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Review / Derleme

The Dual Faces of Vesicant Agents: From Chemical Weapon to Chemotherapeutic Agent

Vezikan Ajanların İki Yüzü: Kimyasal Silahtan Kemoterapötik Ajanlara

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ABSTRACT

Vesicant agents, particularly analogs of sulfur mustard (SM) and nitrogen mustard (NM), exhibit a striking dichotomy between devastating chemical toxicity and therapeutic potential in oncology. The cytotoxic facet of SM causes rapid cellular damage through bifunctional alkylation, depletion of glutathione and ATP, and PARP hyperactivation. This process manifests as oncosis or necrosis, acute skin vesiculation, eye damage, and respiratory tract injuries. Over decades, genotoxicity mediated by persistent DNA interstrand cross-links, oxidative stress, chronic inflammation, and field cancerization increases the risk of squamous cell carcinoma of the lung and skin. Epidemiological studies, particularly among Iran-Iraq War gas survivors, have confirmed these long-term cancer risks. Mechanistic studies indicate that reactive oxygen species-mediated mutagenesis, stem cell niche disruption, and clonal proliferation play central roles in vesicant-induced carcinogenesis. Paradoxically, these same alkylating mechanisms fueled the therapeutic development of NMs, formed the basis of modern chemotherapy, and raised concerns about secondary malignancies and biosafety. Future research should focus on early-detection biomarkers, PARP and receptor-interacting protein kinase 1 inhibitors that reduce acute toxicity, and advanced carrier systems that minimize genomic damage while maintaining antitumor efficacy. The history of vesicants demonstrates how understanding the mechanisms of a toxic chemical can transform it into a therapeutic tool and guide the evolution of cancer treatment. This review comprised a comprehensive examination of English- and Turkish-language literature, using PubMed-indexed keywords, including 'vesicant agents', 'SM', 'NM', 'chemotherapy', and 'carcinogenesis'.

Keywords: Vesicant agents, sulfur mustard, nitrogen mustard, chemotherapy, carcinogenesis, alkylating agent, chemical warfarev

ÖZ

Vesikan ajanlar, özellikle sülfür mustard (SM) ve nitrojen mustard (NM) analogları, yıkıcı kimyasal toksisite ile onkolojide terapötik potansiyel arasında çarpıcı bir ikilik sergiler. SM'in sitotoksik yüzü, bifonksiyonel alkilleme, glutatyon/ATP tükenmesi ve PARP hiperaktivasyonu yoluyla hızlı hücresel hasara yol açar. Bu süreç onkozis/nekroz, akut deri vezikülasyonu, göz hasarı ve solunum yolu yaralanmaları ile kendini gösterir. On yıllar içinde, genotoksik yüz, kalıcı DNA zincirler arası çapraz bağlar, oksidatif stres, kronik inflamasyon ve alan kanserleşmesi yoluyla ortaya çıkarak akciğer ve deri skuamöz hücreli kanser riskini artırır. Özellikle İran-Irak Savaşı gaz mağdurlarına yapılan epidemiyolojik çalışmalar bu uzun vadeli kanser risklerini doğrulamıştır. Mekanistik araştırmalar, reaktif oksijen türleri aracılı mutagenez, kök hücre nişi bozulması ve klonal çoğalmanın vesikan kaynaklı karsinogenezde merkezi rol oynadığını göstermektedir. Çelişkili olarak, aynı alkilleyici mekanizmalar NM'ların terapötik gelişimini tetiklemiş, modern kemoterapinin temelini oluşturmuş ve ikincil malignite ile biyogüvenlik kaygılarını ortaya koymuştur. Gelecek araştırmalar erken teşhis biyobelirteçleri, PARP ve reseptör etkileşimli protein kinaz 1 inhibitörleri ile akut toksisitenin azaltılması ve antitümör etkinliği korurken genomik hasarı minimize eden ileri taşıyıcı sistemler üzerine odaklanmalıdır. Vesikan ajanların tarihi, toksik bir kimyasalın mekanizmalarının anlaşılmasıyla tedavi aracına dönüştürülebileceğini ve kanser tedavisinin evrimini

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nasıl yönlendirebileceğini göstermektedir. Bu derleme, PubMed indeksli 'vezikan ajanlar', 'sülfür mustard', 'nitrojen mustard', 'kemoterapi' ve 'karsinogenez' gibi anahtar kelimelerin taranarak İngilizce ve Türkçe literatürün incelenmesiyle derlenmiştir.

