Introduction

Why be concerned with species-associated differences in Absorption, Distribution, Metabolism, and Elimination (ADME)? In general, most of the differences among these species with regard to their susceptibility to negative or positive impacts of various drugs and other toxicants are related to two major factors: (i) differences in the likelihood and degree of exposure; and (ii) differences in processes involved in ADME. Much less often, marked differences among the susceptibility of specific receptors explains the variation in effect on vertebrate species.

Safety assessment studies that reliably predict hazards of various drugs and other chemicals to human beings or other species "of concern" can be achieved only through selection of appropriate species for study. Thus, identification of laboratory animal species that absorb, distribute, metabolize, and eliminate xenobiotics in ways similar to those in human beings or the other species "of concern" is essential for rational research on the safe use of toxicants in and around these species.

Currently, much of the activity of industrial toxicologists addresses the question of whether and why human beings are less susceptible to the toxic effects of a given xenobiotic than the more sensitive laboratory animal species. When human beings are demonstrated to be less sensitive than the laboratory animals in which problems have been detected, this usually means less controversy, less regulation, and sometimes, more sales of the xenobiotic under review.

For example: Recent work at the (Chemical Industry Institute of Toxicology (CIIT)) has shown that the air pollutant, 1,3-butadiene, which was listed as hazardous in the Clean Air Amendments, may pose less of a risk of cancer to humans than originally thought. Mice were especially sensitive to the carcinogenic effects; while rats were 1,000 times less sensitive. In comparative studies of liver metabolism, human beings metabolized 1,3-butadiene in much the same way as rats. This was good news for the manufacturers of 1,3-butadiene.

Similarly, mice hydrolyze 6-propylthiopurine to mercaptopurine which causes potent carcinogenesis; whereas human beings oxidize the drug in two positions without hydrolysis, and the end products are not carcinogens.

Although it is to the advantage of manufacturers to direct attention to the limits of extrapolation (because of species differences) with regard to human safety - it is to their disadvantage to do so with regard to effects on other species in the environment. Typical protocols for the "ecological" effects of toxicants involve assays of direct toxicity to one or two algal species, a vascular plant, a daphnid, a bivalve (sometimes), a fish (or two, usually a cold water [e.g., trout] and warm water [e.g., bluegill] species), and a bird (occasionally two species - most often a mallard and a quail). From these species, regulations are drawn that, in effect, extrapolate to all other life forms in the area exposed to the chemical under development. Generally, safety factors (typically 1:100 to 1:1,000,000 when applied to avoid human health), which allow for ignorance of the potential effects of a chemical as well as individual variation, are minimized with regard to wildlife. Thus, despite the usual absence of knowledge on the direct toxicity or the ADME in a range of exposed non-target species, small or non-existent safety factors are the rule in effluent permitting (point-source contamination) as well as in approval to market chemicals for purposeful outdoor application with anticipated "non-point-source" environmental contamination (e.g. agricultural or lawn pesticides).

A key aspect of pesticide toxicology is selectivity. Unfortunately, target species virtually always co-inhabit places with closely related non-target species. Selective toxicity is exploited to the greatest degree in control of weeds that compete for space and nutrients with crop plants,
and in control of pests (including pathogens such as bacteria, protozoa, fungi, helminths, and arthropods) on or in animals, and to a lesser
degree in control of unwanted herbivorous and omnivorous birds and rodents, as well as mammalian carnivores. Problems arise when the
differences in susceptibility and exposure between the target species and the non-target species are insufficient to protect the latter. In the
view of the author, although acute effects of pesticides on ecosystems are highly visible and thus often controlled, *direct subacute and
even indirectly indirect toxic effects*, may readily impact ecosystem functioning.

**Animal/Environmental Interactions that Predispose to Poisoning (Vary with Species)**

- Animals explore the environment in part by tasting what they find.
- When hungry, animals must eat whatever food is available.
- Overgrazing or sudden introduction to a new environment increases the likelihood of ingestion of poisonous plants.
- Co-evolved species tend to be poisoned less often than domestic species.
- Animals often drink from streams, puddles, and wells not suited for humans or animals.
- Animals breathe whatever air is available and are often trapped indoors (and less often outdoors) in toxic gases. Roaming increases
  likelihood of exposure to other chemicals-potentially resulting in accidental or malicious poisoning.

**Maturation and Aging**

Differences among species in rates of aging are believed to be attributable to differences in metabolic rates and associated cumulative
oxidative injury.

A range of factors may influence ADME (Absorption, Distribution, Metabolism and Excretion) and other aspects of susceptibility to hazards
related to a given toxicant. Included among many, these are: Maturity at birth.

**Time to sexual maturity.**

**Life span.**

**Age-Related Differences in Absorption**

Drug absorption in the neonate is influenced by a number of factors that differ from the adult. For example, relative to the adult, the neonate
will tend to differ as noted below:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Neonate</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric acid secretion</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal motility</td>
<td>Immature</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal anatomy</td>
<td>Immature</td>
<td></td>
</tr>
<tr>
<td>Microbial population</td>
<td>Stomach - high (human) Rumen low</td>
<td></td>
</tr>
<tr>
<td>Intestinal enzymate activity</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Mucosal absorbing area</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Blood perfusion</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Potential interactions with milk (calcium, protein)</td>
<td></td>
</tr>
</tbody>
</table>

**Miscellaneous Factors Related to Maturation and Aging**

- Infant BBB is much more permeable than in the adult.
- Several enzymatic processes of metabolism are very low or virtually absent the first few weeks of life.
- Infant has lower glomerular filtration rate.
- Young of some species rely on milk as the major source of nutrition, which may put them at risk of high level exposure to persistent,
fat soluble toxicants. Other species may rely on egg yolk, which like milkfat tend to contain considerable concentrations of fat soluble,
difficult-to-metabolize toxicants.
- Caloric intake in most domestic species is relatively high - especially in the young of rapidly growing species > pigs, dogs, cattle,
horses, etc.
- Old dogs/cats commonly have decreased glomerular filtration rates, reduced metabolic capacity > longer of xenobiotic half-lives.
- Diseases of old age are common in dogs, cats, some horses.
- Diseases of old age are not as often a significant problem in food animals (shipped for slaughter).

**Disease-Related Differences**

Regardless of the age, disease status may alter organ function, hydration, body temperature, metabolic rate, and other physiologic parameters,
and thus may influence ADME and susceptibility to various xenobiotics.

The following are a few examples:

- Parasitism may be a serious problem, and may alter the intestinal or dermal barrier as well as serum protein status, and sometimes the function of the liver, kidneys, lungs or other organs involved in ADME.
- Infectious diseases may be a common or rare factor compromising the patient in various ways depending on the organs involved and the character/severity of the process.
- Preexistent metabolic disorders, glandular disorders, or organ failure are relatively common and can complicate diagnosis and management.

