Accessible version can be found here:
https://www.cdc.gov/nceh/hsb/elearning/toi/Mod2/

Toxicological Outbreak Investigation Course

Module Two:

Toxicological Principles

Module 2 Objectives

- Distinguish characteristics of an outbreak caused by a toxic agent
- Define toxidromes
- Identify the factors affecting toxicity
- Describe toxicokinetic principles of absorption, distribution, metabolism, and elimination

Background Levels of Toxic Agents

- People are continuously exposed to different toxic agents.
- Toxic agent exposures depend on…
  - Where you live.
  - What you do.
  - What you eat.

Hypothetical Laboratory Results from a Healthy Adult

Analyte	Level
Antimony	0.066 µg/L
Arsenic	6.85 µg/L
Barium	1.49 µg/L
Cadmium	0.412 µg/L
Cesium	4.35 µg/L
Cobalt	0.316 µg/L
Lead	0.766 µg/L
Molybdenum	39.7 µg/L
Thallium	0.155 µg/L
Tungsten	0.071 µg/L

- If a person living in the United States is tested randomly for heavy metals, a portion of their results might look like this

Hypothetical Laboratory Results from a Healthy Adult (cont.)

Analyte	Level
Antimony	0.066 µg/L
Arsenic	6.85 µg/L
Barium	1.49 µg/L
Cadmium	0.412 µg/L
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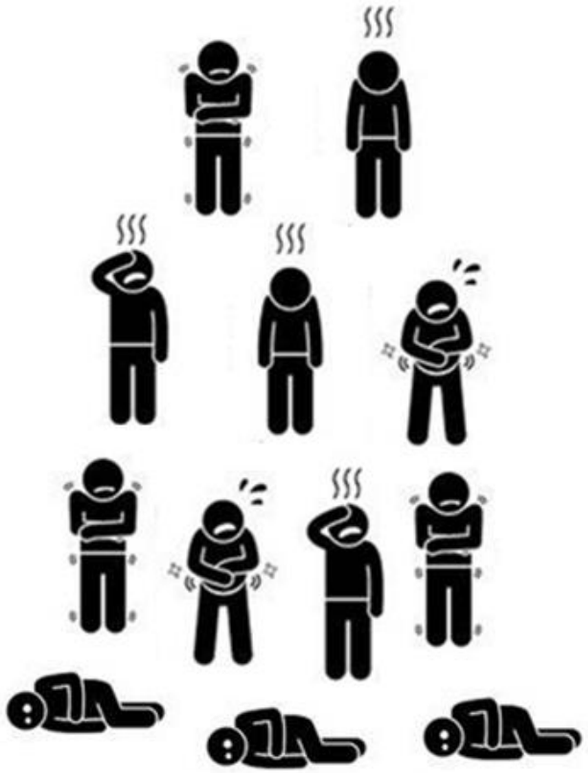
Tungsten	0.071 µg/L

- Individuals may have detectable levels of chemicals indicating background exposures in the body without having any signs of illness.
- These background levels can vary depending on a person's diet, occupation, and other factors.

Outbreak Scenario



- You receive a phone call regarding a situation in which a dozen agricultural workers are developing:
  - Nausea
  - Vomiting
  - Sweating
  - Dizziness
  - Difficulty breathing

What is the cause?

Is this from a potentially toxic exposure?

How might you be able to distinguish a toxic exposure from other etiologies?

How to Distinguish a Toxic Agent Outbreak

Key Characteristics
❑ Fever less likely
❑ Short latency time
❑ Dose-response relationship
❑ May involve animal illness at same time
❑ Similar symptoms across cases

- Outbreaks that are caused by a toxic agent usually share some key characteristics that may aid in distinguishing a toxicological etiology from other etiologies (i.e. infectious).

How to Distinguish a Toxic Agent Outbreak

Key Characteristics
✓ **Fever less likely**
❑ Short latency time
❑ Dose-response relationship
❑ May involve animal illness at same time
❑ Similar symptoms across cases

Fever is less likely

- Although fever can result as part of the body's response to a toxic agent, most toxic agents do not directly cause a fever.
- If fever is a predominant symptom of most suspected cases then it is less likely that the outbreak is caused by a toxic agent.

How to Distinguish a Toxic Agent Outbreak

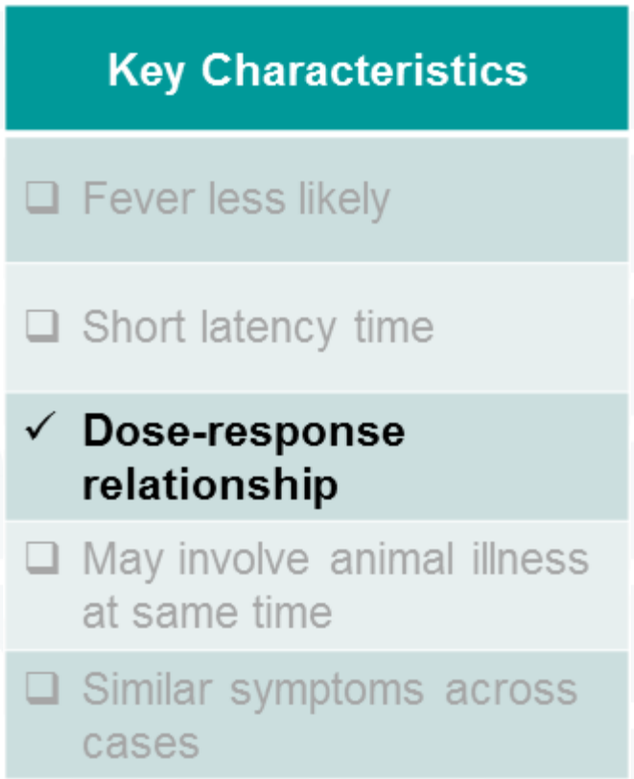
Key Characteristics
❑ Fever less likely
✓ **Short latency time**
❑ Dose-response relationship
❑ May involve animal illness at same time
❑ Similar symptoms across cases

Short Latency Time

- Toxic agents usually have a short latency (i.e., the time between becoming exposed and symptoms appearing).
- Onset of symptoms from a toxic exposure usually occurs very soon after exposure (seconds to minutes or a few hours).