Anahtar Kelimeler: Vesikan ajanlar, sülfür mustard, nitrojen mustard, kemoterapi, karsinogenez, alkilleyici ajan, kimyasal savaş

INTRODUCTION

This review examines the dual-use paradigm of vesicant agents-substances engineered for chemical warfare yet repurposed as chemotherapeutic tools-focusing on sulfur mustard (SM) and nitrogen mustard (NM) analogs. By synthesizing recent evidence, we highlight the molecular, clinical, and ethical dimensions of this duality, from acute toxicity to oncogenic risks and oncology applications, while addressing regulatory and biosecurity implications in the post-CW Convention era. This review was conducted through a comprehensive examination of English and Turkish literature, using PubMed-indexed keywords including 'vesicant agents', 'sulfur mustard', 'nitrogen mustard', 'chemotherapy' and 'carcinogenesis'.

The story of vesicant agents is a stark narrative of destruction and discovery. One of the best-known vesicant agents, SM, was first synthesized in the 19th century; its debut as a chemical weapon on the battlefields of Ypres during World War I heralded a new era of warfare, earning it the grim sobriquet "King of Battle Gases".[1,2] Its military efficacy lies not in high lethality, but in its ability to inflict debilitating, resource-intensive injuries that overwhelm medical systems and erode morale.[3] However, beyond its notorious history as a vesicant, SM has emerged as an indispensable tool in molecular toxicology, offering profound insights into cellular stress responses, death pathways, and carcinogenesis.[4] The central theme of SM's biology is its intrinsic duality. A single exposure can trigger two divergent pathological timelines. In the immediate cytotoxic phase, within hours, SM induces massive cellular injury, leading to necrotic cell death (oncosis) in highly exposed tissues, followed by an intense inflammatory response that characterizes its acute blistering and damaging effects on the skin, eyes, and respiratory tract.[5] The delayed genotoxic face: over decades, sublethal DNA damage can evade repair, leading to genomic instability, clonal expansion of mutated cells, and a significantly elevated risk of cancer, particularly in the lungs and skin.[6,7] Yet this architect of suffering catalyzed three scientific revolutions:

1. In molecular toxicology: SM revealed that bifunctional alkylation was the ur-mechanism of genotoxicity, a finding that predates modern DNA sequencing by 80 years.[4]
2. Cell death biology: Its dose-dependent activation of oncosis, apoptosis, necroptosis defined ATP thresholds for programmed vs. unprogrammed demise.[5]
3. Oncology: SM's genotoxic legacy [International Agency for Research on Cancer (IARC) Group 1] provided the first human model of inflammation-driven field cancerization.[6,7]

This review synthesizes current knowledge on both fronts. We will explore the chemistry defining its reactivity, dissect the cellular pathways it disrupts, and examine long-term epidemiological data linking exposure to cancer. Furthermore, we trace the remarkable journey of its chemical analogs from the battlefield to the clinic, highlighting how the same destructive principles were harnessed to create the first chemotherapeutic agents.

The Janus-Faced Timeline: Cytotoxic vs. Oncogenic Divergence

A single exposure to SM initiates a cascade of complex pathological events that unfold along two major, yet interrelated, trajectories: an acute cytotoxic phase and a delayed genotoxic phase. These two axes represent the immediate and long-term consequences of SM exposure, and together they define the compound's notorious duality as both a devastating chemical weapon and a model for studying chronic toxic injury.