Various Genetic Factors Influence Individual Variation

Interspecific Differences -

Example - Non-steroidal Anti-inflammatory Drugs

Plasma halflife of drugs in four species of experimental mammals. Differences among species are related to pharmacokinetic variations in ADME.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Rat</th>
<th>Dog</th>
<th>Monkey</th>
<th>Human Being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piroxicam</td>
<td>6 (males)</td>
<td>45</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>16 (females)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4</td>
<td>0.3</td>
<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>Naproxen</td>
<td>5</td>
<td>35</td>
<td>1.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1</td>
<td>2.5</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>72</td>
</tr>
<tr>
<td>Fenprofen</td>
<td>8</td>
<td>4</td>
<td>0.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Sulindac</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
</tbody>
</table>

Human beings are predisposed to phenylbutazone toxicosis since the halflife in man averages 3 days as compared to the monkey, dog, horse, rabbit, rat, and guinea pig, which metabolize the drug more readily and have halflives of 3 to 6 hours.

1. Species Differences in Absorption

Dietary Habits of Various Species Groups - Diet, as well as the structures and physiologic adaptations that accommodate various diets, affect the material available to bind the toxicant, degree of mastication of the material containing the toxicant, microfloral reactions, acidification, digestion, rate of passage, and rate of absorption.

1. Mammals (>4,000 species)

A. Carnivores - Simple digestive tract for easily digested, nutrient-rich food
   a. Felids (eat viscera of prey)
   b. Vampires
   c. Odontocete and baleen whales
   d. Insectivores

Evolutionary strategy of carnivores -
Let the herbivores deal with (avoid, metabolize, and eliminate) plant toxins and mycotoxins on plants - after all, they typically are less toxic than the plants they eat - plus they are nutrient-dense).

Evolutionary liabilities of carnivores -
Don't thrive when there are not enough herbivores to eat. Highly exposed to fat-soluble, slowly metabolized xenobiotics that accumulate via food chains - especially when they rely on long aquatic food chains. Bioaccumulation factors (the ratio between the concentration in animal tissues and that in the environment, e.g., water) can reach many orders of magnitude.

B. Omnivores - More complex digestive tracts: e.g. swine, some rodents
C. Herbivores - Much more complex - longer transit times, efficient absorption
   a. Ruminants
Structure/function is even more age-dependent than in monogastrics

**Preruminant vs. ruminant** - depends on age and diet - young **calf** or **lamb** is more like a monogastric than a ruminant - until adapted to high roughage diet. This influences ruminal toxification, detoxification, and dilution of toxic agents.

Rumen dilutes and detoxifies many toxicants but toxifies others. For example, the rumen is a highly anaerobic place which tends to reduce a number of compounds (thus converting nitrate to much more toxic nitrite). Rumen is a reducing environment:

\[
\text{Nitrate (NO}_3^-\text{) converted to nitrite (NO}_2^-\text{)}
\]
\[
\text{Nitrite then oxidizes hemoglobin (Fe}^{++}\text{) to methemoglobin (Fe}^{+++}\text{)}
\]

Dilution of xenobiotics in the rumen is greater than in the stomach of a monogastric and occurs immediately after ingestion.

Binding to fiber (high fiber diets) can significantly reduce bioavailability of some xenobiotics - e.g. some mycotoxins.

**Microbes** in the rumen metabolize many xenobiotics:
- Break epoxides of trichothecenes, which detoxifies these compounds.
- Convert non-protein nitrogen sources (NPN e.g. urea, biuret) to ammonia and then ammonia to microbial protein, which is later digested in the abomasum and intestine. The animal is protected from ammonia toxicosis only when the intake of NPN is sufficiently low, the rate of hydrolysis is sufficiently slow, the rate of microbial protein synthesis is sufficiently high.
- When the rumen contains excess ammonia, the pH increases (ruminal alkalosis) due in part to conversion of ammonia (NH3) to ammonium ions (NH4+). As more ammonia is generated, and fewer protons are available for this reaction, the neutral NH3 is absorbed across the rumen and causes clinical signs of toxicosis. Also, the elevated pH causes a lack of rumen motility, which results in acute bloat.
- Despite the ruminal alkalosis, the affected animal develops a systemic acidosis and hyperkalemia, which can result in cardiac arrhythmias that terminate in death.

   b. Camelids
Similar to ruminants, but forestomachs are configured differently.

   c. **Posterior fermenters** e.g. horses, guinea pigs, hamsters
Microbial digestion of plant material by flora in the cecum and especially the colon is essential for the horse. Predisposed to antibiotic-induced entero-colitis.

   d. **Fruit eaters** e.g. some bats, some primates.

D. Omnivores
Many **rodents**.

**Swine** have some characteristics of posterior fermenters.

II. Birds
Raptors
Fish-eating birds (herons; also some raptors)
Dabbling ducks
Diving ducks
Insectivores
Seed eaters
Nectar-feeding birds (hummingbirds)
Algae/crustacean filter feeders (flamingos)

III. Reptiles
A. **Carnivores**
Venomous, non-venomous
B. **Herbivores**
C. **Insectivores**

IV. Amphibians
Herbivorous as tadpoles (often eat algae); insectivorous/carnivorous as adults

V. Fish
Herbivores, carnivores

**Differences in pH and Motility in the Upper Digestive Tract**

**Monogastrics** - (carnivores and omnivores) tend to have low pH in the stomach (e.g. in the dog and pig, gastric pH range is usually 3 to 4):
Ion traps weak bases (adds a proton to form -NH₃⁺ or >NH₂⁺) - which delays absorption. Weak acids (adds a proton to form -COOH) are neutral when protonated and therefore are absorbed directly from the stomach.

**Posterior fermenters** - (e.g. horses) tend to have a higher gastric pH (of around 5.5) than most other species. The stomach is rarely empty in the horse. Because of it's small stomach (relative to its body size), the animal is nearly a continuous feeder. **Ruminants** tend to have a slightly acid ruminal pH (diet dependent - increase in grain lowers pH).

In common production systems, ruminal pH may approximate 5.5 to 6.5. The rumino- reticular environment does not favor absorption of most drugs. However, drugs of sufficient lipid solubility will traverse the stratified squamous epithelium of the mucosa via passive non-ionic diffusion. Well-absorbed drugs include non-ionized forms of weak acids in the mildly acidic rumen content.

Abomasal (true stomach of ruminants) pH is typically around 3, which is similar to that of the stomachs of monogastrics. However, the flow of ingesta through the abomasum is more continuous than in the stomach of most nonruminants.

![Diagram of Stomach Contents and Intestinal Contents](image)

Proportions of nonionized and ionized forms of acetylsalicylic acid (pKa = 3.5) in biological fluids. Note - This pertains to upper digestive tract pH, as well as that of the intestine, blood, interstitial fluid, and urine.

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**Comparing Differences in Gastrointestinal Absorption Experimentally**

To compare differences in absorption among species, you must have both oral and intravenous dosing data (plasma-concentrations vs. time postdosing) on the species of interest.

**Differences in Respiratory Uptake**

Birds in general are highly effective at moving air through their lungs and tend to come to equilibrium with gases in their environment faster than mammals. This makes them uniquely sensitive to gaseous toxicants!

Birds typically inspire into their air sacs, followed by flow through tubes (parabronchi) in the lungs that have great surface area (small outpouchings along their length) (no true flow into and out of alveoli) and then to the outside. A counter current mechanism (blood flow in the direction opposite that of air flow) is involved which also increases the efficiency of gaseous exchange. The mechanics of the system make dead space much less of an issue than in mammals. Thus, whooping cranes even have a large tracheal loop imbedded in their breast bone.

