

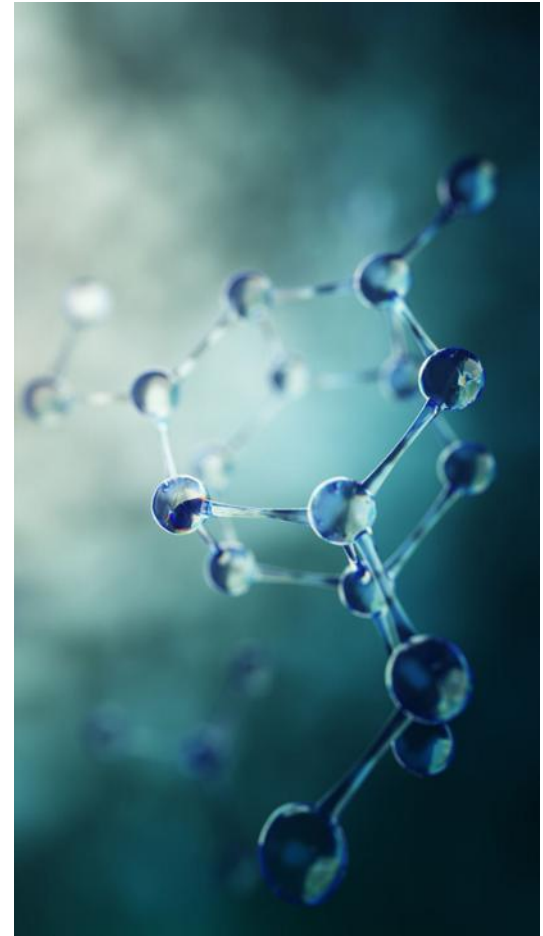
Toxicological Outbreak Investigation

Module 2: Toxicological Principles



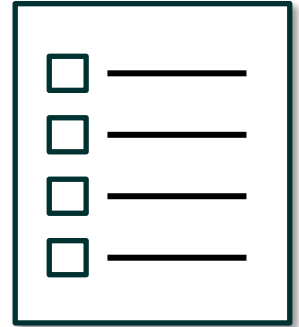
Welcome

- Welcome to Module 2 of Toxicological Outbreak Investigation.
- In this module, we will
 - Consider what an outbreak caused by a toxic agent looks like and the characteristics to look for when determining whether one is taking place
 - Define toxidromes and discuss the various factors that affect toxicity
 - Examine two key concepts used by toxicologists



Module 2 Objectives

- After completing this module, you will be able to
 - Identify characteristics of an outbreak that suggest that it might be caused by a toxic agent
 - Define toxidromes
 - Identify factors affecting toxicity
 - Describe the principles of toxicodynamics and toxicokinetics
 - Describe the toxicokinetic principles of absorption, distribution, metabolism, and elimination



Agricultural Worker Outbreak Scenario



- You receive a phone call regarding a situation in which a dozen agricultural workers are developing symptoms:

- Nausea
- Vomiting
- Sweating
- Dizziness
- Difficulty breathing



- ? Do you think the cause could be a toxic exposure?
- ? What considerations could help you distinguish outbreaks that might have a toxic cause from those that might have other causes?

Characteristics Suggesting a Toxicological Outbreak

- Some characteristics of an outbreak can aid in distinguishing a toxicological etiology from other etiologies (i.e., infectious).
- **However, none of these characteristics completely distinguish between toxicological and infectious outbreaks.**

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Absence of Fever

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Absence of fever

- Although fever can be 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 in most of the suspected cases, then it is less likely that the outbreak is caused by a toxic agent.
- Note: Absence of fever does not completely rule out an infectious cause. Presence of fever also does not rule out a toxic cause.

Short Latency Time

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Short latency time (for acute outbreaks)

- Toxic agents can have a short latency time (i.e., the time between exposure and the appearance of symptoms).
- Symptoms from a toxic exposure can occur very soon after exposure (minutes or a few hours).
- In contrast, infectious agents typically have a latency period of hours, days, or even weeks before symptoms develop.
- Note: Toxic exposures can also lead to health effects that develop over a longer period.

Similar Symptoms Across Cases

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Similar symptoms across cases

- Toxic agents often produce predictable, consistent 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.
- Many toxic agents cause non-specific symptoms and signs. However, some lead to unique sets of symptoms and signs (toxidromes).

Setting or Affected Population Suggests Potential Toxic Exposures

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Setting or affected population suggests potential toxic exposures

- When an illness occurs among specific groups of people (e.g., workers) or people in a specific geographic area and when there are unique potential toxic exposures, the illness suggests a toxic etiology.
- When an environment or food has unusual characteristics (e.g., unusual smell or taste) and is shared by affected people, it might suggest a toxic etiology.

