Factors affecting Xenobiotic Actions

- The term **xenobiotic** is derived from the Greek words ξένος (xenos) = foreigner, stranger and βίος (bios, vios) = life)
- The term **xenobiotics** is very often used in the context of pollutants such as dioxins and polychlorinated biphenyls and their effect on the biota, because xenobiotics are understood as substances foreign to an entire biological system, i.e. artificial substances, which did not exist in nature before their synthesis by humans
- A **xenobiotic** is a toxicants which is found in an organism but which is not normally produced or expected to be present in it. Specifically, drugs such as antibiotics are xenobiotics in humans because the human body does not produce them itself, nor are they part of a normal diet.
- Natural compounds can also become xenobiotics if they are taken up by another organism, such as the uptake of natural human hormones excreted from humans by fish downstream of sewage treatment plant outfalls or the chemical defenses produced by some organisms as protection against predators.

1. Chemical Defense

- Animals which synthesize their own toxin are able to convert chemical compounds in their body to a poison.
- There are many amphibians that produce skin toxins. The skin toxins are produced by special poison glands, usually located on the animal's back or throughout the skin.

Photo courtesy of Dr. John Daly

The poison dart frog has poison glands scattered all over its body.

1. Chemical Defense

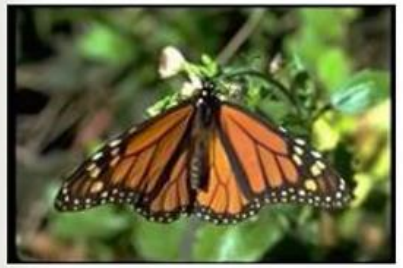


Photo courtesy of T. W. Davies, Cal. Acad. of Sciences.

Many animals accumulate toxin from their food rather than synthesizing it from scratch.

For example, the larvae of Monarch butterflies accumulate toxins from the plants they inhabit. Birds that eat the Monarchs vomit and learn to avoid them in the future. Their bright coloration allows birds to remember and avoid them.

1. Chemical Defense

- Interestingly, many organisms which are distasteful advertise this fact to predators by having bright body colors or markings, as if to say, "Notice me! I'm dangerous!"