Birds are highly sensitive to carbon monoxide (CO) poisoning despite the lower sensitivity of their hemoglobin to CO-induced inhibition of oxygen-carrying capacity. As compared to mammals, the more efficient ventilation of birds increases their rate of uptake of inhaled toxicants. Note that coal gas (gas derived from coal) often contained toxic amounts of CO. In the USA, this gas has largely been replaced by the use of natural gas (rich in methane). The presence of CO in coal deposits lead to the use of the "coal miner's canary", as described below in a bulletin for miners published in 1916.

*Birds and mice may be used to detect carbon monoxide, because they are much more sensitive to the poisonous action of the gas than are men. Experiments by the Bureau of Mines show that canaries should be used in preference to mice, sparrows, or pigeons, because canaries are more sensitive to the gas. Rabbits, chickens, guinea pigs, or dogs, although useful for exploration work in mines, should be used only when birds or mice are unobtainable, and then cautiously, because of their*
greater resistance to carbon monoxide poisoning.

Many experiments have shown that if a canary is quickly removed to good air after its collapse from breathing carbon monoxide it always recovers and can be used again and again for exploration work without danger of its becoming less sensitive. Breathing apparatus must be used where birds show signs of distress, and for this reason birds are of great value in enabling rescue parties to use breathing apparatus to best advantage (Burrell and Seibert, 1916).

2. Species Differences in Distribution

Role of Plasma Proteins

Unbound compounds in plasma are generally regarded as free to enter the tissues and exert an effect, while bound xenobiotics generally serve as a depot. Therefore, differences in protein binding among species can account for significant differences in potency of certain drugs and other toxicants.

The fraction of a xenobiotic bound in the plasma proteins is a function of the drug concentration, the protein concentration, the affinity of one for the other, and competition with other endogenous and exogenous compounds that may compete for binding sites. The health and plane of nutrition of the animal can sometimes influence plasma protein concentrations. For example, malnourished animals or parasitized individuals as well as animals with severe liver or kidney disease may have low serum albumin.

Displacement of drugs from binding sites (e.g. warfarin) by other drugs, is a major cause of adverse drug reaction in human beings. In part, this is because of the high protein bound fraction of warfarin and the common use of multiple drugs. It is also a result of the intended use of warfarin at a dose that has a limited effect on blood clotting, i.e. by design there is a significant amount of free drug in the blood which is able to enter the liver.

Thus, if the person has 95% bound + 5% free and only 1% is displaced by another drug (e.g., a sulfonamide), there will be a 20% increase in free warfarin (5 - 6%).

With most drugs, regardless of the species, animals are exposed at doses that do not cause saturation of plasma proteins. Nevertheless, with some drugs, such as sulfonamides, salicylates, and phenylbutazone, therapeutic levels bring about near-saturation concentrations and, as they increase, the percentage bound decreases. Such drugs may therefore have a tendency toward drug interactions in a range of species. Variability among species with regard to the extent of protein binding in the serum depends upon the specific xenobiotic and the doses involved. Salicylates exhibit marked differences among species with regard to binding to plasma proteins.

Although most drugs are bound primarily to albumin, some drugs, such as beta-adrenoreceptor blockers (oxyphenolol, propranolol), antiarrhythmics (lidocaine), and tricyclic antidepressants are bound primarily to alpha1-acid glycoprotein (α1-AGP; an acute phase protein).

There is less α1-AGP in the serum than albumin, therefore, drugs that bind this protein may tend to exceed the serum protein binding capacity more often than those that bind to albumin.

Note - There may be considerable intra-species variation with regard to α1-AGP concentrations in the blood - which can greatly influence individual response to a range of xenobiotics. Therefore, individual variation among dogs with regard to response to drugs with an affinity for α1-AGP (lidocaine, oxyphenolol, propranolol), is much greater than with drugs with an affinity instead for albumin (digitoxin, phenytoin, and diazepam).

Body Fat

Marked differences exist among species, strains, and individuals with regard to the amount of body fat and its mobilization. Some species of wildlife and domestic animals normally have periods of marked mobilization of lipid stores.

Birds - Egg laying, migration

Offspring may be disproportionately exposed via the yolk. Birds may sometimes experience acute toxicoses due to redistribution of persistent insecticidal compounds from the adipose tissue to the brain.

Mammals - Migration; winter starvation; lactation; estivation/hibernation.

Mobilization of fat can greatly reduce the availability of adipose tissues to serve as a depot for xenobiotics. For acute exposures this can increase the amount of xenobiotic in non-adipose tissues including the brain as well as sites of metabolism and excretion. For animals chronically exposed to lipid soluble metabolically-resistant compounds, mobilization of body fat can elevate plasma concentrations of the xenobiotic increasing the likelihood of toxicosis in the animal (or in it's developing or nursing offspring).

Absorption by the Embryo and Fetus: Separation of the Maternal and Fetal Blood

The number of layers that separate maternal and fetal blood influence not only the rate of passage of small proteins, but also that of a range of xenobiotics. The molecular size and polarity of the molecule may influence the rate of transfer from the dam to the offspring and back.
3. Species Differences In Metabolism
Factors Intrinsic and Extrinsic to the Liver

Differences among species in the rate of metabolism by the liver are a function of factors intrinsic to the liver and factors extrinsic to the liver. For most drugs, biotransformation is dependent primarily upon factors intrinsic to the organ, e.g. constitutive enzyme profile of the species and/or enzyme induction brought about by xenobiotics, including dietary components. In this case, biotransformation is restricted to the fraction of the drug that is free in the plasma.

The process in this case is termed restrictive, non-flow dependent.

For some drugs, however, (e.g. lidocaine and propranolol), the primary determinant in biotransformation by the liver is extrinsic, e.g. blood flow to the organ.

The process in this case is termed non-restrictive, flow-dependent.

Read: Introduction to the Toxicology of the Liver

Phase I Reactions
Phase I reactions involve enzyme-mediated changes in the xenobiotic molecule that typically cause it to become more water soluble (e.g., hydroxylation or epoxide formation by P450 enzymes; or hydrolysis by alcohol dehydrogenases).

Examples of Species Differences -
The anti-oxidants, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are potent inducers of epoxide hydrolases in mice but not in rats. In general, rats have low epoxide hydrolase activity relative to mice and rabbits.

Hydroxylation (at least of sulfonamides) occurs in human beings and dogs. Some hydroxy-metabolites are excreted by active renal tubular secretion, while others are conjugated with glucuronic acid before excretion.

Other Sources of Variation -
Differences among strains, sexes, ages, and individuals also exist.
Diet is a significant factor. Diets deficient in protein may caused greatly reduced P450 activity. This is believed to account for reductions in susceptibility to carbon tetrachloride in partially starved animals as compared to controls (starved animals less able to bioactivate CCl4 via P450 to highly reactive and toxic metabolites).

Phase II (Conjugation) Reactions
There are 6 major metabolic conjugation reactions in mammals - and these can be divided into two types: i) those deriving the required energy from an activated endogenous conjugating agent, most often a nucleotide; and ii) those where the xenobiotic undergoes metabolic activation before conjugation.
Acetylation
Acetylation of xenobiotics is catalyzed by N-acetylases and acetylcoenzyme-A. It is believed to be an ancient process, being found in snails and turtles. In mammals, it is present at birth. In some species, acetylation is an important aspect of sulfonamide metabolism. Some species contain strains/individuals that are slow and others that are fast acetylators. The fast acetylators have an enzyme that is missing in the slow acetylators.