Apparent Dose-Response Relationship

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

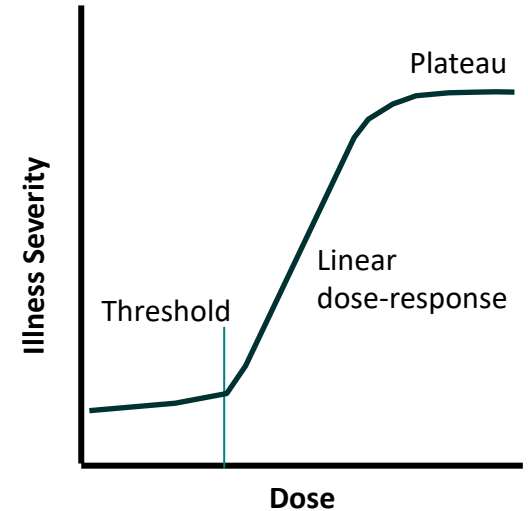
Concurrent animal illnesses

Apparent dose-response relationship

- Toxic agents usually display a dose-response relationship, meaning that attack rates and illness severity usually increase with higher dose.
- Dose-response relationships can be difficult to identify in some situations.

Dose-response Relationship Characteristics

- **Threshold effect level:** This is the dose above which there is an observed response or symptoms.
- **Linear dose-response relationship:** Above the threshold level, there is a linear relationship between symptoms and dose. Symptoms grow stronger or more frequent as dose increases.
- **Plateau/ceiling effect:** This is the point of maximal observed effects even if dose continues to increase.
- **Note:** Not all dose-response relationships have all of these characteristics.



Absence of Person-to-Person Transmission

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Absence of person-to-person transmission

- Typically, toxicologic outbreaks involve multiple people who are exposed to the same toxic agent.
- Illness in a toxicologic outbreak is not usually transmitted from an affected person to others who did not share that exposure.
- However, sometimes apparent person-to-person transmission can occur if the toxic agent is passed from one person to another (e.g., lead passed to family members through a worker's clothing).

Concurrent Animal Illness

Characteristics

Absence of fever

Short latency time (for acute outbreaks)

Similar symptoms across cases that are consistent with the effects of a toxic agent

Setting or affected population suggests potential toxic exposures

Apparent dose-response relationship between symptoms and a suspected exposure

Absence of person-to-person transmission

Concurrent animal illnesses

Concurrent Animal Illness

- Animals and livestock might become sick or die around the same time human cases are identified.
- This often occurs when the outbreak was caused by contaminated food or water consumed by both humans and animals.
- Note: Outbreaks caused by infectious agents can also involve concurrent animal illness.

Challenge #1

- **Which of the following are true statements? Select all that apply.**
 - A. If fever is a predominant symptom in most of the identified cases, it is less likely that a toxic agent is the cause of an outbreak.
 - B. Reaction to a toxic agent can occur within a few minutes to hours.
 - C. If animals and humans are sick, the outbreak is probably not caused by a toxic exposure.
 - D. Toxic agents often produce predictable, consistent effects across all cases.

Challenge #1 Answers

- The correct answers were:

Yes **A. If fever is a predominant symptom in most of the identified cases, it is less likely that a toxic agent is the cause of an outbreak.**

Yes **B. Reaction to a toxic agent can occur within a few minutes to hours.**

No C. If animals and animals are sick, the outbreak is probably not caused by a toxic exposure.

Yes **D. Toxic agents often produce predictable, consistent effects across all cases.**

Agricultural Worker Outbreak Scenario



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

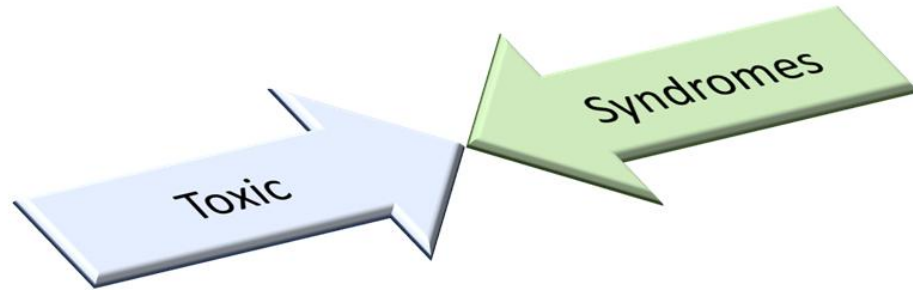


Based on these characteristics, you suspect a toxic cause.

How might you determine which toxic agent is the culprit?

The Toxidrome

Some toxic agents cause a unique set of signs and symptoms, called a “toxidrome.” A toxidrome can help toxicologists to quickly identify the toxic agent that caused the signs and symptoms.



Toxidrome Examples

This table shows two examples of toxidromes. Other examples can be found in the Tool Kit.

| 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 | <ul style="list-style-type: none">• Nicotine• Organophosphate insecticides• Carbamate insecticides• Medicinal carbamates (i.e., physostigmine) |
| Anticholinergic | Cutaneous flushing, hyperthermia, dry skin, mydriasis, dry mucous membranes, disorientation, hallucination, seizures, tachycardia, hypertension, urinary retention | <ul style="list-style-type: none">• Belladonna alkaloids• Jimsonweed/<i>Datura</i>• Angel's Trumpet/<i>Brugmansia</i>• Diphenhydramine |

Toxidrome Caveats

- Many toxic agents do not have a specific toxidrome.
- Many outbreaks involve cases 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 the symptoms all the time.
- Clinical presentation can vary depending on the dose of a toxic agent.

Challenge #2

True or false. All toxic agents have toxidromes.

- True
- False

Challenge #2 Answer

The correct answer is False.

Some toxic agents do not have a specific toxidrome.

Agricultural Worker 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



Agricultural Worker 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.