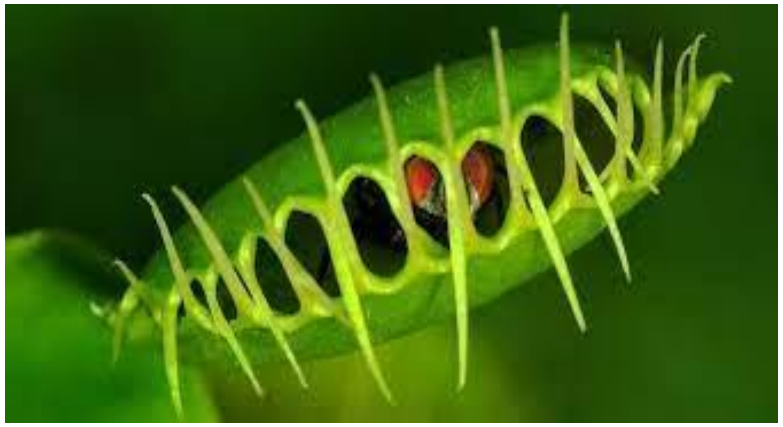
1. Chemical Defense

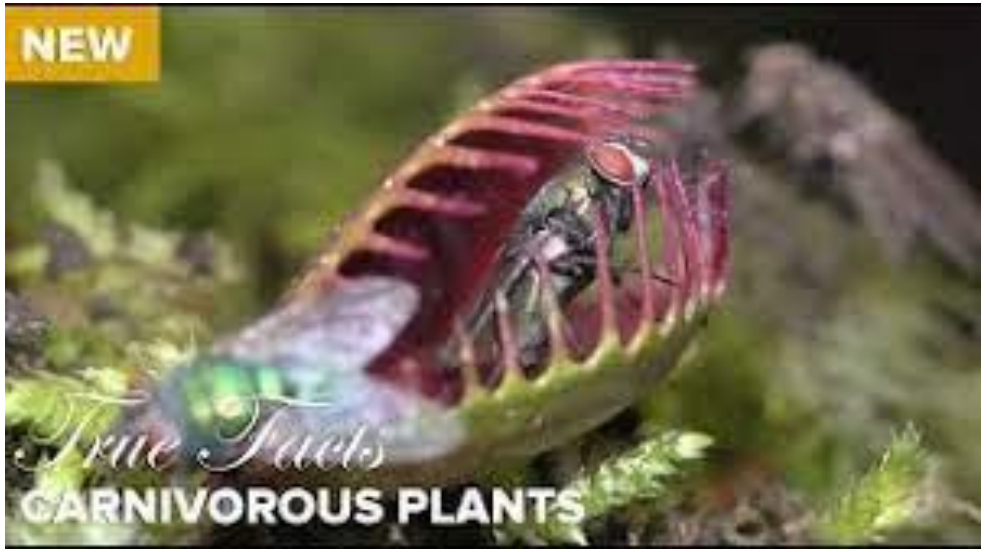
You can see this in the bright colors of the Monarch and the poison dart frog.

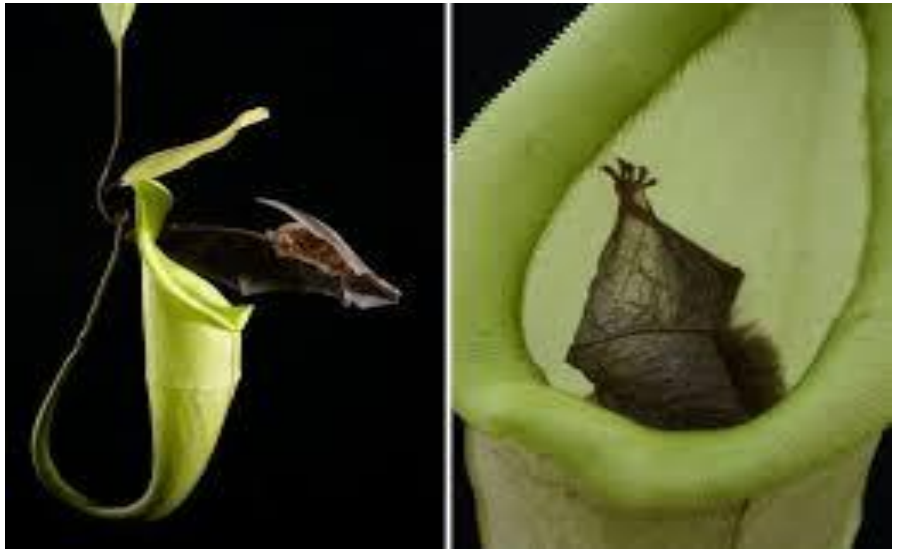
Photo courtesy of T. W. Davies, Cal. Acad. of Sciences.

Photo courtesy of Dr. John Daly

Plant predators







Factors affecting Xenobiotic Actions

- Physicochemical properties of toxicants;
- Dose or concentration;
- Mode and duration of exposure;
- Environmental factors;
- Interaction, and
- Biological and nutritional factors

Physicochemical properties of toxicants

- Physical and chemical characteristics: solid, liquid or gas
- Whether soluble in water or in lipid?
- Organic or inorganic materials?
- Ionized or non-ionized? etc.
- Above characteristics can affect the ultimate toxicity of a pollutant
- For instance, a non-ionized substance may be more toxic than an ionized or charged counterpart because the non-ionized species can pass through the membrane more easily than ionized species, and therefore, is more readily absorbed and able to elicit its toxic action.