In contrast, infectious agents usually have a latency period of hours to days and sometimes even weeks (e.g., Ebola) before symptoms develop.

How to Distinguish a Toxic Agent Outbreak



Dose-Response Relationship

- Toxic agents usually display a dose-response relationship.
- Attack rates and illness severity usually increase with higher exposure.

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."
-Von der Besucht,
Paracelsus, 1567

These concepts are discussed further in Module 5, Steps of an Toxicological Outbreak Investigation

Dose-Response Characteristics

Dose-response relationships have these characteristics:

- **Threshold effect level**: The dose above which there is an observed response or symptoms
- **Linear dose response relationship**: At doses above the threshold level, there is a linear trend for symptoms and dose. Symptoms begin to appear and grow stronger as dose increases.
- **Plateau/ceiling effect**: A point at which health outcomes/responses do not change even if the dose continues to increase. (Note: not all toxins will have a plateau or ceiling effect)

How to Distinguish a Toxic Agent Outbreak

Key Characteristics
❑ Fever less likely
❑ Short latency time
❑ Dose-response relationship
✓ **May involve animal illness at same time**
❑ Similar symptoms across cases

Concurrent Animal Illness

- Animals and livestock may become sick or die at around the same time human cases are identified.
- Often occurs when the outbreak results from contaminated food or water consumed by both humans and animals.

How to Distinguish a Toxic Agent Outbreak

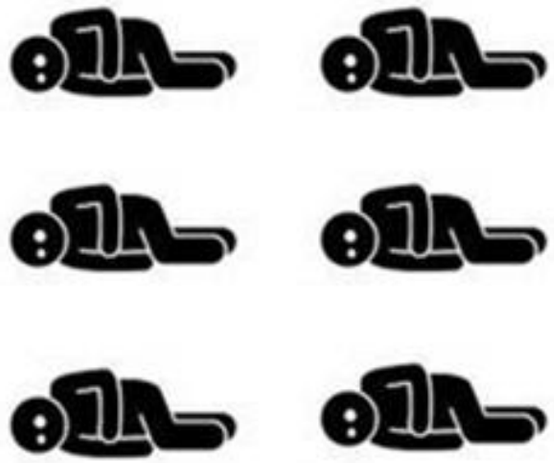
Key Characteristics
❑ Fever less likely
❑ Short latency time
❑ Dose-response relationship
❑ May involve animal illness at same time
✓ **Similar symptoms across cases**

Similar Symptoms Across Cases

- Toxic agents produce predictable, universal effects.
- Most people exposed to a particular toxic agent at a dose high enough to produce a response will experience similar physical reactions and symptoms (e.g., toxidrome).

Note: Similar symptoms across cases may also be seen in infectious outbreaks.

Agricultural Worker Outbreak Scenario



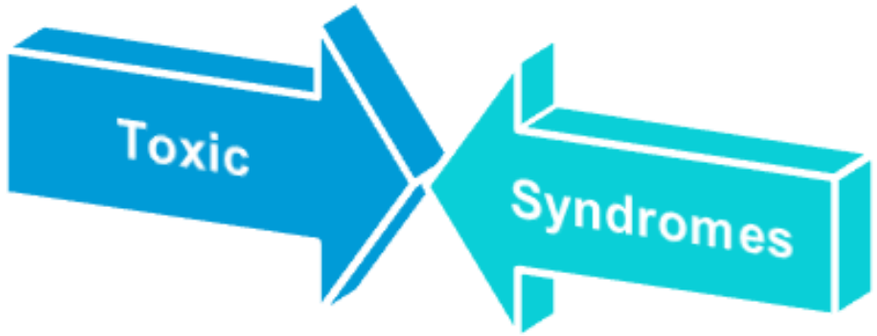
- The agricultural workers do not have a fever
  - They became sick suddenly
  - Those who were at work all day were the sickest
  - The workers share the same symptoms
- Farm animals are sick too

You suspect a toxic cause based on these key characteristics

How do you decide which toxic agent is the culprit?

The Toxidrome

- Some toxic agents cause a unique set of signs and symptoms that allow toxicologists to quickly identify them, called a “toxidrome”
- Determining the toxidrome, can be helpful in identifying the specific toxicological agent



Toxidrome Examples

Toxidrome	Signs and Symptoms	Potential Toxic Agent
Cholinergic crisis	Salivation, diarrhea, lacrimation, bronchorrhea, diaphoresis, urination Miosis, fasciculations, weakness, bradycardia or tachycardia, hypotension or hypertension, altered mental status, seizures	• Nicotine • Organophosphate insecticides • Carbamate insecticides • Medicinal carbamates (e.g., physostigmine)
Anticholinergic Crisis	Cutaneous flushing, hyperthermia, dry skin, mydriasis, dry mucous membranes, disorientation, hallucination, seizures, tachycardia, hypertension, urinary retention	• Belladona alkaloids • Jimson Weed/Datura • Brugmansia • Diphenhydramine

This table shows two examples of toxidromes.

Other examples can be found in the Tool Kit.

Toxidrome Caveats

- Some toxic agents do not have a specific toxidrome
- Many cases present with nonspecific signs and symptoms (such as nausea, vomiting, and dizziness), which are common effects from many toxic and infectious agents
- Even toxic agents with a toxidrome may not cause all of the symptoms all of the time
- Clinical presentation can vary depending on amount of exposure to a toxic agent

Outbreak Scenario

- The investigation team consults with a toxicologist.
- Toxicologists study the effects of toxic agents on people.
- During an investigation, toxicologists can….
  - Help determine which toxic agents cause illnesses similar to what you are seeing
  - Advise on what exposures and clinical signs/symptoms to ask about
  - Help interpret laboratory results

Include toxicologists in your investigation team when responding to outbreaks you suspect are caused by a toxic agent.