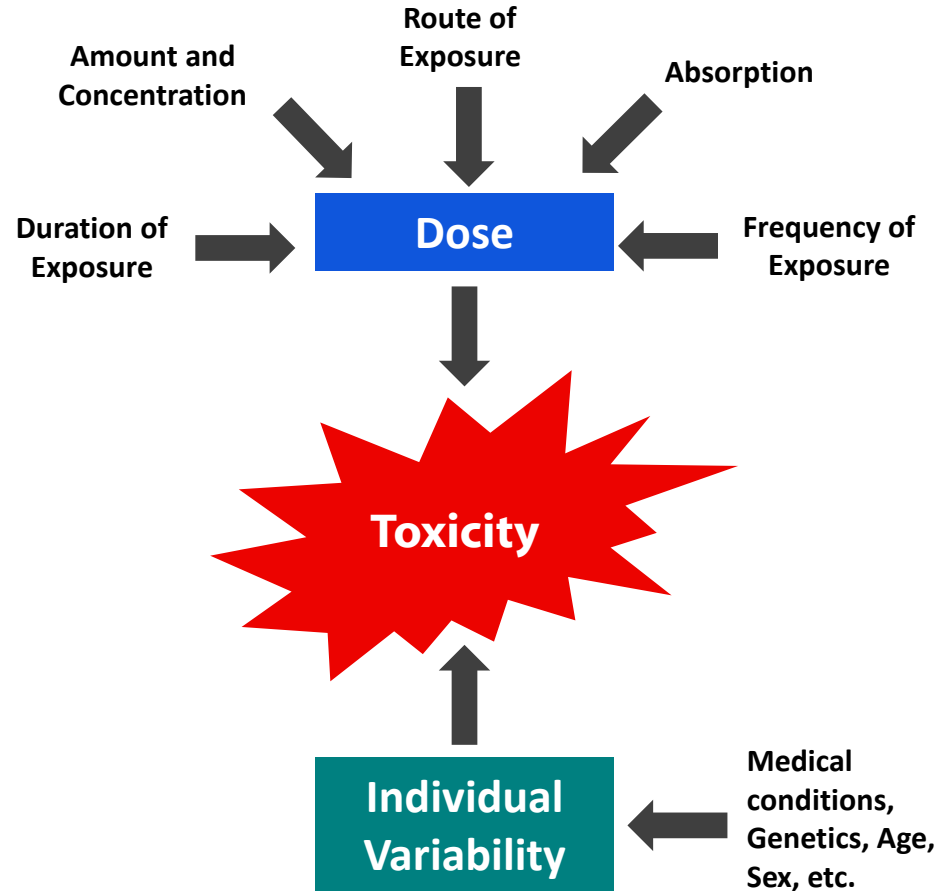


People are asking why some workers have more severe illnesses than others.

What are some factors to consider when addressing their question?

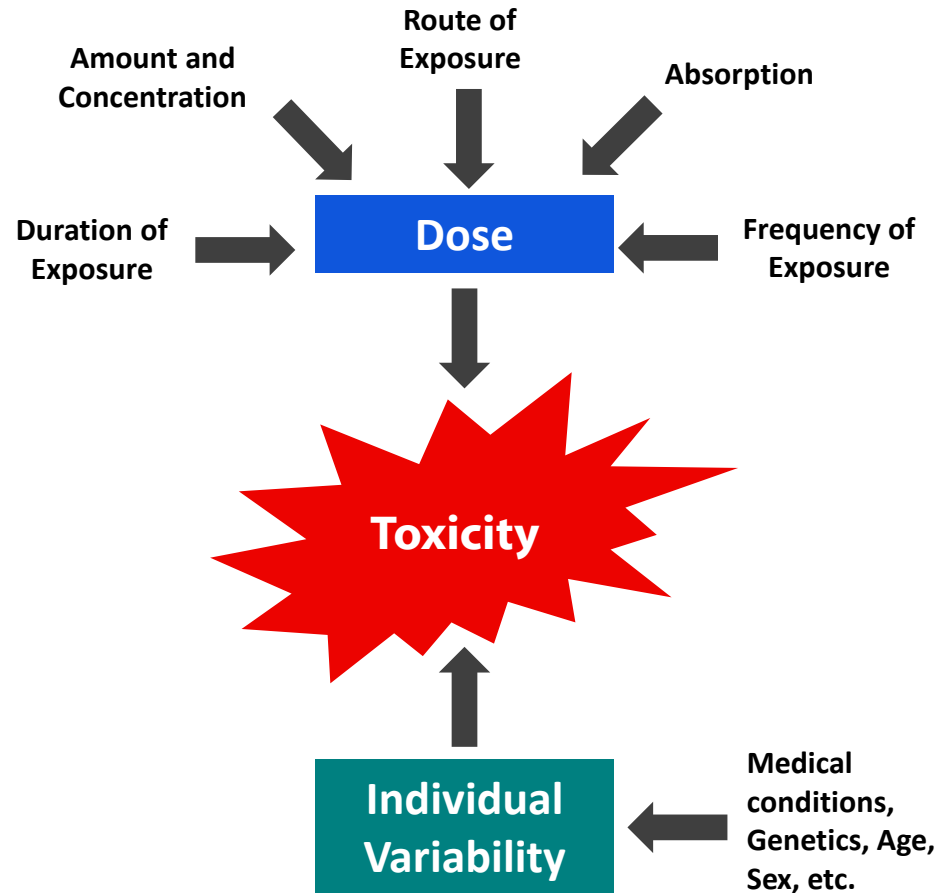
Factors Affecting Toxicity

- Just being exposed to a toxic substance does not necessarily mean that a person will be poisoned or become ill.
- Several factors need to be considered to determine whether exposure to a toxic agent might be harmful.
- A toxicologist can help evaluate these factors for specific toxic agents 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, and
 - provide sample questions to help capture this information.



