceutical companies worldwide. The first chapters trace the development of our understanding of drug metabolite toxicity, covering basic concepts and techniques in the process, while the second part details chemical toxicophores that are prone to reactive metabolite formation. This section also reviews the various drug-metabolizing enzymes that can participate in catalyzing reactive metabolite formation, including a discussion of the st