Outbreak Scenario

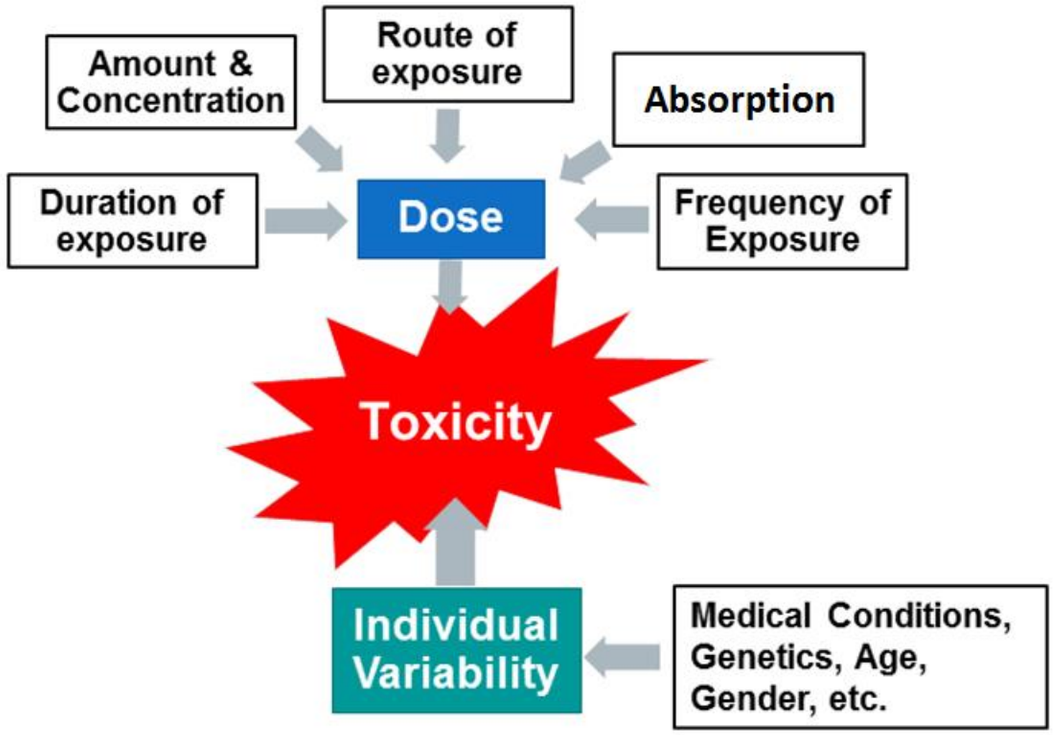
- The toxicologist recognizes a cholinergic toxidrome among the cases.
- The agricultural workers were spraying a carbamate pesticide that could cause a cholinergic response.
- You get more phone calls from other people who were also in the field today who are concerned that they may become sick.

What are the factors that contribute to toxicity in exposed persons?

What is the toxic dose?

Are all people at the same level of risk?

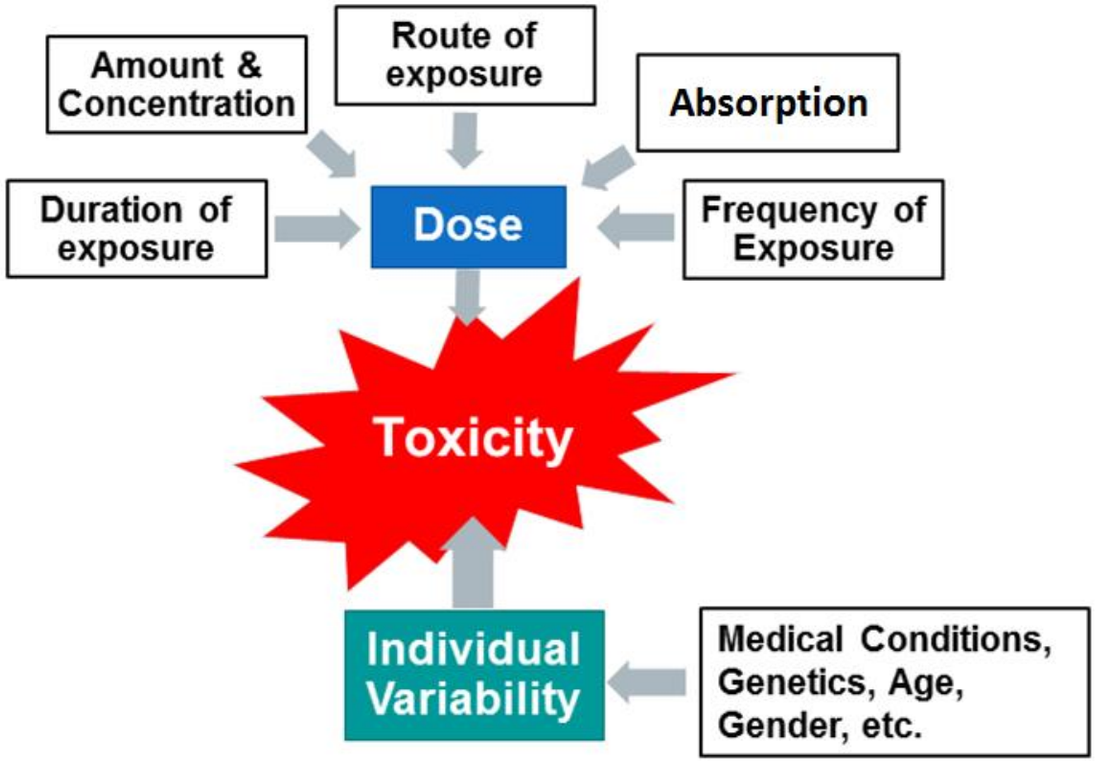
Factors Affecting Toxicity



There are several factors that need to be considered to determine if exposure to a toxic agent might be harmful.