Fast-slow acetylation has been demonstrated in human beings, some species of monkeys, and rabbits. Cats, including domestic cats and lions, as well as the civet (a member of the Viviridae, not the Felidae) are able to acetylate sulfadimethoxine. The fraction of a dose acetylated was 18% in the domestic cat, 48% in the lion, and 66% in the civet. Dogs and related species (e.g. hyena) cannot N-acetylate sulfadimethoxide or sulfanilamide. Since acetylsulfanilamide tends to precipitate in renal tubules, the inability to produce the acetyl derivative tends to protect dogs against renal damage with this compound. Dogs are unable to acetylate isoniazid, which predisposes them to isoniazid toxicosis. Failure of dogs to N-acetylate aromatic amines results in their high susceptibility to methemoglobinemia following exposure to these compounds. With some xenobiotics, dogs and related species also sometimes exhibit such rapid de-acetylation that it falsely appears that acetylation never occurred.

Dogs acetylate the S-substituted cysteines that serve as penultimate intermediates in the conversion of glutathione conjugates to mercapturic acids.

Guinea pigs can acetylate a number of types of amines, but they are unable to acetylate the S-substituted cysteines. Thus, although they can form glutathione conjugates, they are unable to excrete mercapturic acids.

Sheep and pigeons may exhibit similar rates of acetylation and deacetylation.

Sulfation
Sulfation is important in that it is used by a range of species to make some types of xenobiotics (but not others) more water soluble and thus excretable.

Example - PAPS is used to sulfate aryl amines but not aliphatic amines. Sulfation occurs in most species of animals including invertebrates, fish, amphibians, reptiles, birds, and mammals. For example, sulfation of phenols is a highly conserved and thus widely employed mechanism of detoxification. Swine have low sulfotransferase activity, and thus little ability to conjugate xenobiotics to sulfate.

<table>
<thead>
<tr>
<th>Species</th>
<th>Percentage of Dose Conjugated</th>
<th>Ratio S/G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sulfate</td>
<td>Glucuronic Acid</td>
</tr>
<tr>
<td>Human &amp; old wld monkeys</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>New world monkeys</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Rat &amp; mouse</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Cat</td>
<td>93</td>
<td>1</td>
</tr>
<tr>
<td>Pig</td>
<td>2</td>
<td>95</td>
</tr>
</tbody>
</table>

Phenol Conjugation to Sulfate and Glucuronic Acid in Various Species

<table>
<thead>
<tr>
<th>Species</th>
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</tr>
</tbody>
</table>
Sulfation and glucuronidation systems tend to balance one another, since similar functional groups are conjugated by the two systems. Sulfation generally involves enzymes with a high affinity, but low capacity to conjugate phenols. Conversely, glucuronidation enzymes generally have a low affinity but a high capacity for conjugating phenols.

**Glucuronide Conjugation**
Glucuronide conjugation is a major detoxification pathway for a range of xenobiotics. For example, glucuronide conjugation is involved in metabolism of steroids, salicylates, morphine, and codeine. Glucuronide conjugation occurs in most laboratory animals and man, but not hens or spiders. The Gunn rat is used in research as a model of "defective" glucuronyl transferase. Cats (domestic shorthair, lion, lynx) have "defective" glucuronyl transferase (see below under cats). Thus, cats, including domestic cats, lions, and lynx, as well as the civet are unable to glucuronidate 1-naphthyl-acetic acid. Domestic cats form little or no glucuronide conjugates with phenol, naphthol or morphine, but they readily form glucuronides with bilirubin, thyroxin, certain steroids, and phenolphthalein. Cats are highly susceptible to aspirin toxicosis (related to low glucuronide conjugation). The half-life of aspirin in cats is 3 - 4 times longer than in dogs.

**Glutathione (GSH) Conjugation**
GSH conjugation occurs in the cytosol by the action of GSH-transferases. This is an induceable process, unlike most other cytosolic conjugating enzyme systems. Induction of GSH transferases may be on the order of a two or three fold increase in activity. Induction of GSH transferase activity varies among species. The anti-oxidant, butylated hydroxyanisole (BHA) is a potent inducer of GSH transferases in mice but is less effective in rats.

**Amino Acid Conjugation**
Taurine conjugation occurs in many species, but is well developed only in carnivores. Chimpanzees conjugate aromatic and heterocyclic carboxylic acids to glutamine. Human beings conjugate benzoic acid to glycine (this combination = hippuric acid).
Note - Five conjugation reactions seem to occur only in human beings and other primate species. One of these involves the amino acid glutamine:

Glutamine conjugation of arylacetic and aryloxyalkyl acids (human beings, apes, old & new world monkeys).

The other four are:

N'-glucuronidation of certain methoxysulfonamides (all primates).
Quaternary N-glucuronidation of tertiary aliphatic amines (human beings and apes only).
C-glucuronidation of pyrazolone rings (man and apes only).
O-methylation of 4-hydroxy-3,5-diiodobenzoic acid (human beings, old & new world monkeys).
Metabolic Rates and Species Differences during Different Seasons

- Body temperature. **Homeotherms** vs. **poikilotherms**.

- Influences whether the species will be out and about, and thus potentially exposed, at various times of the year (climate - latitude - dependent).
- Influences metabolic rate, and thus the rate of metabolism and elimination of xenobiotics, at different times of the year.

Evaporation rates in summer vs. winter.

- Influences rate of elimination of volatile substances (may be greater in summer).

Differences in metabolism in different seasons.

- Especially important in animals that hibernate. Metabolism may slow, but fat mobilization may be marked over time, causing a xenobiotic to lose its adipose tissue depot - and thereby increasing the opportunity for the liver to act on it.

The metabolic rates of **birds** is very high.

- Blood glucose is around 200 mg% in normal birds. Therefore starvation for comparatively short periods of time may result in death more often than in mammals. Birds that do not eat voluntarily may require feeding by hand, by tube, and/or parenterally.

### 4. Species Differences in Elimination

**Renal Elimination**

The kidney of **birds** differs from that of most mammals. In birds, renal lobules are located throughout the organ. The different lobules are not readily separated from one another but instead are intermingled with their neighbors. In birds, the kidneys have a central vein, somewhat like the liver.

**Birds** have two types of nephrons, the short "reptilian type" which have no loops of Henle, and the long, medullary, "mammalian type" which have loops of Henle. The different types are coordinated through intermittent contractions of afferent arterioles, depending on the salt and hydration status of the individual.

**Birds** also have a renal portal system, in which much of the blood perfusing the kidney (50 to 75%) is derived from the external iliac and sciatic veins. The fraction of blood from the common iliac vein that is diverted into the renal portal vein is determined by the degree of closure of the renal portal sphincter. This sphincter is under nervous control and has both adrenergic and cholinergic receptors. When the sphincter is relaxed and thus open, blood can bypass the renal portal system, going on into the posterior vena cava.