Dose or Concentration

- Dose or concentration of any pollutant to which an organism is exposed is often the most important factor affecting its toxicity
- Once a pollutant gains entry into a living organism and reaches its target site, it may exhibit an injurious action
- Any factors capable of modifying internal concentrations of the pollutant can alter its toxicity
- The effect of the pollutant is a function of its concentration at the locus of its action
- A pollutant may either depress or stimulate normal metabolic function
- Example: Kuitan city: western China: Arsenism disease (many residents suffer from arsenism) : consuming well water containing high level of As

✓0.12mg As/l for 10 years showed 1.4% prevalence rate of the city population

✓0.6mg As/l for 6 months showed 47% prevalence rate of the city population

Dose or Concentration

- Plants exposed to different kinds of pollutants often show depressed growth or enzyme activity

✓For example: mung bean seedling exposed to varying concentrations of sodium fluoride (NaF) for 3 days showed significant decreases in root elongation and activity of invertase, a key enzyme responsible for the breakdown of sucrose into glucose and fructose

✓Invertase activity in seedling exposed to 0.2, 1.0, and 2.0m*M* NaF was decreased by 9, 22, and 41% respectively, compared with control treated with water

Duration and Mode of Exposure

- Long term duration of exposure: severe injury
- The dose or concentration of a toxicant is also important
- The mode of exposure of plants or animals to toxicants, continuous or intermittent, and the activity level of an exposed animal are also important in affecting pollutant toxicity
- Rats exposed to ozone (O_3) continuously for a sufficient period may develop pulmonary edema
- During intermittently exposed with same dose of O_3 : no pulmonary edema develop
- Reason behind: may be: living organism often can, to some extent, repair injuries caused by environmental chemicals

Environmental Factors

- Environmental factors, such as temperature, pH, humidity, and others, may affect pollutant toxicity in different ways

Temperature

- Changes in ambient temperature affect the metabolism of xenobiotics in animals
- e.g., the rate at which chemical reactions occur increases with increase in temperature
- With fish, an increase in temperature leads to faster assimilation of waste and therefore faster depletion of oxygen.
- Fish and other aquatic life can live only within certain temperature ranges
- For metals, toxicity may increase with either an increase or decrease in ambient temperature
- Plants: affects the response of vegetation to air pollution. Plant sensitivity to oxidants increases with increasing temperature, up to 30^{o}C.

Environmental Factors

pH

- Maintenance of a particular pH in body fluids is critical for the well-being of animals and humans
- Human body fluids must be maintained at very near to **pH 7.4** for the body's metabolism to proceed properly, because most body enzymes function best when the pH remain around neutral.
- Soil: Increases in acidity (low pH) enhance the mobilization of metals in soil. Acid precipitation, may greatly increase the availability of toxic metals, such as, aluminum, to plants. Zinc availability increases drastically in soil with low pH (Alloway, 1995),

Environmental Factors

Humidity

- The sensitivity of plants to air pollutants increases with increase in relative humidity
- High relative humidity has been found to contribute to acute damage to forest vegetation caused by sulfur dioxide (SO_2)
- Injurious effects of O_3 and nitrogen dioxide (NO_2) on vegetation have also been found to be greater when the relative humidity is high
- Similar effect with: fluoride toxicity, gladiolus plants when relative humidity increased from 50 to 80%.

Interaction

- The actions of individual toxicants are affected by many factors, such as portals of entry, mode, metabolism, and others described before
- Organisms are generally exposed to a complex mixture of different pollutants
- Simultaneous exposure to more than one toxicant can have a dramatic impact on the outcome of exposure
- Toxicants may interact to produce additive, potentiation, synergistic, or antagonistic effects.

Interaction

- Additive: interaction occurs where the combined effects of two compounds are simply additive

$$2 + 2 = 4$$

- Synergism: describes a combined toxicity that is greater than the simple additive effect of two compound

$$2 + 2 >>> 4 \text{ (maybe 10 times or more)}$$

- Potentiation: describes synergism where one compound is generally assumed to have little or no intrinsic toxicity when affect alone

$$0 + 2 > 2, \text{ not just } 2$$

Antagonism: is the opposite of synergism. It is the situation where the combined effect of two or more compounds is less toxic than the individual effects

