

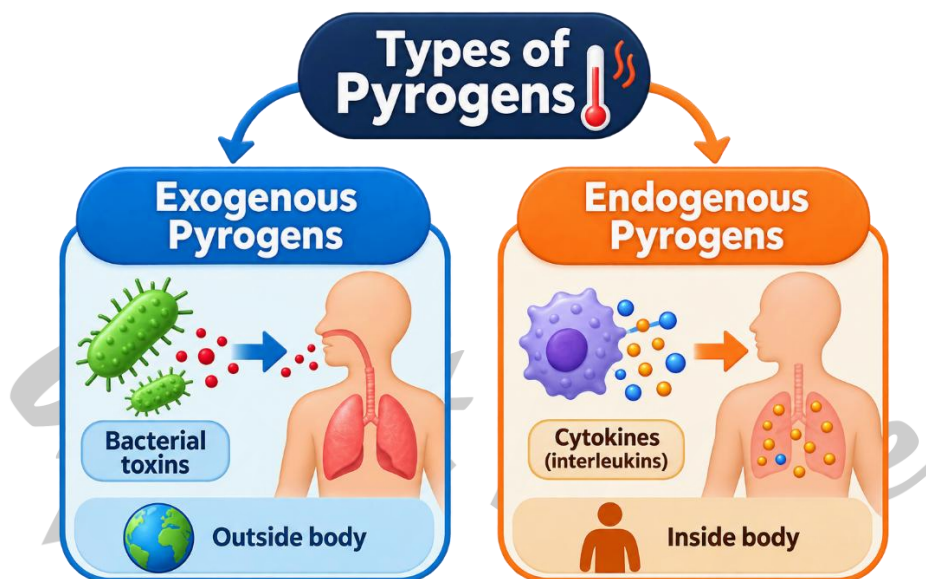
Pyrogens

Pyrogens and Sources of Pyrogens

Definition of Pyrogens

- Pyrogens are substances that can cause **fever (rise in body temperature)** when they enter the body.
- They are especially important in **parenteral preparations** (injections, IV fluids).
- Even very small amounts can produce strong fever reactions.

Types of Pyrogens



1. Exogenous pyrogens

- Come from outside the body
- Example: bacterial toxins

2. Endogenous pyrogens

- Produced inside the body
- **Example:** cytokines (like interleukins)

Main sources of pyrogens



A. Microbial sources (most important)

1. Gram-negative bacteria

- These are the primary and most dangerous source of pyrogens.
- Their cell wall contains endotoxins, which are strong fever-producing substances.

2. Gram-positive bacteria

- They can also produce pyrogens, but generally less potent compared to Gram-negative bacteria.

3. Fungi (yeasts and molds)

- Can produce pyrogenic substances during growth.

4. Viruses

- Some viral components may indirectly act as pyrogens by stimulating immune responses.

B. Non-microbial sources

1. Chemical substances

- Certain chemicals used in manufacturing processes may act as pyrogens.

2. Glassware and equipment contamination

- Improperly cleaned containers or instruments can carry pyrogenic residues.

3. Water used in preparation

- Water is a major source if not properly purified (especially water for injection).

4. Dust and environmental contaminants

- Airborne particles may carry microbial fragments that act as pyrogens.

C. Endogenous pyrogens (produced inside the body)

- These are produced by the body's immune cells.
- Examples include cytokines such as interleukins and tumor necrosis factor (TNF).
- They are released when the body detects infection or foreign substances.

Factors influencing presence of pyrogens

- Poor sterilization processes
- Improper storage conditions
- Use of contaminated raw materials
- Inadequate quality control during manufacturing

Importance of Controlling Pyrogens

- Prevents fever reactions in patients
- Ensures safety of injectable drugs
- Required by pharmacopoeial standards

Chemistry and Properties of Bacterial Pyrogens (Endotoxins)

Definition of Endotoxins

- Endotoxins are toxic substances present in the outer membrane of Gram-negative bacteria.
- They are released when bacteria:
 - Die
 - Multiply

Chemical Nature

Endotoxins are mainly composed of
Lipopolysaccharides (LPS)

Structure of LPS

a) Lipid A

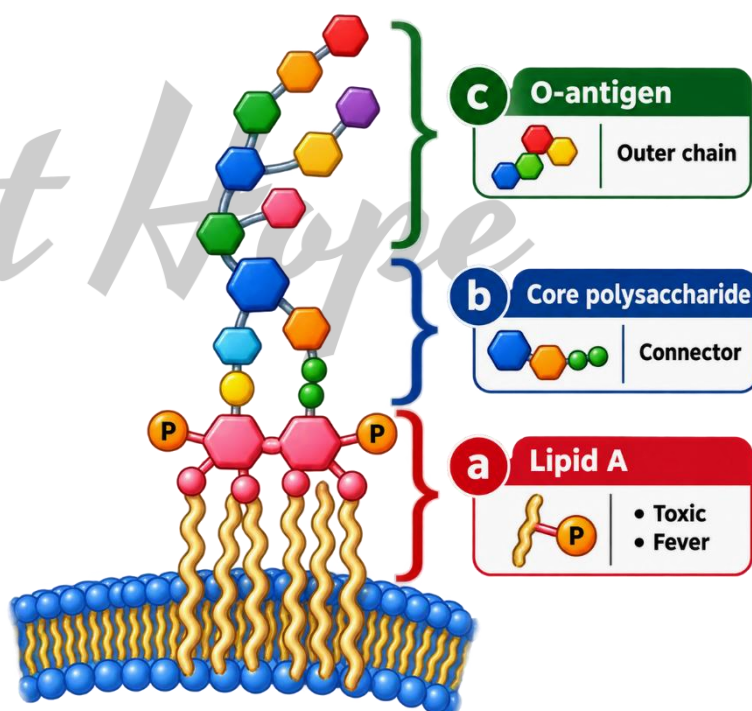
- Toxic part
- Responsible for fever

b) Core polysaccharide

- Connects Lipid A and O-antigen

c) O-antigen

- Outer carbohydrate chain
- Varies among bacteria



Properties of bacterial pyrogens (endotoxins)