**Birds**, at least some strains of domestic fowl, have comparatively low glomerular filtration rates. As compared to mean GFR values of 2.5 to 4.0 mL/min/1.73 m² in humans, and 0.8 mL/min/1.73 m² in dogs, the mean GFR in domestic fowl is approximately 0.3 mL/min/1.73 m².
5.1 ml/kg/min in cats and 3.0 to 4.2 ml/kg/min in dogs, GFR values in domestic fowl ranged from 1.4 to 4.7 ml/kg/min, with most values below 3. The primary nitrogenous excretory product in birds is uric acid, which is less water soluble than urea and which readily precipitates in renal tubules and eventually other sites in animals dehydrated for a range of reasons. The formation of crystals of uric acid results in a loss of its osmotic activity, such that water reabsorption can continue. This contributes to the observation that dehydrated fowl can reabsorb 99% of the fluid filtered by the glomerulus. The low GFR and high reabsorption of water from avian excreta seems to increase their susceptibility to toxicoses caused by agents that normally leave via the urine, such as excess salts, water soluble drugs such as arsanilic acid, and heavy metals.

Urine pH (alkaline in ruminants, and rabbits, often acid in carnivores) influences the rate of elimination of specific xenobiotics via the urine. At least in part, this is because the rate of passive reabsorption under different pH conditions is influenced by the pKa (the pH at which a molecular site is half-ionized) as well as the lipid solubility. Molecules in the renal filtrate that are neutral and nonpolar are more likely to be reabsorbed than those that are charged and polar. Ruminants tend to have a urine pH that is alkaline (pH of 8 - 9) as well as a high rate of urine output. These factors decrease the passive tubular resorption, and thus promote the elimination of sulfonamides.

Human urine pH generally is in the 5 to 7 range.

Dog urine varies in pH from 6 to 9.

Effect of urine pH on excretion of acetylsalicylic acid (aspirin = ASA) via the kidney. - Dog, male, 12 kg, hydrated with water (250 ml orally) 1 hr before the experiment. ASA (0.5 g orally) was given 45 min before the experiment. ASA (50 mg) in 0.9% NaCl in water (150 ml) was continuously infused during the experiment. At 20 to 25 min NaHCO3 (0.5 g) was given intravenously. Urine collections were made at 15-min intervals from a bladder catheter.

Dogs have a relatively poor ability to excrete organic acids (their organic anion excretion system is poorly developed) - which increases susceptibility to the phenoxy herbicides, such as 2,4-D.

Elimination Via the Milk
The milk of cows tends to be slightly acidic (pH of 6.5 to 6.9) relative to the plasma (pH of 7.2 to 7.4), and it contains considerable milkfat (note many species have much more fat in their milk than cows).
Therefore, milk tends to concentrate basic, as well as fat soluble drugs and toxicants. This may result in relay of toxicants from cows, especially to beef calves and human beings with a high milk intake (e.g. infants).
The toxic principles of white snakeroot (Eupatorium rugosum), apparently partitions into milk preferentially such that lactating cows ingesting the plant are protected from poisoning, whereas nursing calves and human beings that ingest the milk are highly predisposed to poisoning.

Other Individual Species Characteristics/Differences of Importance in Clinical and Environmental Toxicology
Some of these Relate to Species Differences in Absorption, Distribution, Metabolism and Excretion (ADME)
General Considerations:

- Different species vary widely with regard to their likelihood of exposure to given toxicants (environments vary, food varies).
- Different species once exposed often vary widely in their susceptibility to various toxicants (different gastrointestinal environments, different enzymes involved in toxification or detoxification).
- Different species may manifest toxicosis due to a single agent in quite different ways.
- Sometimes, within a species different breeds may vary with regard to their susceptibility to a single toxicant.
- The use of adsorbents and cathartics is common to most species, but the other measures that should be used to terminate gastrointestinal absorption vary widely among species. For some species, emetics or enterogastric lavage are NEVER recommended.
- Appropriate antiarrhythmics vary among species.
- Appropriate anticonvulsants vary among species.
- Appropriate drugs for other purposes often vary among species.
- Drug dosages often vary among species.
- Some clinical pathology parameters (e.g. serum enzymes) vary widely among species.

Human Beings

- Uniquely sensitive to idiosyncratic reactions to chloramphenicol, which may cause irreversible aplastic anemia.
- Relatively sensitive to lead toxicosis; prone to decreased CNS function; and anemia may be associated with chronic exposure.
- The skin of swine and guinea pigs tends to give a rather good approximation of the absorption by human skin. However, there are marked exceptions, and data must be determined and compared among these species on a case-by-case basis.

Dogs

- Unlike man, fetal hemoglobin of dogs is the same as adult hemoglobin [fetus has decreased concentrations of 2,3,diphosphogluatrate (2,3-DPG)].
- Indiscriminate eating habits: Commonly consume garbage (source of bacterial and fungal organisms and toxins), dead animals (carrion = sources of bacterial organisms and toxins), lead objects, motor oil, rock salt, antifreeze, owner's or their own medications (especially chewable products) in huge quantities.
- Dogs occasionally ingest anesthetizing (and possibly lethal) doses of euthanasia drugs given to large animals (especially when they eat the viscera = frequently the first thing consumed by a carnivore). Often, such drugs are not well distributed in the body by the time that death occurs.
- Extreme differences in size among breeds - influences xenobiotic doses in 2 ways.
  - Size alone - often an animal eats all of a toxicant available. Whatever quantity is there, when ingested by a small dog, comprises a larger dose as compared to ingestion by a larger dog.
  - For some drugs, lower doses on a mg/kg basis have been recommended for large dogs than for smaller dogs.
- Aging rates vary among breeds - Chihuahua vs. great Dane.
- Susceptibility to selected toxicants varies among breeds.
  - Some collies are very susceptible to the anthelmintic ivermectin since the blood-brain barrier is not effectively in excluding the drug.
  - Some sight hounds such as greyhounds seem to be quite susceptible to some organophosphorus insecticides.
  - Some Bedlington terriers are prone to copper storage diseases > copper builds up > liver failure.
- Dogs pant (shallow, rapid respiration) to thermoregulate in warm surroundings which may alter respiratory exposure.
- Dogs are low to the ground, and carbon monoxide is slightly lighter than air, but dogs still tend to be more sensitive to carbon monoxide than man. Dogs may die before man from smoke inhalation.
- Canids are slightly more susceptible to the "canicide" Compound 1080; relay toxicosis can readily occur in canids.
- Dogs are quite susceptible to, and commonly ingest, brodifacoum and diphacinone (anticoagulant rodenticides).
- Dogs are quite susceptible to cholecalciferol (vitamin D3) containing rodenticides.
- Dogs are prone to eat methylxanthine-containing products such as caffeine tablets and chocolate in massive (toxic) quantities.
- Dogs often have an acid urine which contributes to their high susceptibility to sulfonamides (also, See acetylation above).
- Dogs are relatively susceptible to ethylene glycol and commonly ingest it.
- Dogs are relatively susceptible to onion toxicosis > Heinz body anemia. Note that, while human beings have only two exposed (reactive) sulfhydryl groups on the globin beta chains of their hemoglobin, dogs have four such sulfhydryls.
- Dogs are relatively susceptible to blue-green algae toxins.
- Dogs are comparatively susceptible to estrogen-induced aplastic anemia. (Cats given doses five times greater than those that caused aplastic anemia in dogs developed only mild stem-cell depression).
- Unlike hamsters and rabbits, dogs are susceptible to carbaryl-induced teratogenesis.