$$2 + 2 < 4$$

Interaction: Examples

- Smoking and exposure to asbestos-synergistic effect-increased lung cancer
- The presence of particulate matter such as sodium chloride (NaCl) and SO_2 and sulfuric acid mist would have potentiation or synergism effects on animals
- Exposure of plants to both O_3 and SO_2 simultaneously is more injurious than exposure to either of these gases alone
- Single exposure to O_3 at 0.03 ppm and to SO_2 at 0.24 ppm for 2 hours or 4 hours did not injure tobacco leaves. However, when the leaves were exposed to a mixture of O_3 at 0.031 ppm and SO_2 at 0.24 ppm for 2 hours, moderate (38%) injury to the older leaves of Tobacco occurred

Interaction: Synergism(2 + 2 >>> 4)

- A single exposure to O_3 at 0.03ppm and to SO_2 at 0.24 for 2 hours or 4 hours did not injure tobacco leaves
- However, when the leaves were exposed to a mixture of O_3 at 0.031ppm and SO_2 at 0.24ppm for 2 hours, a moderate (38%) injury to the older leaves of Tobacco occurred

Table 5.1 Synergistic Effect of Ozone and Sulfur Dioxide on Tobacco Bel W3 Plants

	Pollutant (ppm)		
Duration (hours)	O_3	SO_2	Leaf damage (%)
2	0.03	0	0
2	0	0.24	0
2	0.031	0.24	38

Source: Menser, H.A. and Heggestad, H.E., *Science*, 153, 424, 1966.

Interaction: Additive and Synergistic

- An additive effect was observed on yield depression of bush beans in solution culture exposed to 2 x 10^{-4} *M* cadmium (Cd) and 2 x 10^{-5}*M* nickel (Ni), whereas synergistic effects on yield depressions were observed in solution culture for 5 x 10^{-5}*M* zinc (Zn), 3 x 10^{-5}*M* Cu, and 2 x 10^{-5}*M* Ni

Interaction: Antagonism (2 + 2 < 4)

- A situation in which the toxicity of two or more chemicals presents is less than would be expected were chemicals acted separately
- May be due to chemical or physical characteristics of the pollutants, or to the biological actions of the chemicals involved

Interaction: Antagonism (2 + 2 < 4)

- Cd is known to induce anemia and nephrogenic hypertension, as well as teratogenesis, in animals
- Zn and selenium(Se) act to antagonize the action of Cd. May be due to inhibition of renal retention of Cd by Zn and Se
- Oil mists have been shown to decrease the toxic effects of O_3 and NO_2

Biological Factors: Plants

- Genetic variation: most important factor affecting plant response to environmental pollutants.
- Varies between species of a given genus and between varies within a given species; due to morphological, physiological, and biochemical characteristics of plants

Biological Factors: Plants: Examples

- DDT applied to soil at a rate of 50 microgm/g inhibited germination, seedling height, and fresh dry weight in oil seed plants, but no effect on rice, barley, and mung bean plants
- In the oil seed plants, the DDT exposure caused a reduction in cell number and length and inhibited ion uptake, especially potassium ions (K^{+}) and calcium ions (Ca^{++})

Biological Factors: Plants: Examples

- The effects of DDT on the germination and growth of plants were studied using many crop species. Of the species tested, oil-rich seeds of plants, such as peanut (*Arachis hypogaea*) and mustard (*Brassica juncea*), were more prone to DDT induced inhibition of germination and subsequent plant growth than cereals, pulses and fibre crops, like rice (*Oryza sativa*), barley (*Hordeum vulgare*), mung bean *Vigna radiata*), pigeon pea (*Cajanus cajan*) and cotton (*Gossypium hirsutum*)(Source: Elsevier, Environnemental Pollution Volume 61, Issue 2, 1989, Pages 157-170)

Biological Factors: Animals and Humans

- Important factors that affect the response to pollutant toxicity: genetics, development, health status, gender, and behavior.

- Genetic factors:
- In animals variation between species, as well as variation between strains within the same species, occurs.