A toxicologist can help evaluate these factors for specific toxins, and for specific individuals.

Factors Affecting Toxicity



In the next few slides, we will:

- Define the factors that affect toxicity
- Discuss their relevance to toxicological outbreak investigations
- Provide sample questions for the data collection tools to help capture this information

Dose

- **Dose** is the amount of a toxic agent that enters the body.
- Depends on many factors:
  - Amount and concentration
  - Duration and frequency of exposure
  - Route of exposure
  - Absorption (we will discuss this concept later in the presentation)

In an outbreak scenario, it is vital to collect information to help you determine if a dose is toxic

Factors Affecting Dose: Amount and Concentration

- The **amount** of a toxic agent in the environmental sample to which an individual is exposed.
- The **concentration** of a toxic agent is the amount of a toxic agent contained within a solution. As the concentration of a toxic agent increases so does illness severity.

The toxicologist can help you determine if the amount of a toxic agent that someone was exposed to was harmful.

For this, he/she needs to know at least an estimate of how much of a product someone was exposed to. If that substance is a liquid, you may also need to know the concentration of the toxic agent and how much the individual drank.

Factors Affecting Dose: Amount and Concentration

- Examples of questions that capture information about the amount and concentration:
  - *How many servings of the food did you eat?*
  - *Approximately how many 8 ounce cups of the beer did you drink?*
  - *How many of the _____ did you eat at the meal?*
  - *How many teaspoons of the medication did you drink?*
  - *What was the concentration of the medication that was used? (e.g. case patient may know mg of medication taken or could provide pill bottle)*

Note: When developing the questions, be as specific as possible when defining a unit of measure.

Questions should be tailored to the situation that you are attempting to investigate.

Factors Affecting Dose: Duration and Frequency of Exposure

- **Duration** is the length of time a person is exposed.
- **Frequency** is how many times a person is exposed.
- **Frequency** and **duration** both influence whether an exposure is acute or chronic. You may want to know if an exposure is acute or chronic in an outbreak scenario.

Factors Affecting Dose: Duration and Frequency of Exposure

- **Acute exposure** - exposure for a short period of time, often measured in minutes to hours
- **Chronic exposure** - repeated or continuous exposure for an extended period of time

Example of acute exposure: an agricultural worker is exposed *once to high concentrations* of toxic vapors and passes out within a few minutes

- frequency: once
- duration: three minutes

Example of chronic exposure: an agricultural worker is exposed *everyday* to *low concentrations* of toxic vapors for *one month* and complains of worsening headache

- frequency: everyday
- duration: one month

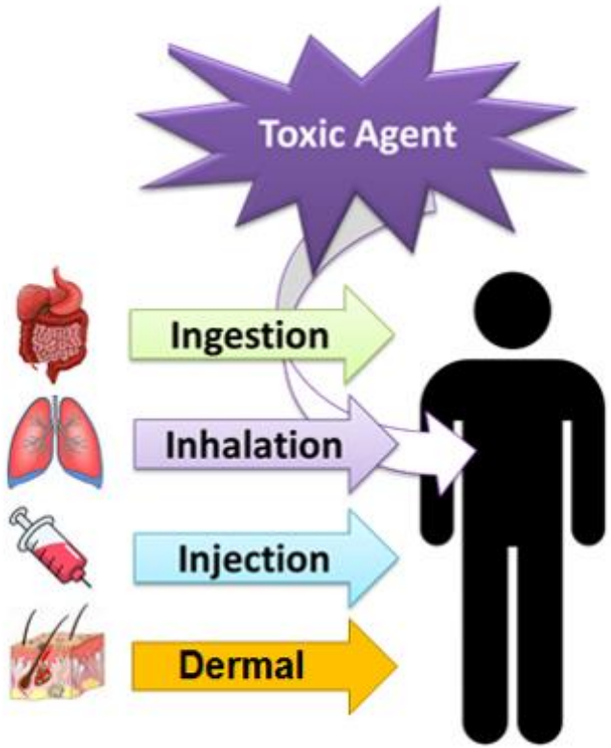
Factors Affecting Dose: Duration and Frequency of Exposure

- Examples of questions that capture information about frequency and duration of exposure
  - *For how many days did you consume that food?*
  - *How many meals per day did you drink the beer with?*
  - *How often do you eat the _____ each day?*
  - *For how many days did you take the medicine?*
  - *For approximately how many minutes were you in the room where the carbon monoxide gas was detected?*

Note: Some outbreaks may result from a suspected single, one-time exposure (e.g., meal). Others may result from repeated exposure to a toxic agent multiple times over a period of time.

Questions should be tailored to the situation that you are attempting to investigate.

Factors Affecting Dose: Route of Exposure



- The **route** of exposure is how the toxic agent enters or comes into contact with the body
- The same toxic agent can cause different patterns of illness depending on the route of exposure

The primary routes of exposure include ingestion, inhalation, injection, and dermal.

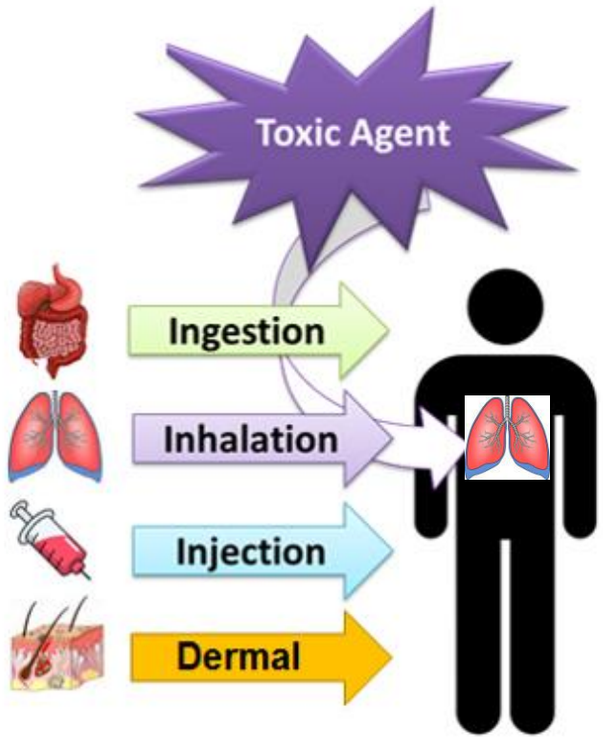
Route of Exposure: Ingestion

Ingestion

- Exposure of the body to a toxic agent via the oral route (eating or drinking)
- Examples:
  - Eating from ceramic dishes painted with lead based paint
  - Taking cold medication containing a toxic alcohol

Click on hyperlinks for more information on the examples.