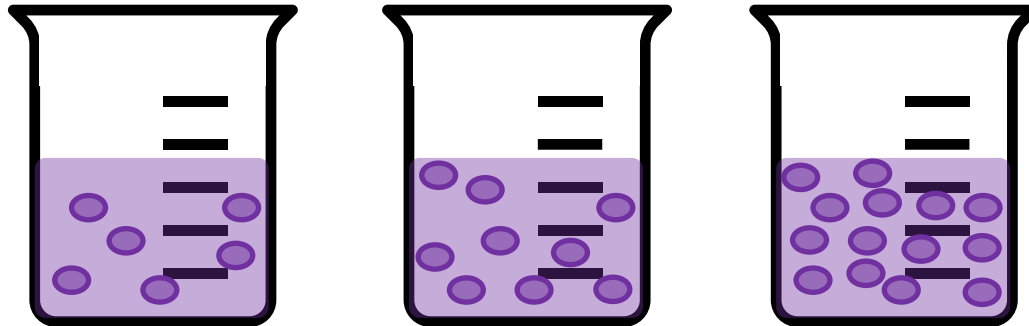
Factors Affecting Toxicity: Dose



- Dose is the amount of a toxic agent that enters the body.
- Dosage depends on several factors:
 - Amount and concentration of the toxic agent
 - Duration and frequency of exposure
 - Route of exposure
 - Absorption (will be discussed later in the module)
- In an outbreak scenario, it is vital to collect information to help determine whether the dose of a toxic agent that people received could lead to clinical effects.

Factors Affecting Dose: Amount and Concentration

- If a person is exposed to a product or food that contains a toxic agent, the dose of the toxic agent that a person receives will depend on
 - Amount: how much of the product or food someone was exposed to
 - Concentration: the mass of the toxic agent that is present per unit of mass or volume of the product or food



Developing Questions to Determine Amount and Concentration

- Here are examples of questions that capture information about amount and concentration:
 - How many servings of the food did you eat?
 - Approximately how many 8-ounce cups of 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/ml for the medication taken or could provide the bottle)
- Note: When developing questions, be as specific as possible when defining a unit of measure.
- Questions should be tailored to the situation that you are investigating.

Factors Affecting Dose: Duration and Frequency of Exposure

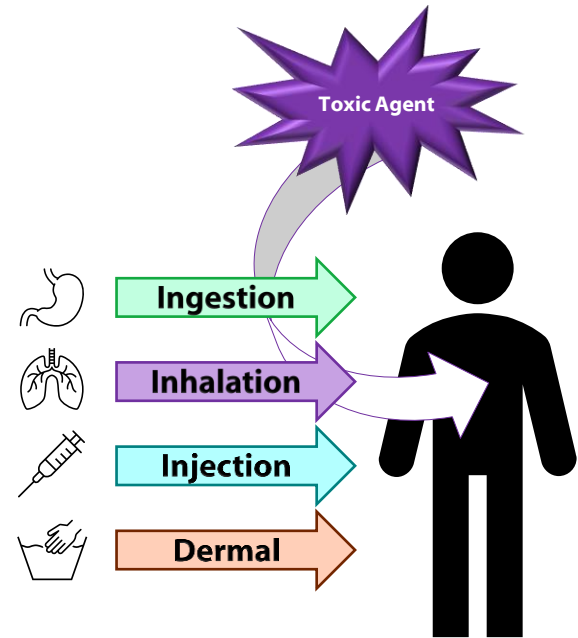
- Duration is the length of time a person is exposed.
- Frequency is how many times a person is exposed in a given period.
- Frequency and duration influence whether an exposure is acute or chronic.
 - **Acute exposure** is for a short period, often measured in minutes to hours.
 - An example of acute exposure is an agricultural worker who is exposed once to high concentrations of toxic vapors and passes out within a few minutes.
 - Duration: three minutes
 - Frequency: once
 - **Chronic exposure** involves repeated or continuous exposure for an extended period.
 - An example of chronic exposure is an agricultural worker who is exposed every day for one month to low concentrations of toxic vapors and who complains of worsening headaches.
 - Duration: one month
 - Frequency: every day in past month

Developing Questions to Determine Duration and Frequency of Exposure

- Data collection for a toxicological outbreak should include questions about the duration and frequency of exposure.
 - Some outbreaks result from a single, one-time exposure (e.g., meal).
 - Others result from repeated exposure to a toxic agent over a period.
 - Questions should be tailored to the situation that you are investigating.
- These are examples of questions that capture information about frequency and duration of exposure:
 - How many days did you consume that food?
 - With how many meals did you drink the beer each day?
 - How many times do you eat the _____ each day?
 - 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?