Table: Toxicity of DDT and Dieldrin

Compound	Organism	LD_{50} (mg/kg body weight)
DDT	Housefly	8
DDT	Bee	114
Dieldrin	Housefly	1.3
Dieldrin	Bee	87

Animals and Humans: Genetics

- In humans, such factors as serum, red blood cells, immunological disorders, and malabsorption can contribute to differences in individuals' response to stresses caused by environmental pollutants.

✓Examples: People, suffering from nutritional deficiencies, lead to an increased susceptibility to toxicants

- Individuals with sickle-cell anemia are more susceptible to the effect of toxicants than are individuals without the anemia

Animals and Humans: Developmental factors

- Aging, immature immune system, pregnancy, immature detoxification systems, and circadian rhythms
- Examples:

✓Decline in renal function as a result of aging

✓Lack of γ (gamma) globulin needed to cope with invading bacteria and viruses

✓Lack of receptors needed in hormonal action

✓Greater stresses encountered by pregnant women when metabolizing and detoxifying xenobiotics

✓Immature hepatic Mixed Function Oxidase (MFO) system in the young.

Animals and Humans: Diseases

- Diseases in lungs, heart, kidneys, and liver predispose a person to more severe consequences of pollutant exposure
- These organs are responsible for metabolism, storage, and excretion of environmental pollutants
- Cardiovascular and respiratory diseases of other origins decrease an individual's ability to withstand superimposed stresses
- Disorders in the liver can disrupt the proper detoxification process

Animals and Humans: Behavioral Factors/Lifestyles

- Life style examples: Smoking, drinking, and drug habits that can affect response to toxicants
- Smoking act synergistically with several environmental pollutants
- Asbestos workers or uranium miners who smoke are known to have higher lung cancer death rates than those who do not smoke
- Heavy drinking: disorder in the brain and liver
- Drug:??

Animals and Humans: Gender

- The rate of metabolism of foreign compounds varies in animals and humans according to gender
- Response to $CHCl_3$ (trichloromethane) exposure shows distinct variation in laboratory mice
- Male mice are highly sensitive to $CHCl_3$, and death often results than female mice

Nutritional Factors

- Important factor affecting pollutant to toxicity
- Human populations exposed to environmental fluoride may or may not exhibit characteristic fluoride poisoning, depending on their nutritional status, such as the adequacy of protein, or vitamins A, C, D, or E.

Nutritional Factors: Fasting and Starvation

- Fasting or starvation, most severe forms of nutritional modulation
- Influence xenobiotics toxicity in such a way that they may cause depressed metabolism and so reduced clearance of chemical agents; consequently, increased toxicity

Nutritional Factors: Proteins

- Deprivation may impair the metabolism of toxicants that occur in the body
- Increased toxicity of chemical compounds e.g., pesticides, such as chlorinated hydrocarbons, herbicides, fungicides and acetylcholinesterase (AChE) inhibitors, increased by protein deficiency

Table 5.3 Effect of Protein on Pesticide Toxicity[a]

	LD_{50} (mg/kg body weight)	
	Diet 3.5% casein	**Diet 26% caesin**
Chlorinated hydrocarbons		
DDT	45	481
Chlordane	137	217
Toxaphene	80	293
Endrin	6.69	16.6
Organophosphates		
Parathion	4.86	37.1
Malathion	759	1401
Herbicide and fungicides		
Diuron	437	2390
Captan	480	12,600

[a]Male rats fed for 28 days from weaning on diets of varying casein contents.
Source: Tandon, A., Dhawan, D.K. and Nagpaul, J. P., *J. Appl. Toxicol.*, 18, 187, 1998.

Nutritional Factors: Carbohydrates and Lipids

- A high carbohydrate diet usually leads to a decreased rate of detoxification
- Dietary lipids may affect the toxicity of environmental chemicals by delaying (lipophobic substances) or enhancing (lipophilic substances) their absorption
- Lipid can also affect toxicant metabolism
- High fat diets are known to increase Pb absorption and retention
- High fat diet causes increased body burden of fluoride, resulting in higher toxicity