Route of Exposure: Inhalation

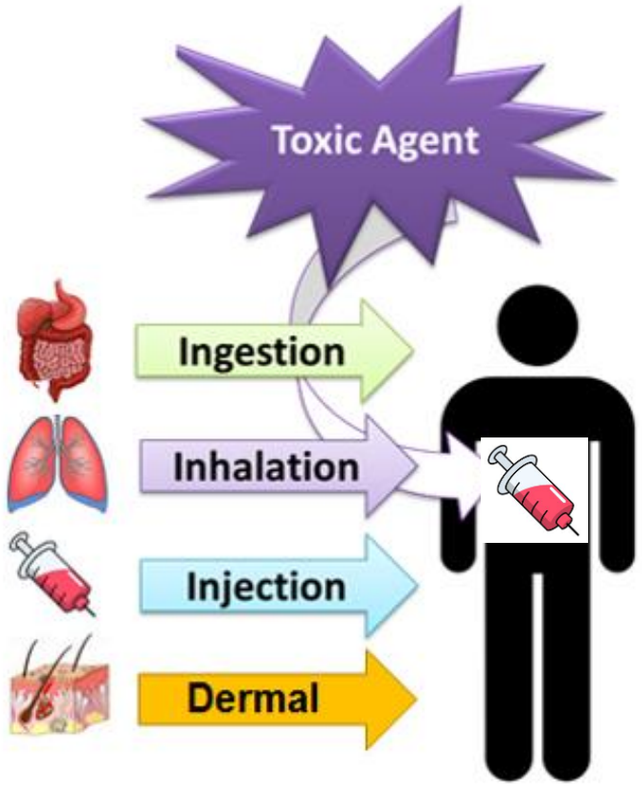


Inhalation

- Exposure of the body to a toxic agent via the respiratory system (breathing)
- Examples:
  - Breathing in coal dust
  - Breathing in pesticide vapors

Click on hyperlinks for more information on the examples.

Route of Exposure: Injection

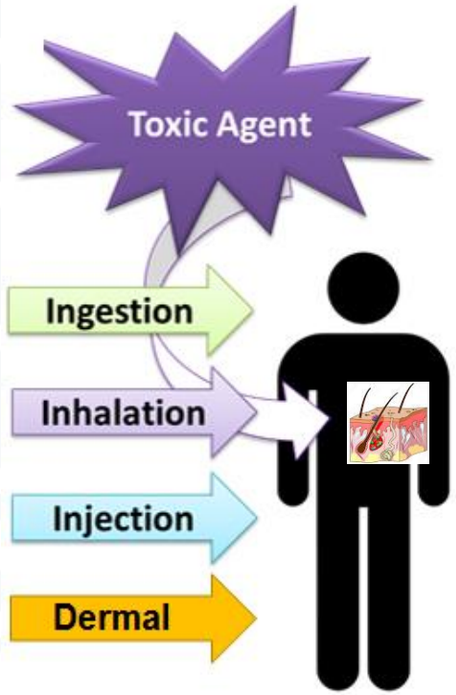


Injection

- Exposure of the body to a particular substance via the circulatory system
- Examples:
  - Injecting intravenous heroin contaminated with tetanus

Click on hyperlinks for more information on the examples.

Route of Exposure: Dermal/Mucus Membrane



Dermal

- Exposure of the body to a toxic agent via the skin or mucous membranes
- Examples:
  - Tobacco harvesting causing green tobacco sickness in agricultural workers
  - Organophosphate poisoning in pesticide workers

Click on hyperlinks for more information on the examples.