Factors Affecting Dose: Route of Exposure

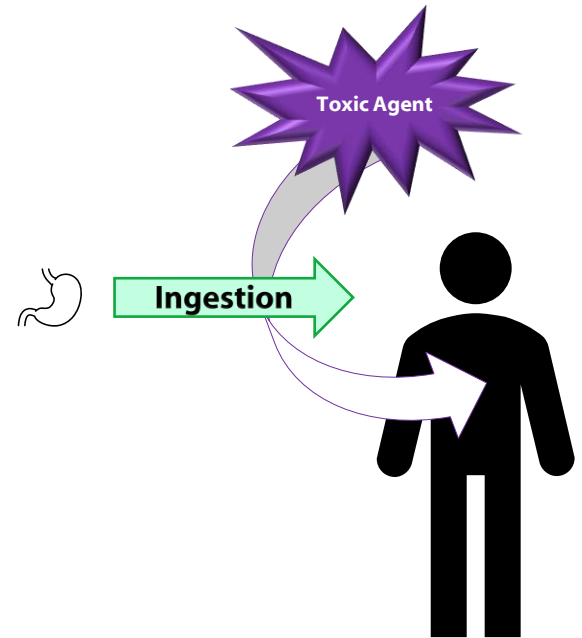
- The route of exposure is how the toxic agent enters or comes into contact with the body.
- A toxic agent can cause different patterns of illness depending on the route of exposure.
- The route of exposure also affects the dose (the amount of a toxic agent that enters the body).
- The primary routes of exposure are through ingestion, inhalation, injection, and dermal contact.



Ingestion

- Exposure to a toxic agent via the oral route (eating or drinking)
- Examples
 - [Eating from ceramics with lead-based paint](#)
 - [Taking cold medication containing a toxic alcohol](#)

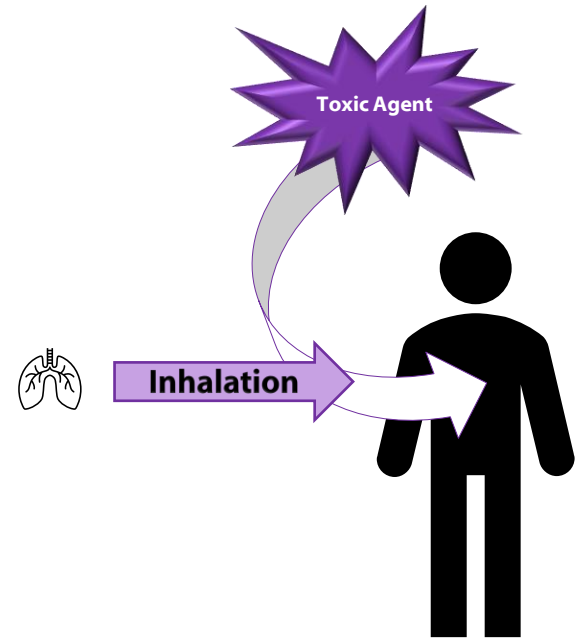
Select the hyperlinks for more information on the examples.



Inhalation

- Exposure to a toxic agent via the respiratory system (breathing)
- Examples
 - [Breathing in coal dust](#)
 - [Breathing in pesticide vapors](#)

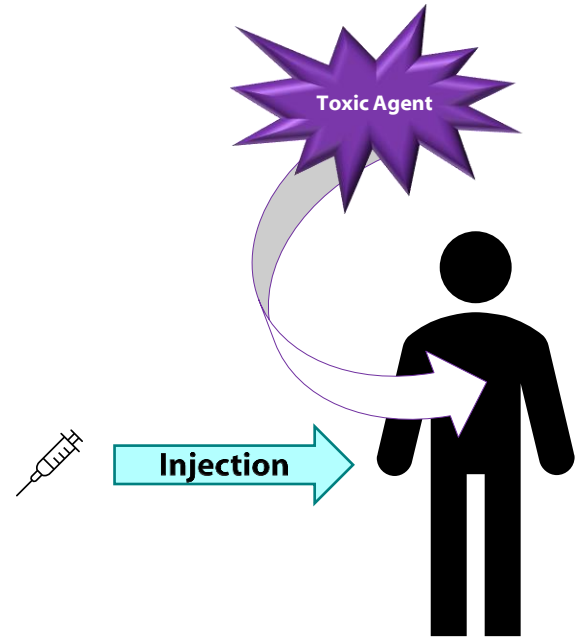
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Injection

- Exposure to a particular substance via the circulatory system
- Example
 - [Tetanus associated with injecting intravenous heroin](#)

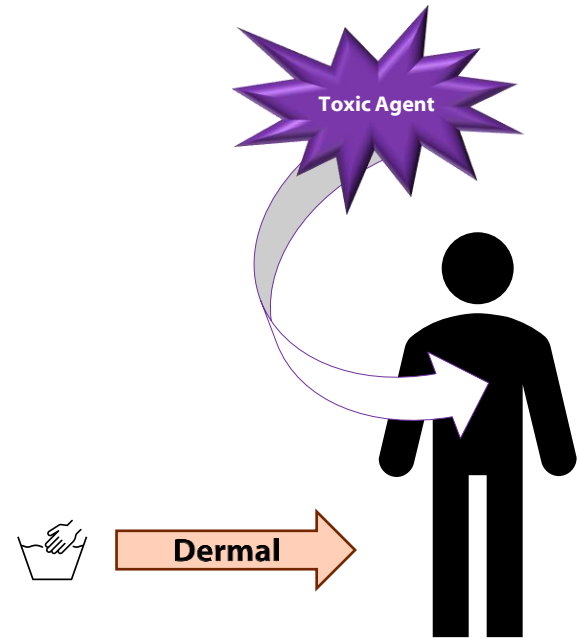
Select the hyperlinks for more information on the examples.