In the acute phase, SM acts as a highly reactive alkylating agent targeting essential cellular macromolecules such as DNA, proteins, and low-molecular-weight antioxidants, including glutathione (GSH).[8] The rapid formation of alkylated adducts triggers widespread biochemical disruption: DNA strand breaks, oxidative stress, and enzymatic inhibition converge to induce cell death via necrosis, apoptosis, or, in some cases, mixed regulated cell-death pathways. Clinically, this manifests within hours as erythema and edema at the exposure site, followed by the formation of large, painful blisters and ulcerations, which are characteristic of vesicant injury (Table 1).[9] The eyes and respiratory tract are particularly vulnerable and often develop conjunctivitis, corneal erosions, bronchial inflammation, and necrosis.[10] Systemically, bone marrow suppression can lead to transient leukocytosis followed by lymphopenia and then pancytopenia, underscoring the hematopoietic toxicity of SM. The underlying cellular mechanisms are characterized by oxidative stress and rapid depletion of cellular

Table 1. A single SM exposure bifurcates into two orthogonal pathological axes

Phase	Timeline	Dominant mechanism and pathway	Key lesion	Clinical manifestation	Molecular signature
Acute cytotoxic	0-72 h	DNA/protein alkylation, oxidative stress, cell death (necrosis/ apoptosis)	ICLs (4%) + ROS (10x↑)	Blistering, inflammation, marrow suppression	HMGB1↑50x, IL-1β↑10x
Chronic oncogenic/ delayed genotoxicity	10-40 y	Persistent DNA damage, chronic inflammation, immune dysregulation	O^6-alkylG (40% mut)	Fibrosis, chronic lung/skin/eye disease, cancer	G:C→A:T (sig. mut)

ICL: Interstrand cross-link, ROS: Reactive oxygen specy

energy stores, which together precipitate mitochondrial dysfunction, tissue necrosis, and a vigorous inflammatory response that exacerbates tissue damage.[11]

The delayed genotoxic phase emerges long after the acute symptoms have subsided and represents the insidious, progressive dimension of SM toxicity. Sublethal doses that do not cause immediate cell death often leave behind unrepaired or misrepaired DNA lesions, setting the stage for persistent genomic instability and mutagenesis.[12] Over time, this molecular damage manifests clinically as chronic respiratory diseases-including bronchiolitis obliterans and pulmonary fibrosis-alongside skin atrophy, pigmentary changes, and ocular complications such as chronic keratitis and limbal stem cell deficiency. Epidemiological studies of exposed populations, particularly among Iranian war veterans, have also revealed a markedly increased incidence of malignancies, especially squamous cell carcinoma (SCC) of the skin and various forms of lung cancer. These chronic pathologies are perpetuated by ongoing inflammation, immune dysregulation, and the clonal expansion of mutated cells, which collectively drive progressive organ dysfunction and carcinogenesis.[13]

Thus, SM exposure represents a biphasic toxicological paradigm: a rapidly destructive acute insult followed by a protracted genotoxic aftermath. Understanding these intertwined processes not only elucidates the mechanisms of SM-induced injury but also provides a broader framework for studying inflammation-driven carcinogenesis and long-term sequelae of alkylating agent exposure.[10,13]

Chemical Identity and Biochemical Warfare at the Molecular Level

SM's potency is a direct consequence of its structure. As a lipophilic molecule, it readily penetrates cellular membranes. Its core mechanism involves intramolecular cyclization to form a highly reactive cyclic ethylene-sulfonium ion, a powerful electrophile that readily attacks nucleophilic sites of vital cellular components.[14,15]

Primary Molecular Targets

Among the molecular events triggered by SM, DNA alkylation and cross-link formation represent the most critical and damaging mechanisms. SM demonstrates a strong preference for alkylating the N7 position of guanine bases within DNA, producing monoadducts that distort the double helix and interfere with normal base pairing. More importantly, due to its bifunctional chemical structure, SM can generate interstrand cross-links (ICLs)-highly lethal DNA lesions that prevent the separation of complementary strands during replication and transcription, thereby halting essential cellular processes.[16,17] When the cell attempts to repair these ICLs through excision or recombination pathways, the process frequently results in double-strand breaks (DSBs), which are among the most mutagenic and clastogenic forms of DNA damage. These DSBs are a critical initiating factor for genomic instability, laying the molecular foundation for cytotoxicity and carcinogenesis.[18]