Factors Affecting Dose: Route of Exposure

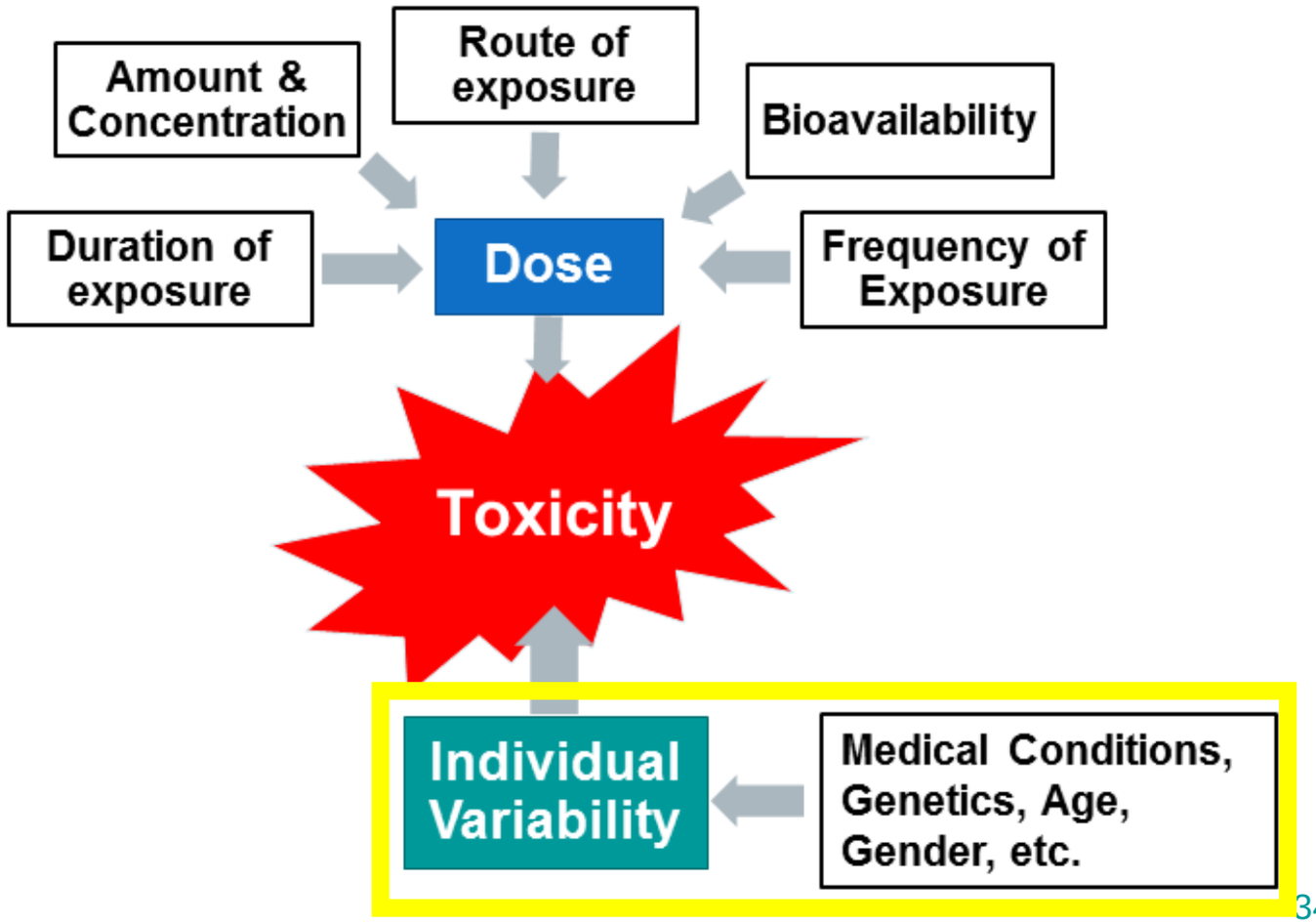
- Examples of questions that capture information about the route of exposure (when exposure is unknown):
  - *Did the food or beverage have an unusual taste? (suspected oral exposure)*
  - *Did you notice an unusual smell in the room when you entered? (suspected inhalational)*
  - *Were you exposed to any agents by injection? (suspected injection]*
  - *Did you notice any skin irritation, burning or pain when you were handling the _____? (suspected dermal)*

Important to note:

- There may be more than one route of exposure. This often depends on the agent.
- More than one agent may be responsible.

Questions should be tailored to the situation that you are attempting to investigate.

Factors Affecting Toxicity

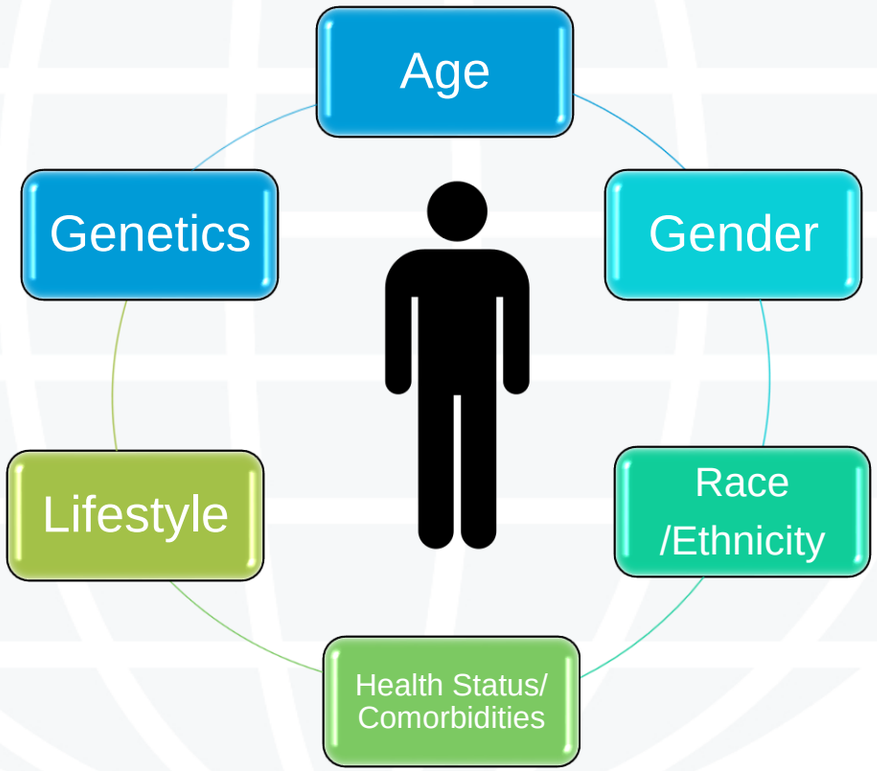


Individual variability is another major determinant of toxicity.

This term refers to the various differences between people in a wide variety of categories such as gender, age, and comorbid diseases such as high blood pressure.

Certain conditions (e.g., older age) may predispose a person to developing symptoms.

Individual Variability



Many variables collected to describe the demographics of an affected population are factors that contribute to individual variability.

A toxicologist can help identify additional important variables to collect which might also contribute to toxicity and help inform the subsequent data analysis.