Dogs readily vomit.
  - Preferred emetic: apomorphine.
  - Second choice: 3% hydrogen peroxide or syrup of ipecac.
Enterogastric lavage can be used in dogs.
Peritoneal dialysis can be used in dogs to enhance elimination of water soluble xenobiotics and/or to detoxify animals with renal failure.

Cats

- Most are more selective in their eating habits than dogs, but sometimes still consume toxic quantities of human medications and occasionally massive amounts of chewable veterinary drugs - e.g., L-1-methionine, a urinary acidifier.
- Fastidious grooming habits tend to increase oral exposure to substances on the skin.
- Domestic cats are a species well adapted to an arid environment, with a rather concentrated urine which may predispose them to poisoning by certain water soluble toxicants. This may play a role, for example, in their considerable sensitivity to ethylene glycol poisoning.
- The number of reactive sulphydryl groups on the beta chain of the globin molecule of the hemoglobin molecule of various species is correlated with the susceptibility of the molecule to oxidative injury. In contrast to human beings (who have two) and dogs (that have four), cats have eight or more reactive sulphydryls on their globin component. The hemoglobin of cats is therefore extremely sensitive to oxidative stress, readily forms methemoglobinemia (normal hemoglobin with Fe²⁺ converted to methemoglobin with Fe³⁺ & Heinz bodies). Heinz bodies are denatured hemoglobin molecules that become attached to the inner surface of the erythrocyte cell membrane, thus causing it to be deformed. The deformed red blood cells are then prematurely "picked off" and destroyed by the spleen, thus resulting in Heinz body anemia. **Note** - Limited numbers of Heinz bodies are seen in normal cats, and the feline spleen is less able to remove defective erythrocytes than in other species, so Heinz body-bearing cells persist longer in the blood of cats than in other domestic species.
  - High susceptibility to acetaminophen is presumed to be a function of limited glucuronide conjugation (and subsequent depletion of GSH) coupled with subsequent oxidative injury in erythrocytes leading to oxidation of hemoglobin (Fe²⁺) to methemoglobin (Fe³⁺). The usual syndrome seen with acetaminophen toxicity in cats (methemoglobinemia) differs from that in human beings and dog (species that more often develop liver failure).
  - Other substances that may cause methemoglobinemia in cats include: benzocaine, methylene blue (high enough doses), phenoazopyridine, para-aminobenzoic acid, and onions.
- Feline erythrocytes have a considerably shorter life-span than those of most other species. The mean life span ranges from 66 to 79 days, and this may increase susceptibility to "depression anemias", such as that associated with chloramphenicol exposures. Chloramphenicol-induced anemia is nevertheless reversible in cats (and dogs).
- Cats are very sensitive to arsenic including sodium arsenate insecticides.
- Cats are highly susceptible to organochlorine insecticides of all types.
- Cats seem to be more susceptible than most species to pyrethrin and pyrethroid insecticides.
- Persians seem to be even more susceptible than other breeds of cats to insecticidal dips.
- Cats are quite susceptible to organophosphorus insecticides.
- Feline RBCs are extremely low in cholinesterase. Therefore, almost all of whole blood cholinesterase activity is from plasma. Consequently, blood cholinesterase is a sensitive indicator of exposure, but it may be depleted to "zero" activity even with only subtoxic exposures.
- Cats have a low tolerance for lidocaine as an antiarrhythmic agent. Signs of toxicity include drowsiness, emesis, nystagmus, tremors, and seizures.
  - Usually a b-blocker is used to treat cats for serious tachyarrhythmias, and atropine for bradyarrhythmias.

**Cats readily vomit.**
- There is no safe and effective dose of apomorphine in the domestic cat.
- Preferred emetics for cats = 3% hydrogen peroxide, or syrup of ipecac; some veterinarians like xylazine = Rompun ®. Note: depression from xylazine can be reversed with yohimbine or similar drugs
- Enterogastric lavage can be used for cats.
- Peritoneal dialysis can be used for cats.

Ferrets

- Ferrets have more submucosal glands in their bronchial walls and an additional generation of terminal bronchioles. These features are more similar to the airways of human beings than those of dogs.
- Female ferrets are induced ovulators and, in the absence of males, mature females experience endogenous estrogen-induced bone marrow suppression and death.

Swine

- Swine readily vomit.
- As compared to other domestic animals, the morphology and physiology of swine tend to make the species a preferred model for extrapolation to human beings
- Used increasingly in cardiovascular and pulmonary and digestive system research.
- Pulmonary function criteria in swine are similar to those of human beings. Also, airway diameters are similar in size. However, the complex turbinates of swine filter out particulates more effectively than in human beings.
- Fetal hemoglobin is the same as adult hemoglobin.
- Piglets are still very sensitive to carbon monoxide - perhaps due to the difference in 2,3-DPG
- Ingestion of feces by young (<5-week-old pigs) provides them with vitamin K which offsets the requirement for supplementation (as well as the associated hypoprothombinemia and lethal hemorrhage).
- Swine are extremely susceptible to poisoning by anticoagulant rodenticides.
- Hydrogen sulfide gas is a relatively common problem in pigs raised in captivity > lethal to man as well and acts rapidly in any species > respiratory paralysis.
- Some strains of swine commonly react to halothane by developing malignant hyperthermia.
- Swine are very sensitive to clay pigeon (contain phenolic compounds) poisoning.
- Diesel fuel used as a vehicle for topically applied insecticides causes abortion in swine.
- Swine are relatively susceptible to blue-green algae toxins.
- Swine are highly sensitive to infertility and signs of estrogenism caused by the mycotoxin zearalenone.
- In response to exposure to toxic concentrations of the mycotoxin fumonisin in feed, pigs develop pulmonary edema, mild liver and pancreatic damage, and possibly immunosuppression.
- Swine are very sensitive to perirenal edema and nephrosis from ingestion of pigweed (Amaranthus retroflexus).
- Swine are prone to congestive heart failure as a result of exposure to gossypol.
- Swine are highly sensitive to water deprivation/sodium ion toxicosis.
- In swine, phenylarsonic feed additives cause demyelination > paralysis; and arsanilic acid (ρ-aminobenzenearsonic acid) may cause blindness.
- Swine are relatively tolerant of lead.
- Swine readily vomit. Emetic of choice in pigs: 3% hydrogen peroxide, which can be given slowly via the nares. Note - Apomorphine is ineffective in swine.
- Activated charcoal administration. Swine can be given activated charcoal via the snout (slowly). Hold animal with a snare, rinse with water when done.
- Enterogastric lavage is not practical + concern re potential distension and rupture of the spiral colon.
- Large herds may necessitate triage and may make getting enough activated charcoal or antidotes difficult.
- For topical exposures, swine can be crowded together, dusted with powdered detergent and rinsed thoroughly with a hose.