Dermal

- Exposure to a toxic agent via the skin
- Examples
 - [Tobacco harvesting causing green tobacco sickness in agricultural workers](#)
 - [Organophosphate poisoning in pesticide workers](#)

Select the hyperlinks for more information on the examples.

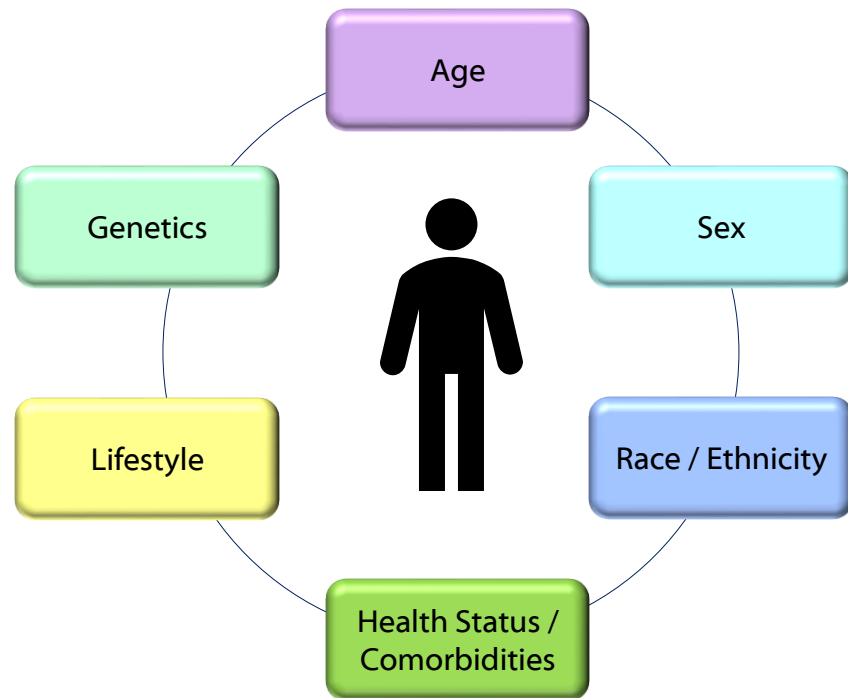


Developing Questions to Determine Route of Exposure

- Data collection for a toxicological outbreak should include questions about the route of exposure, which should be tailored to the situation that you are investigating.
- It is important to note that depending on the agent, there may be more than one route of exposure.
- These are examples of questions that capture information about route of exposure:
 - 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 inhalation)
 - 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)

Factors Affecting Toxicity: Individual Variability

- Individual variability is another major determinant of toxicity.
- This term refers to the differences between people, such as sex, age, and comorbid diseases (e.g., high blood pressure).
- Certain conditions (e.g., older age) may predispose a person to developing symptoms.
- Many variables collected to describe the demographics of an affected population are factors that contribute to individual variability.
- A toxicologist can help identify important variables, which might also contribute to toxicity and help inform the data analysis.



Challenge #3

True or false. All people have the same level of risk when exposed to the same dose of the same toxic agent by the same route.

- True
- False

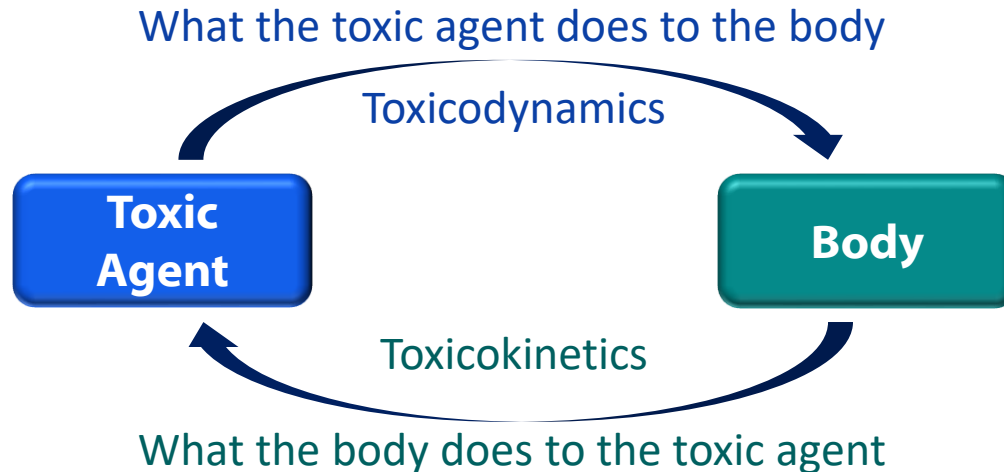
Challenge #3 Answer

The correct answer is False.

Some people might become ill after exposure to a toxic agent. Others do not become ill or they have a less severe illness because of differences in factors such as age, race/ethnicity, health status/comorbidities, lifestyle, and genetics.