Outbreak Scenario: Toxic Agent Known or Suspected

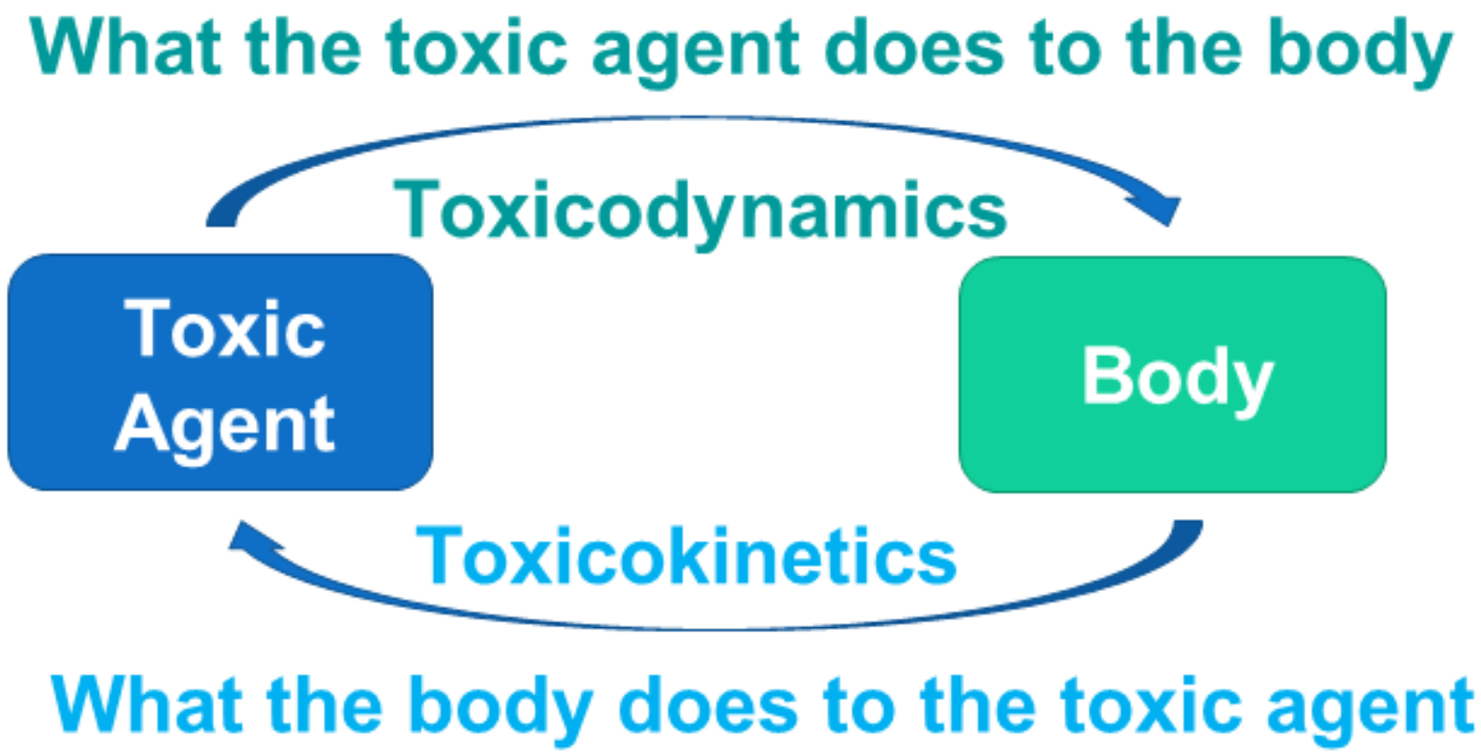
- A cluster of workers become sick after being exposed to an unknown insecticide that was sprayed in a work area.
- A pesticide that inhibits cholinergic neuronal activity is suspected.

What is the clinical presentation of the patients?

What biological tests need to be performed?

If the agent causing the illness is known or suspected, a toxicologist can help guide your investigation by suggesting data variables to collect or lab tests to order.

Toxicodynamics and Toxicokinetics



There are two key concepts that toxicologists use to help determine if a particular toxic agent is causing the outbreak.

Toxicodynamics refers to the signs and symptoms a toxic agent causes.

Toxicokinetics refers to how the body metabolizes and eliminates the agent.

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Toxicodynamics – What the Toxic Agent Does to the Body

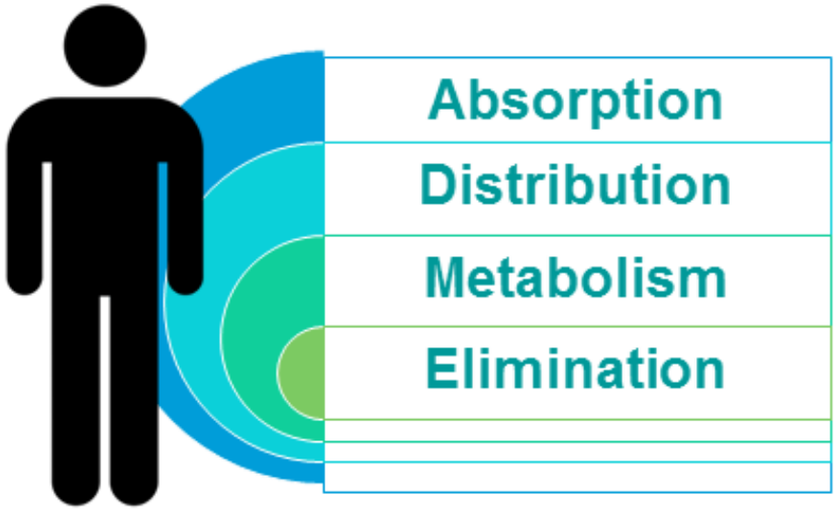
- Toxicologists can inform the development of the data collection tool and make sure that the right questions related to symptoms and illness progression are asked.
- Toxicologists can narrow down potential toxic agents based on the signs and symptoms of the patient AND,
  - other epidemiological data captured (e.g., food diary).

Why is **toxicodynamics** important to consider during an outbreak?

Remember in the outbreak scenario, most case-patients presented with symptoms resembling a cholinergic crisis. Some of their symptoms included:

- Salivation, gastrointestinal distress,
- Slow bradycardia, and cardio-respiratory arrest

Toxicokinetics: What the Body Does to the Toxic Agent



- There are four key concepts in toxicokinetics: absorption, distribution, metabolism, and elimination.
- If toxic agents are absorbed into the body, they are typically distributed through the blood to various organs.
- They are then eliminated through different ways such as urine or feces, or metabolized first and then eliminated.