Cattle

- Energy metabolism is quite different in ruminants than in non-ruminants. Ruminants rely on short chain free fatty acids as their principle energy source. Blood glucose concentrations are normally around 50 mg/dl.
- In grazing situations, food is typically low in energy, and thus must be ingested in high volumes.
- Like other grazing animals, cattle ingest considerable amounts of soil.
- Like other herbivores, bovine urine is alkaline.
- Excretion of toxicants may sometimes contaminate milk (aflatoxin; white snakeroot toxins) or milkfat (persistent organochlorine insecticides). May be unable to market milk with residues in milkfat exceed tolerances (and some tolerances can be lowered by regulations).
- Producers who cannot sell milk go broke fast.
- e.g., heptachlor epoxide residues caused major economic losses several years ago in Arkansas, Missouri, & Oklahoma.
- Bulls and exotic breeds of either sex are extremely sensitive to chlorpyrifos - 7 mg/kg topically can be lethal to mature bulls vs. cats which are also sensitive but survive at up to 40 mg/kg per os.
- In adult ruminants, organic arsenical feed additives cause typical arsenic (GI, shock syndrome).
- Cattle are very sensitive to acute lead toxicosis. In the past, cattle commonly ingested lead in used motor oil; still eat storage batteries, old paint, etc.
- Cattle are very susceptible to molybdenum toxicosis/copper deficiency.
- Although cattle can vomit, they do not do so with ease, and no effective emetics have been marketed.
- Enterogastric lavage is not practical.
- Rumenotomy is done, but is time consuming and somewhat stressful. It is usually not practical for large numbers of animals.
- Rumen lavage is hard work but can be done using either a very large stomach tube or a trochar. Must have running water. Trochar runs some risk of peritonitis.
- Can bathe animals in herds by crowding them together in a pen and washing with power hose and powdered detergent.
- Obtaining activated charcoal in a large enough amounts to treat herds can be a problem. Commonly recommend 1 #/head. Need to ensure 24-hour access ahead of time! Same problem exists with 2-PAM and other antidotes. Regional antidote depots are a good idea: veterinarians are responsible to rapidly replace whatever is used.
Sheep

- Sheep are very susceptible to copper toxicosis/molybdenum deficiency > liver failure > release of copper > hemolysis, and terminal anemia and renal failure.
- Similar to cattle in many ways but different in others. Similar to cattle with regard to emetics and methods of lavage.

Goats

- Eastern states - Commonly eat mountain laurel (*Kalmia*), *Rhododendron*, and similar plants.
- Somewhat like sheep but tend to be much more independent and inquisitive.
- For most toxicoses, therapy considerations in sheep and goats are much like those in cattle.

Horses

- Do not recommend emetics - weak stomach may readily rupture.
- Oral antibiotics commonly cause overgrowth of *Clostridia* > lethal enterocolitis.
- Very sensitive to ionophore feed additives/coccidiostats, such as monensin > heart failure.
- Very sensitive to thiaminase-containing plants, such as horsetail (*Equisetum*) and bracken fern (*Pteridium*) > neurologic deficits.
- Very sensitive to, and display a unique lesion in response to the mycotoxin fumonis in in moldy corn > leukoencephalomalacia (also develop liver damage; and may die from liver failure).
- Very sensitive to atropine-induced colic > can be life-threatening. Use atropine only in serious cases of OP or carbamate insecticide toxicoses in horses and give *in fluids while ausculting abdominal viscera* > avoid cessation of motility !!
- Vitamin K3 > single injection at recommended dose > lethal nephrosis (injectable no longer marketed).

Rabbits

- Rabbits "must" consume their own feces unless supplemented with compensatory vitamins.
- Some strains have high atropinase, which protects them from toxicosis caused by atropine-containing plants such as *Atropa belladonna*. In such individuals, therapy for organophosphorus insecticide toxicosis may necessitate comparatively high doses of atropine (use with care, not all strains have high atropinase).
- Significant crystalluria is normal in rabbits which have a rather alkaline urine (pH 8.2). Phosphate and carbonate crystals predominate.
- Urine is normally turbid and cloudy yellow to red-brown.
- Do not recommend emetics - weak stomach may readily rupture.
- Oral antibiotics commonly cause overgrowth of *Clostridia* > lethal enterocolitis.

Guinea Pigs

- Young guinea pigs are much larger and more mature when born than are rats and mice.
- Susceptible to antibiotic-induced overgrowth of *Clostridia* > lethal enterocolitis.
- Guinea pigs are extremely sensitive to 2,3,7,8-tetrachlorodibenzodioxin (TCDD).
- Unlike hamsters and rabbits, guinea pigs are susceptible to teratogenesis induced by carbaryl.
- Guinea pigs are known for their ability to methylate histamine and nicotine, both reactions being catalyzed by the enzyme, azaheterocycle N-methyltransferase. Nicotine is a weak base and methylation of the pyridil nitrogen atom results in the presence of a charge at both nitrogens at physiologic pH. This increases water solubility and urinary excretion.
  - Guinea pigs are sometimes used to study the consequences of methylation of other xenobiotics.
- Cannot vomit.

Rats

- Have no gallbladder.
- Different capacities of DNA repair of various tissues have been explored in the rat.
  - In rats, a single high dose of dimethylnitrosamine induces kidney, but not liver, cancer because of the capability of liver repair enzymes to remove the alkylated DNA.
  - Similarly, ethynitrosourea causes formation of DNA adducts in the liver, kidney, and brain, but because of the limited DNA repair capacity in brain tissue, the animals often develop cancer there whereas, they rarely develop renal cancer, and almost never develop cancer of the liver.
Mice

- After several hundred bioassays, it has become apparent that the B6C3F1 mouse is much more sensitive to exposure to a number of carcinogens than is the Fisher 344 rat (these two species have been used most widely in bioassays of chronic chemical exposure).
  - For example, of 85 chronic bioassay studies, the mice developed hepatomas in 45 studies, while the rats did so in only 15 studies.
  - The Nutrition Foundation ad hoc review panel concluded that the mouse, unlike the rat, develops tumors from agents found to be non-genotoxic in mutagenesis assays. Therefore, it was suggested that the mouse may possess more pre-initiated cells in the liver, and, therefore, the non-genotoxic toxicants are simply acting as tumor promoters. If this theory is valid, the question that remains is whether human beings have many or few pre-initiated cells (whether various human beings resemble the mice or the rats).

Woodchucks = Groundhogs = *Marmota monax*

- May have woodchuck hepatitis virus (WHV), which is a close relative of human hepatitis B virus (HBV).
  - Woodchucks with chronic active hepatitis induced by WHV are predisposed to hepatocellular carcinoma (similar to human beings with HBV).
  - Chronic carriers of WHV are available in nature and are not expensive to maintain in captive colonies.
  - Recent epidemiologic studies suggest that, if human exposure to aflatoxin causes liver cancer, "it almost always does so in the presence of HBV" (Bruce, 1990). Therefore, the woodchuck may be a species of choice for future studies of aflatoxin and its bioactivation/detoxification/elimination in the presence and absence of virally-induced chronic active hepatitis.