Toxicodynamics and Toxicokinetics

- There are two key concepts that toxicologists use to help determine if a particular toxic agent is causing an outbreak.
 - **Toxicodynamics** refers to the signs and symptoms a toxic agent causes.
 - **Toxicokinetics** refers to how the body metabolizes and eliminates the agent.



Toxicodynamics: What the Toxic Agent Does to the Body

- In an outbreak setting, a toxicologist can use their knowledge of toxicodynamics to
 - Identify toxic agents that could cause the symptoms and signs that people are experiencing
 - Identify symptoms and signs expected after exposure to a particular toxic agent
 - Make recommendations regarding
 - Conducting clinical laboratory tests (e.g., blood cell counts, electrolytes, liver enzymes) that can help identify effects of a toxic agent on the body
 - Developing data collection tools to ensure that the right questions about symptoms and illness progression are asked, and the right information is obtained from medical records, given the situation and the objectives of the investigation



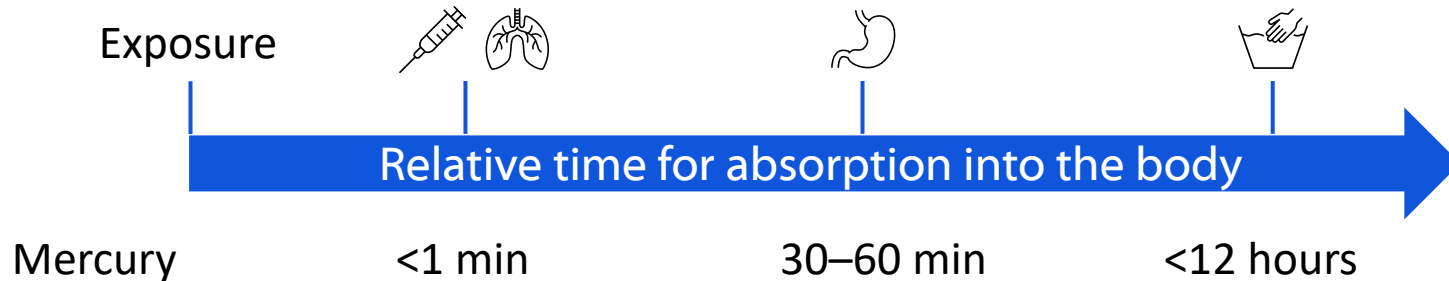
Toxicokinetics: What the Body Does to the Toxic Agent

- Understanding the toxicokinetic properties of a toxic agent can help determine which biological tests should be performed to confirm exposure to a 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.
- Toxic agents can be eliminated in various ways, such as through urine or feces. Some toxic agents can be eliminated unchanged, while others are metabolized first and then eliminated.



Toxicokinetics: Absorption of Toxic Agent

- Like route of exposure, absorption is how the toxic agent enters the body.
- Absorbing a harmful agent does not necessarily mean poisoning will occur.
- Absorption through skin can be greater if there are skin breaks or abrasions.
- For most toxic agents, absorption proceeds most rapidly after intravenous or inhalational routes, followed by ingestion and then by dermal routes.
- Knowledge about the absorption of specific toxic agents can help guide questions about exposures.

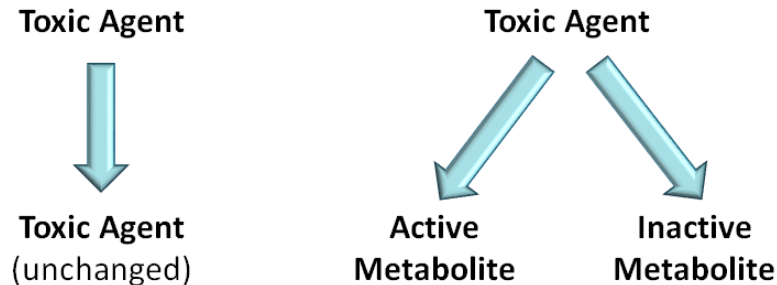


Toxicokinetics: Distribution of a Toxic Agent

- Distribution is how the toxic agent is spread throughout the body.
- Understanding how agents are distributed in the body helps toxicologists determine which biological specimens should be collected for testing.
- For example, if the toxic agent is rapidly distributed from the blood into organs, there may be no detectable level of the toxic agent in the blood. Therefore, collecting a blood specimen may not be helpful.
- A toxicologist can help decide whether it may be useful to test for a toxic agent hours, days, or weeks after potential exposure.

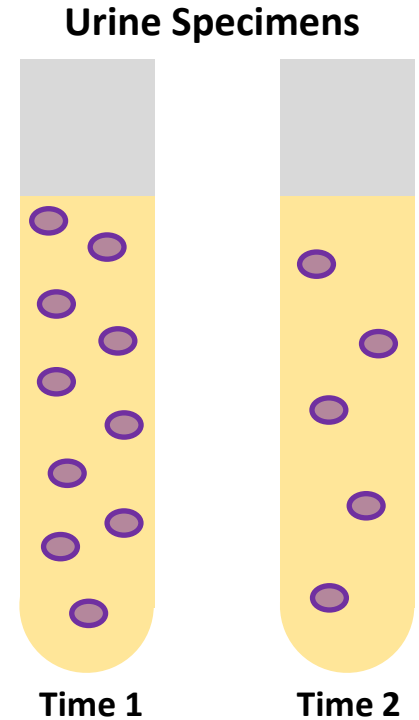
Toxicokinetics: Metabolism of a Toxic Agent

- Metabolism is how a toxic agent is transformed into other chemicals in the body.
- Some toxic agents break down into one or more metabolites, which can be either active or inactive.
- A toxicologist can help decide whether suitable tests exist for either the parent compound or a metabolite.
- This information can be used to help focus 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 the concentration of a toxic agent to be reduced by one half.
 - A half-life differs by type of toxic agent and type of biological specimen.
 - Half-lives can range from minutes to years.
- If the toxic 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, they can make recommendations regarding what you should test for and in which biological medium (e.g., blood, urine).