Why is **toxicokinetics** important to consider during an outbreak?

Understanding the toxicokinetic principles of a toxic agent helps determine which biological tests should be performed to confirm exposure to the toxic agent.

Toxicokinetics: Absorption of Toxic Agent

- Similar to route of exposure, **absorption** is how the toxic agent enters the body.
- Absorption for most toxic agents proceeds most rapidly after intravenous or inhalational routes, followed by ingestion, and then by dermal routes.

All of the previously mentioned factors (e.g. dose, individual variability) determine the likelihood and severity of toxicity resulting from an exposure.

Note:

- Absorption of a harmful agent does not mean poisoning will occur.
- Absorption through skin can be greater if there are breaks or abrasions in the skin or in mucous membranes.

Toxicokinetics: Absorption of Toxic Agent

- Laboratory tests can help you determine if a chemical was absorbed into the body.
- Examples of data elements that capture information about absorption:
  - Specialized toxicology testing (if available)
  - Results of common routine clinical laboratory tests (if available), especially from hospital presentation or when symptoms developed:
    - Blood cell count
    - Electrolytes
    - Functional or diagnostic tests for organs

The best way to tell if, and how much, absorption has occurred is through testing the blood and or urine. Other clinical tests can also provide valuable information.

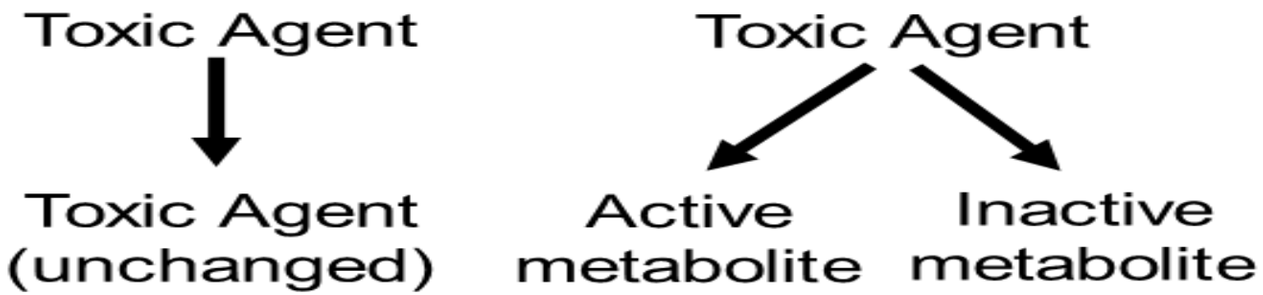
Toxicokinetics: Distribution of Toxic Agent

- **Distribution** is how the toxic agent is spread out in the body.
- Understanding how agents are distributed in the body helps toxicologists determine what biological specimens should be taken from case-patients for testing.
  - For example, if the toxic agent is rapidly distributed from the blood into organs there may be no detectable level of toxic agent in the blood and therefore, collecting a blood specimen may not helpful.

A toxicologist can help decide whether or not it may be useful to try to test for a toxic agent hours, days, or weeks after potential exposure.

Toxicokinetics: Metabolism of a Toxic Agent

- **Metabolism** is how a toxic agent is transformed into other chemicals in the body.
- Toxic agents -break down from the parent compound into one or more **metabolites** which can be either **active** or **inactive.**



A toxicologist can help decide whether or not suitable tests exist for either the parent compound or a metabolite.

This information can be used to help target your laboratory investigation.

Toxicokinetics: Elimination of a Toxic Agent

- **Elimination** is how a toxic agent is removed from the body.
- **Half-life** is the time it takes for half the amount of a toxic agent to no longer be detected in a biological specimen.
  - Differs by…
    - Type of toxic agent
    - Type of biological specimen
  - Can range from minutes to years

If the agent is known, toxicologists can help you determine if the agent is likely to stay in the body for a long time or be eliminated quickly.

If it stays in the body for a long time, he/she can help inform what you should test for and in which biological medium (e.g., blood, urine).

Outbreak Scenario: Conclusion

- In this outbreak, toxicologists recognized the anecdotally reported symptoms as being consistent with being exposed to an insecticide that yields a cholinergic crisis response.
- They informed the development of the data collection tool used by investigators to include data on the expected signs and symptoms of cholinergic poisoning as well as the normal therapies.
- Blood and urine specimens were targeted for analysis for these types of pesticides over others, which optimized testing with limited biological specimens.

What lessons were learned from this outbreak?

Outbreak Scenario: Conclusion

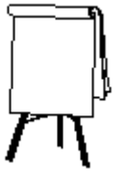
- Specific tests for measuring pesticides and their metabolites may not be available.
- Cholinesterase levels are a more commonly available lab tests that can help assess exposure to certain classes of pesticides (e.g., organophosphastes and carbamates).
  - If very low, a cholinesterase test can provide laboratory confirmation of exposure
- Decreased cholinesterase levels were detected in 100% of serum specimens collected from agricultural workers.

Outbreak Scenario: Conclusion

- A pesticide known as a carbamate was suspected.
- Carbamates are very similar to organophosphates except that their action on the enzyme acetylcholinesterase does not last as long.
- Further specialized testing for carbamate exposure in human biological specimens was positive.

Summary: Lessons Learned

- The presence of **key characteristics** can help distinguish a toxicological etiology from other etiologies.
- The determination of a **toxidrome** can identify the specific toxic agent.
- Factors that affect toxicity include the **dose**, **duration** and **frequency** of the exposure, and **individual characteristics** of the exposed person.
- The principles of **toxicodynamics** and **toxicokinetics** are important to consider in investigating outbreaks of non-infectious etiology.



Module Conclusion

What questions do you have about the information presented in this module?