Birds

- See the section above on Metabolic Rate.
- In some species the crop is a major storage site of food where it is moistened and softened before passing into the remaining digestive tract. In others, such as geese, the esophagus is a site of considerable storage. Geese are therefore predisposed to local damage in the esophagus from damage induced by direct acting toxicants, such as the more toxic trichotheccenes.
- Some species have a gizzard which has a highly muscular wall and a thick stratified squamous mucosa. In this organ, grinding of the food occurs in the presence of small stones. This can wear down solid toxicants, such as lead objects and the seeds of toxic plants, thus increasing their surface area and hence, their bioavailability and toxicity.
- The amino acid used by many species of birds to conjugate aromatic and heterocyclic carboxylic acids in ornithine.
- Birds tend to be much more tolerant than mammals to the acute effects of DDT. Nevertheless, falcons, bald eagles, brown pelicans, and mallard ducks were susceptible to DDT-induced eggshell thinning. By contrast, gallinaceous species (chickens, etc.) were resistant to this effect.
- Chickens are highly resistant to carbon tetrachloride toxicosis.
- Ducks, especially ducklings, are highly sensitive to aflatoxin and sometimes serve as a sentinel species.
- Waterfowl commonly develop botulism. When they die, their bodies serve as anaerobic substrates for production of more toxin by *Clostridium botulinum*, and when fed on by maggots, which in turn are eaten by other waterfowl, a vicious cycle occurs which can result in the deaths of thousands of the birds.
- See section above on Renal Elimination.
- See section above on Differences in Respiratory Uptake.
  - Caged birds are very sensitive to gases and particulates released from overheated Teflon or Silverstone cookware > deaths occur at concentrations of breakdown products in the air that are subtoxic or minimally toxic to other species.
  - There may be reason to be concerned with regard to exposure to volatile vehicles used indoors to apply household pesticides or dip solutions to dogs or cats.
- Many bird species are highly sensitive to organophosphorus insecticides.
  - Organophosphorus insecticides such as malathion are detoxified by aliesterases and carboxylesterases which induce hydrolysis of the compound. Many bird species have comparatively low levels of these esterases which causes them to be comparatively sensitive to malathion.
  - Thus, diazinon granular insecticide (an OP) is extremely toxic to waterfowl and some passerine species.
  - Cage birds may be extremely sensitive to chlorpyrifos.
- The adult hen is susceptible to organophosphorus-induced delayed neuropathy, and it manifests the syndrome with a markedly altered gait. This has resulted in it's use in bioassays for this effect.
- The structure of the digestive tract precludes vomiting in most species. Some species, however, seem to be able to voluntarily eliminate the contents of the upper digestive tract (e.g. vultures). No emetics known. Most cage bird species have a crop which can be lavaged by a skilled veterinarian. Activated charcoal can be given by crop gavage.
Reptiles

- Poikilothermic to semi-warm blooded: when body temperature is reduced, metabolism and elimination may be greatly slowed.
- The primary nitrogenous excretory product is uric acid (see section above on Renal Elimination, especially the parts that pertain to birds).
- Urate crystals cause visceral gout and renal constipation (brought on by a buildup of uric acid crystals). This can result from an excess of protein or organ meats in the diet.
  - The buildup of uric acid in the animal may lead to severe liver failure and granuloma formation.
  - Reptiles with infectious diseases often drink less water than normal. This, coupled with their treatment, predisposes them to antibiotic toxicoses. For example, therapy with gentamicin must often be accompanied by fluid therapy to avoid renal tubular degeneration, which slows excretion of uric acid and thus, contributes to visceral gout.
  - Sulfonamide toxicosis in reptiles may be accompanied by similar visceral gout.
  - Certain tortoises have been known to survive after eating both azalea (*Rhododendron*) and oleander (*Nerium oleander*) leaves in quantities that would rapidly prove lethal to sheep or goats weighing a hundred fold more than the tortoises.

Amphibians

- Two-phase "amphibious" life cycle of most species results in exposure of eggs, embryos, and tadpoles via the water; of tadpoles via microscopic plants (e.g., green algae) (and sometimes zooplankton) in the water; and adults via the land and air as well as via the food chain (depending on the makeup of their diet - often insects; vertebrates).
- As compared to mice, frogs are 22 times as tolerant of the organophosphorus compound paraoxon. They are also more tolerant of the carbamate eserine, another cholinesterase inhibitor. This is an apparent result in differences in the structure of amphibian cholinesterases as compared to those of mice.

Fishes

- The gills are major organs of respiration and elimination.
- Kidneys vary among fish species, but often include a kidney primarily for urine production, and a head kidney, which functions more like bone marrow of mammals. Sometimes the two types of kidneys are joined together.
- Fishes breathe water, hence the resultant high level of exposure of lipid membranes of the gills to a range of lipid soluble compounds results in some partitioning into the fish; and if the compound is resistant to biodegradation, accumulation in body lipids results.
- Often uptake of persistent halogenated compounds by fish is greater via the food than via absorption across the gills. Predatory fish are exposed both via the water and, especially, from ingestion of contaminated lipids of lower members of the food chain.
- Fish are often highly effective in glucuronidation and sulfation of xenobiotics.
- Glutathione-S-transferases have been found in many terrestrial species, including birds, reptiles, and amphibians, insects, and plants. The lack of GSH-transferases in fishes suggests that the enzymes evolved to protect terrestrial organisms from oxidative injury and xenobiotics in the food and air. Aquatic organisms are bathed in a rich source of nucleophilic material, water, that can hydrolyze many reactive compounds, thus, reducing their toxicity.
- Freshwater fishes have to eliminate excess water. Consequently, they may be less prone to bioaccumulate water soluble toxicants than terrestrial organisms (the latter are more dehydrated).
- Saltwater fishes have to conserve water and eliminate excess sodium.
- Different species of fishes live at different temperatures, and oxygen tensions, and have varied diets.
- Bottom dwellers tend to have higher mixed function oxidase activities than do fishes that liver in the upper water column. This may be an evolutionary response to the greater exposure of the former to lipid soluble toxicants at the interface of the water and sediment.

Arthropods

- Crustaceans *Daphnia pulex* may produce up to $13 \times 10^2$ offspring.

- Insects
  - A single pair of houseflies breeding from April to August is able to produce $191 \times 10^4$ offspring.
  - Organophosphorus insecticides such as malathion are more readily hydrolyzed by mammals than by insects, which have lower levels of esterases. This is one mechanism of selective toxicity.

- Arachnids The amino acid used by some arachnids to conjugate aromatic and heterocyclic carboxylic acids in arginine.
Earthworms

- May accumulate extremely high concentrations of metals (i.e. lead at 330 ppm; zinc at 670 ppm) which would be lethal to mammals.
- Earthworms may be important in the environmental conversion of DDT to DDE. The concentrations of DDE in earthworms, when consumed by birds, may be sufficient to result in eggshell thinning.

Molluscs

Slugs (*Agriolimax reticulatus*) may bioaccumulate diazinon to concentrations (i.e. 400 ppm) that may be toxic to animals that prey upon them.

Coelenterates

- Polyps and jellyfish have both ectoderm and entoderm, as well as the "first" glandular structures.
- They also have connective tissues in the form of mesoglea; and wandering phagocytic cells.
- They have only one opening, which serves as the mouth and anus.
- Among the *Coelenterata*, the cnidarians have tentacles; whereas the ctenophorans have colloblasts instead.
- They have no distinct respiratory or excretory systems.

Sponges (*Porifera*)

- They lack true musculature and a nervous system.
- They generally are sessile marine organisms, but some freshwater species exist.
- Tissues in sponges are perhaps the simplest of all animals and plants.
- They have wandering phagocytic cells.

References


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