Factors Related to the Substance Form and Innate Chemical Activity The form of a substance may have a profound impact on its toxicity especially for metallic elements, also termed heavy metals.A synergistic interaction between the antioxidant butylated hydroxytoluene (BHT) and a certain concentration of oxygen results in lung damage in the form of interstitial pulmonary fibrosis.Other Factors Presence of Other Chemicals The presence of other chemicals, at the same time, earlier, or later may: Decrease toxicity (antagonism) Add to toxicity (additivity) Increase toxicity (synergism or potentiation) For example: Antidotes used to counteract the effects of poisons function through antagonism (atropine counteracts poisoning by organophosphate insecticides).The rates and extent of absorption may vary greatly depending on the form of a chemical and the route of exposure to it. For example: Ethanol is readily absorbed from the gastrointestinal tract but poorly absorbed through the skin.Examples are: Toxicant Acute Toxicity Chronic Toxic Effects Ethanol CNS depression Liver cirrhosis Arsenic Gastrointestinal damage Skin/liver cancer Table 1.Also, environmental chemicals can alter the composition and/or the metabolic activity of the gastrointestinal bacteria, thus contributing in a meaningful way to shape an individual's microbiome.Nicotine binds to cholinergic receptors in the central nervous system (CNS) altering nerve conduction and inducing gradual onset of paralysis.In comparison with men, pharmacokinetics in women generally can be impacted by their lower body weight, slower gastrointestinal motility, reduced intestinal enzymatic activity, and slower kidney function (glomerular filtration rate).For example: Hydrogen cyanide binds to the enzyme cytochrome oxidase resulting in cellular hypoxia and rapid death.In general, pharmacodynamic differences between women and men include greater sensitivity to and enhanced effectiveness, in women, of some drugs, such as beta blockers, opioids, and some antipsychotics.Distribution Within the Body The distribution of toxicants and toxic metabolites throughout the body ultimately determines the sites where toxicity occurs.Some vegetables can accumulate cadmium from contaminated soil; an antagonist for cadmium toxicity is the nutrient zinc.Examples of acute and chronic toxicity Exposure Route The way an individual comes in contact with a toxic substance, or exposure route, is important in determining toxicity.For example, nearly all alcohols are readily absorbed when ingested, whereas there is virtually no absorption for most polymers.Organic mercury is readily absorbed from the gastrointestinal tract; inorganic lead sulfate is not.Factors Related to the Organism Species Toxic responses can vary substantially depending on the species.For example, rats cannot vomit and expel toxicants before they are absorbed or cause severe irritation, whereas humans and dogs are capable of vomiting.Slower renal clearance in women, for example, may result in a need for dosage adjustment for drugs such as digoxin that are excreted via the kidneys.For example, gut microbes can metabolize some environmental chemicals and bacteria–dependent metabolism of some chemicals can modulate their toxicity.For example: Consumption of fish that have absorbed mercury from contaminated water can result in mercury toxicity; an antagonist for mercury toxicity is the nutrient selenium.Cr3+ is relatively nontoxic whereas Cr6+ causes skin or nasal corrosion and lung cancer.Virtually all chemicals can be acute toxicants if sufficiently large doses are administered.Inhaled toxicants immediately enter the general blood circulation and can distribute throughout the body prior to being detoxified by the liver.Inhalation (Image Source: ORAU, (C)) Absorption The ability to be absorbed is essential to systemic toxicity.Delayed gastric emptying in

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women may result in a need for them to extend the interval between eating and taking medications that require absorption on an empty stomach.Gender symbols for female (left) and male (right) (Image Source: iStock Photos, (C)) Metabolism Metabolism, also known as biotransformation, is the conversion of a chemical from one form to another by a biological organism.Generally, detoxification converts lipid-soluble compounds to polar compounds.Risk of toxicity may be increased if a CYP450 enzyme-inhibiting drug is given with one that depends on that pathway for metabolism.For example, rats administered an immunosuppressive drug had severe toxicity in their intestines 7 hours after light onset compared to controls and to other times in the day.For example, the toxicity of mercury vapor differs greatly from methyl mercury.Dosage The dosage is the most important and critical factor in determining if a substance will be an acute or a chronic toxicant.Often the toxic mechanisms and target organs are different for acute and chronic toxicity.For example: Ingested chemicals, when absorbed from the intestine, distribute first to the liver and may be immediately detoxified.Ingestion (Image Source: ORAU, (C)) Diagram of toxic substances being breathed into the lungs Figure 2.Selective toxicity refers to species differences in toxicity between two species simultaneously exposed.Antibiotics are selectively toxic to microorganisms while virtually nontoxic to humans.An individual's life stage can impact that person's response to toxicants (Image Source: iStock Photos, (C)) Gender Gender can play a big role in influencing toxicity.There are two types of metabolism: Detoxification Bioactivation In detoxification, a xenobiotic is converted to a less toxic form.In the elderly, CYP450 metabolism of drugs such as phenytoin and carbamazepine may be decreased.If a toxicant is lipid-soluble, it readily penetrates cell membranes.The kidney is the primary excretory organ, followed by the gastrointestinal tract, and the lungs (for gases).Impaired kidney function causes slower elimination of toxicants and increases their toxic potential.Grapefruit contains a substance that inhibits the P450 drug detoxification pathway, making some drugs more toxic.For example: An insecticide is lethal to insects but relatively nontoxic to animals.Illustrated silhouette people of varying ages and sizes standing outdoors under a tree Figure 3.In bioactivation, a xenobiotic may be converted to more reactive or toxic forms.Cytochrome P-450 (CYP450) is an example of an enzyme pathway used to metabolize drugs.Learn more about human exposure to pollutants and their interaction with the GI microbiota.Excretion The site and rate of excretion is another major factor affecting the toxicity of a xenobiotic.Lipid-soluble toxicants are reabsorbed and concentrated in kidney cells.Health Status The health of an individual or organism can play a major role in determining the levels and types of potential toxicity.Nutritional Status Diet (nutritional status) can be a major factor in determining who does or does not develop toxicity.The rats had changes in their digestive enzyme activity and other physiological indicators at this dosing time.The innate chemical activity of substances also varies greatly.Diagram of toxic substances being ingested Figure 1.Some chemicals are readily absorbed and others are poorly absorbed.Most differences between species are attributable to differences in metabolism.Some chemicals are more toxic to infants or the elderly than to young adults.Physiologic differences between men and women, including differences in pharmacokinetics and pharmacodynamics, can affect drug activity.Studies in animals also have identified gender-related differences.Metabolism is a major factor in determining toxicity.There is awareness that the gut microbiota can impact the toxicity of drugs and other chemicals.A major

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determinant of whether a toxicant will damage cells is its lipid solubility.Different target organs often are affected by different routes of exposure.Others may be due to anatomical or physiological differences.Life Stage An individual's age or life stage may be important in determining his or her response to toxicants.Nitrosamines are more carcinogenic to newborn or young animals.The products of metabolism are known as metabolites.CYP450 metabolism also can be inhibited by many drugs.Lymph .also distributes some materials.Male and female gender symbols Figure 4

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