A. Heat stability

- They are highly heat stable.
- Normal sterilization (like boiling) does not destroy them easily.
- Require dry heat at very high temperatures (e.g., 250°C) for destruction.

B. Water solubility

- Endotoxins dissolve easily in water.
- This makes it difficult to remove from aqueous pharmaceutical preparations.

C. Non-volatile nature

- They do not evaporate, so they remain in solutions.

D. Resistance to chemical disinfectants

- Many disinfectants do not effectively destroy endotoxins.
- This makes control difficult in pharmaceutical industries.

E. High potency

- Even very small amounts can produce fever.
- Measured in nanograms or even picograms.

F. Ability to bind surfaces

- They can stick to glassware, rubber, and plastic surfaces.
- This makes contamination persistent if cleaning is inadequate.

G. Biological activity

- Stimulate immune system strongly.
- Cause release of endogenous pyrogens (like cytokines).
- Lead to symptoms such as fever, chills, low blood pressure, and shock.

H. Not destroyed by filtration alone

- Although bacteria can be removed by filters, endotoxins may still pass through or remain.

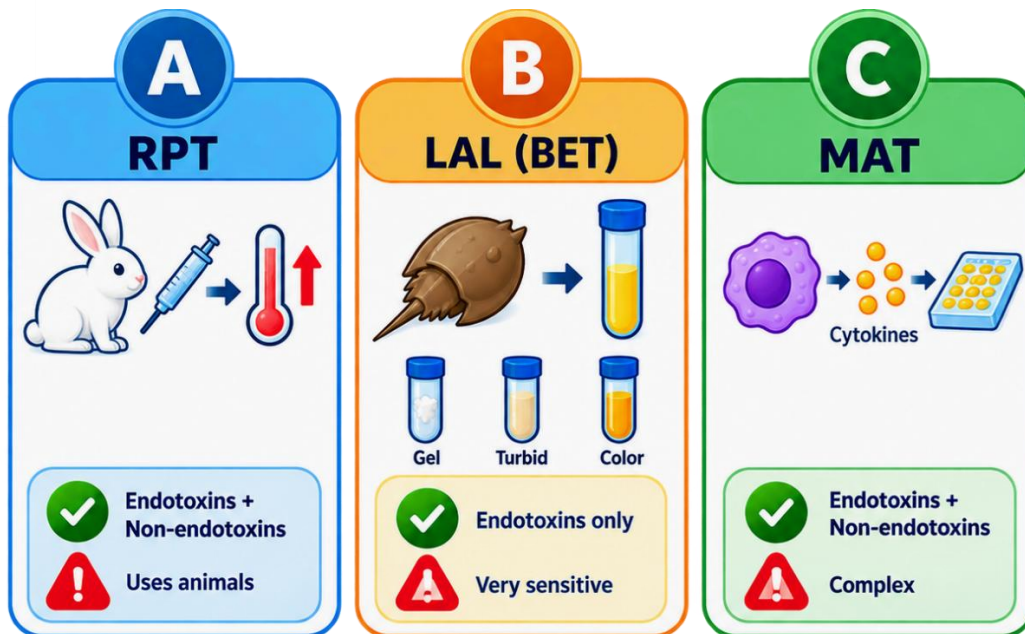
Differences Between Endotoxins and Exotoxins

Feature	Endotoxins	Exotoxins
Location/Origin	Part of the bacterial cell wall	Secreted by bacteria
Release	Mainly released on bacterial cell death	Actively released/secreted by bacteria
Nature	Lipopolysaccharide (LPS)	Protein
Heat Stability	Heat stable	Heat sensitive

Official Pyrogen Tests

- **Pyrogen testing** is essential to ensure that pharmaceutical products, especially injections, are free from fever-causing substances.
- Official pharmacopoeias (such as IP, USP, BP) describe standardized methods for detecting pyrogens.

Main official pyrogen tests



A. Rabbit Pyrogen Test (RPT)

Principle

- Pyrogens, when injected into rabbits, cause an increase in body temperature.
- The rise in temperature is measured and used to determine the presence of pyrogens.

Test animals used

- Healthy adult rabbits
- Each rabbit should be of suitable weight (usually not less than 1.5 kg)
- Rabbits must be free from disease and previously unexposed to pyrogens

Procedure

- Measure the initial body temperature of rabbits (baseline).
- Warm the test sample to body temperature.
- Inject the sample intravenously into the ear vein of rabbits.
- Record the temperature at regular intervals (usually every 30 minutes for 3 hours).

Observation

- Note the maximum rise in temperature for each rabbit.
- Compare the temperature increase with official limits.

Interpretation (general idea)

- If temperature rise is within acceptable limits → sample passes.
- If temperature rise exceeds limits → sample fails.

Advantages

- Detects a wide range of pyrogens (both endotoxins and non-endotoxins).
- Long-established and officially accepted method.



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