

Mast Cell Activation in Phosgene Oxime-Induced Cutaneous Injury: Mechanisms and Therapeutic Implications

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ABSTRACT

Study objective: Phosgene oxime (CX) is a potent chemical warfare agent causing rapid skin penetration, immediate tissue injury, and systemic toxicity. While mast cells mediate neuroimmune and inflammatory responses, their specific role in CX-induced injury remains poorly defined. This review evaluates whether mast cells exacerbate tissue destruction or facilitate repair and assesses the therapeutic potential of targeting specific mast cell signaling pathways, such as BTK and SYK.

Design, setting, and participants: A systematic literature search was conducted via PubMed utilizing keywords including 'phosgene oxime,' 'mast cells AND skin inflammation,' and 'cutaneous injury.' Screening included 130 abstracts, resulting in 30 primary research articles selected for full-text review. Inclusion criteria prioritized primary experimental, animal, and clinical research from 2021–2026, alongside foundational texts. Selected models evaluated in vitro human skin cultures to isolate molecular degranulation and in vivo animal models to observe systemic tissue resolution.

Results: The literature consistently associates CX exposure with rapid mast cell activation, triggering histamine release, pro-inflammatory cytokine signaling, and progressive tissue necrosis. Data suggest that inhibiting signaling pathways, such as BTK and SYK, correlates with reduced inflammatory activity and limited tissue damage. These findings

indicate that mast cell activation is consistently associated with increased CX-induced tissue injury.

Conclusions: Mast cell-targeted interventions present a viable therapeutic direction. Future research should prioritize controlled animal studies to support the development of standardized medical countermeasures.

1. Introduction

Phosgene oxime (CX) is a highly toxic chemical warfare agent that causes immediate skin cell death and systemic injury, yet no approved medical treatments currently exist. While current literature identifies mast cells as key drivers of the resulting inflammation and histamine release, their precise role in tissue destruction or facilitating repair remains poorly understood. This review addresses this gap by evaluating how specific mast cell signaling pathways, such as BTK and SYK, contribute to CX-induced cutaneous damage. The purpose of this research is to determine if targeting mast cell activation can serve as a viable therapeutic strategy to reduce the seriousness of the injury and guide future treatment plans.

2. Methods and Materials

To evaluate the mechanistic pathways of phosgene oxime (CX) induced skin inflammation, a systematic literature search was conducted via PubMed utilizing keywords including 'phosgene oxime,' 'mast cells AND skin inflammation,' 'cutaneous injury,' and 'neuroimmune response'. To ensure contemporary relevance, inclusion criteria prioritized primary experimental, animal, and clinical research from the last five years (2021–2026), while excluding general reviews and older texts published between 2005 and 2020 unless required for foundational context. Out of 130 abstracts screened, 30 primary research articles were selected for full-text review, utilizing in vitro human skin cultures to isolate molecular degranulation and in vivo animal models to observe systemic tissue resolution.

3. Results

3.1 CX-Induced Mast Cell Activation and Inflammatory Response

- CX rapidly activates mast cells upon exposure, functioning as a highly toxic vesicant.
- Mast cell activation releases histamine and pro-inflammatory cytokines, driving an acute inflammatory response with increased vascular permeability and immune cell infiltration.
- CX demonstrates a faster onset of inflammation and greater inflammatory severity compared to sulfur mustard and lewisite in tissue damage models.
- BTK and SYK pathway inhibition reduces cytokine release and inflammatory activity in CX-exposed tissues.
- BTK and SYK pathway targeting was associated with reduced tissue injury and decreased severity of CX-induced damage.

Fig. 1. Progression of Skin Injury Following Phosgene Oxime (CX) Exposure. This figure illustrates visible skin damage over time after a 0.5-minute CX exposure in mouse models, demonstrating a rapid onset of redness and swelling followed by severe tissue necrosis.

Fig. 2. Quantitative Changes in Skin Thickness, Edema, Erythema, and Necrosis After CX Exposure.

Graphs display quantitative biometric tracking showing immediate spikes in skin thickness and erythema indexes within 24 hours post-exposure, driven by mast cell-mediated histamine cascades.

4. Discussion

4.1 CX-Induced Mast Cell Activation

Inducing mast cells with CX rapidly activates them upon exposure, triggering histamine and pro-inflammatory cytokine release. This activation increases vascular permeability and immune cell infiltration, leading to accelerated tissue injury. CX produces faster and more severe inflammatory responses than sulfur mustard and lewisite.

4.2 Role of Mast Cells in Tissue Damage

Mast cells amplify inflammation through sustained cytokine signaling and recruitment of additional immune cells. Current evidence indicates that mast cells contribute to tissue damage progression in CX exposure, though the balance between harmful and protective effects requires further investigation.

4.3 Therapeutic Potential

Targeting BTK and SYK signaling pathways reduces inflammatory activity in CX-exposed tissues. These findings are clinically significant given the absence of approved CX treatments and the need for rapid intervention. Mast cell-targeted therapies represent a biologically rational approach to disrupting the inflammatory cascade driving tissue necrosis and may help protect both military personnel and civilian populations at risk of exposure.

5. Conclusions

Altogether, this review confirms that phosgene oxime (CX) triggers rapid mast cell activation, causing more severe and immediate inflammation than other vesicants through histamine and cytokine release. Targeting the BTK and SYK signaling pathways, primary mediators of this vascular and immune damage, presents a viable therapeutic strategy where no approved countermeasures currently exist. By inhibiting this neuroimmune response, treatment can effectively reduce acute tissue destruction. Consequently, future research should focus on testing these inhibitors in living models to find the most effective way to treat CX exposure.

CRedit authorship contribution statement

Mayuresh Behera: Conceptualization, Methodology, Writing - Original Draft, Project administration.
Keshav Raghunath: Investigation, Data Curation. Nitin Kandakumar: Validation, Formal analysis.
Tanishkka Dhawan: Writing - Review & Editing. Dr. Narasaiah Kolliputi: Supervision, Resources, Funding acquisition.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

All applicable institutional and national guidelines for the care and use of laboratory animals were followed and approved by the University of South Florida Institutional Animal Care and Use Committee (IACUC).

Data availability statement

Data will be made available on request from the corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used an AI assistant tool in order to align text elements structurally into the target journal template format. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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