Challenge #4

Which of the following describes what a toxic agent does to the body?

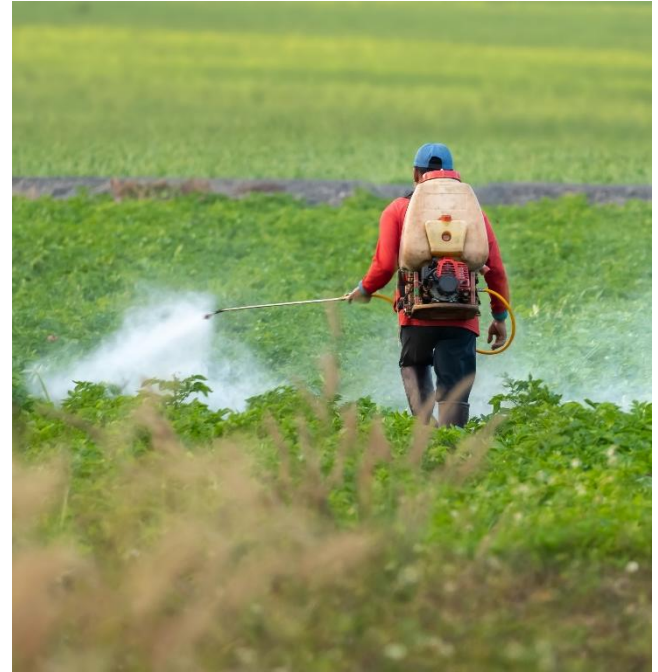
- A. Distribution
- B. Toxicodynamics
- C. Toxicokinetics
- D. Elimination

Challenge #4 Answer

The correct answer is **B: Toxicodynamics**.

Agricultural Worker Outbreak Scenario

- In this outbreak scenario, toxicologists recognized the reported symptoms were consistent with a cholinergic toxidrome that could be caused by an insecticide.
- Based on this information, investigators made sure the data collection tool included questions about expected cholinergic signs and symptoms, as well as typical therapies used to treat cholinergic poisoning.



Agricultural Worker Outbreak Scenario

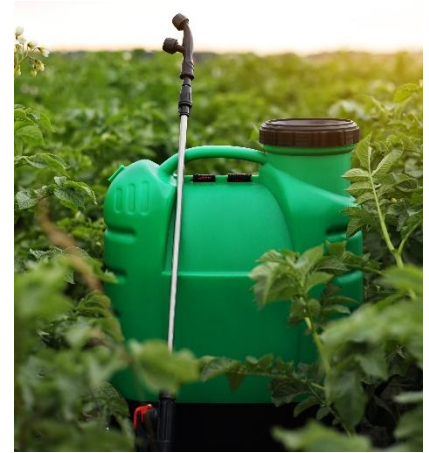
Blood and urine specimens were analyzed for these types of pesticides, which optimized testing with limited biological specimens.

- Specific tests for measuring pesticides and their metabolites may not be available.
- A more commonly available lab test is for cholinesterase levels, which can help assess exposure to certain classes of pesticides (e.g., organophosphates and carbamates). A very low cholinesterase test result can provide laboratory confirmation of exposure.
- In this case, decreased cholinesterase levels were detected in 100% of serum specimens collected from agricultural workers.
 - Cholinesterase levels can be difficult to interpret, especially if pre-exposure baseline levels are not available for individuals.



Agricultural Worker Outbreak Scenario (Cont.)

- Toxicologists suspected a pesticide known as a carbamate was making the workers ill.
- 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.



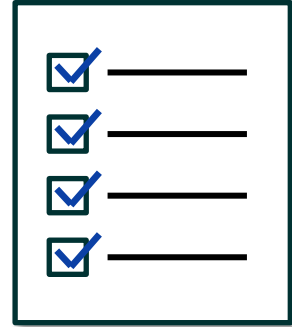
Module Summary

- This concludes Module 2.
- In this module, we considered outbreak characteristics to look for when determining whether an outbreak might have a toxic cause. We defined toxidromes and discussed the various factors that affect toxicity. We also examined two key concepts used by toxicologists.



Module Summary (Conti...)

- You should now be able to
 - Identify characteristics of an outbreak that can suggest that it might be by a toxic agent
 - Define toxidromes
 - Identify factors that affect toxicity, including the dose, duration, and frequency of the exposure, and individual characteristics of the exposed person
 - Describe the principles of toxicodynamics and toxicokinetics
 - Describe the toxicokinetic principles of absorption, distribution, metabolism, and elimination



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