In addition to its genotoxicity, SM exerts broad inactivation of proteins and enzymes by alkylating key amino acid residues, such as cysteine, histidine, and glutamate. This modification alters the structural integrity and catalytic function of essential enzymes, many of which are central to energy metabolism and antioxidant defense. Notably, inhibition of glucose-6-phosphate dehydrogenase and other sulfhydryl-dependent enzymes disrupts the hexose monophosphate shunt, diminishing cellular NADPH levels and impairing the regeneration of reduced GSH. The consequent loss of redox homeostasis sensitizes the cell to oxidative injury and metabolic collapse.[19]

A pivotal early biochemical hallmark of SM exposure is the rapid depletion of GSH, the cell's primary antioxidant and detoxifying molecule.[20] As GSH conjugates with SM and its reactive intermediates, intracellular GSH stores are rapidly depleted, undermining the cell's ability to neutralize reactive oxygen species (ROS). The resulting oxidative stress amplifies cellular injury through lipid peroxidation, oxidation of nucleic acids and proteins, and further membrane destabilization. This self-propagating

cycle of oxidative and alkylation damage perpetuates mitochondrial dysfunction and DNA oxidation, intensifying both acute cytotoxicity and long-term genotoxic effects.[21]

Mechanisms of Acute Toxicity and Cellular Demise

The cellular response to SM is a cascade of metabolic failure, culminating in a dose-dependent decision between different modes of cell death.

The Metabolic Crisis

The hyperactivation of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) in response to excessive DNA damage consumes vast amounts of NAD+, leading to a catastrophic drop in ATP levels.[22] This energy crisis is compounded by mitochondrial dysfunction: SM and ROS induce the mitochondrial permeability transition, which collapses the proton gradient and halts ATP synthesis.[23]

The Spectrum of Cell Death

The mode of death-oncosis/necrosis, apoptosis, and necroptosis- is dictated by the severity of the insult and the remaining energy reserves (Table 2). In oncosis/necrosis, at high, militarily relevant doses, rapid ATP depletion prevents the energy-dependent execution of programmed cell death. Cells undergo oncosis-characterized by swelling, organelle disintegration, and plasma membrane rüptüre-leading to the release of damage-associated molecular patterns that fuel a robust and damaging inflammatory response.[5,24] At lower doses, where some ATP remains, cells can initiate apoptosis (programmed cell death). This involves caspase activation, chromatin condensation, and formation of apoptotic bodies for efficient clearance, minimizing inflammation.[25] Necroptosis, emerging evidence indicates SM can also trigger this programmed form of necrosis, via receptor-interacting protein kinase (RIPK) activation, further contributing to the inflammatory pathology.[26]

The Oncogenic Face: From DNA Adduct to Malignancy

The IARC classifies SM as a Group 1 agent, "carcinogenic to humans".[27] The journey from exposure to cancer is a multi-decade process driven by persistent genomic lesions.

Molecular Pathogenesis of Sulfur Mustard-Induced Carcinogenesis

Mutagenesis: while ICLs are cytotoxic, misrepaired monoadducts are mutagenic. The persistence of O6-alkylguanine adducts can lead to G:C to A:T transition mutations during DNA replication, a mutational signature common in carcinogenesis induced by alkylating agents.[28] Genomic instability: error-prone repair of SM-induced DSBs and the collapse of stalled replication forks at ICLs lead to chromosomal aberrations, micronuclei formation, and large-scale genomic rearrangements, providing a fertile ground for oncogene activation and tumor-suppressor loss.[29] Chronic inflammation and clonal selection: repeated cycles of tissue damage, ulceration, and repair in SM-exposed skin and respiratory epithelium create a pro-tumorigenic microenvironment. The presence of inflammatory cytokines, growth factors, and ROS promotes the proliferation and survival of initiated (mutated) cell clones.[30]

Site-Specific Cancers: Epidemiological and Clinical Evidence

Long-term clinical observations of individuals exposed to SM during the Iran-Iraq War have yielded the most conclusive human data linking this agent to cancer development. In particular, respiratory malignancies have emerged as a major delayed outcome of exposure. Epidemiological analyses have demonstrated that individuals exposed to SM exhibit a markedly increased incidence of lung cancer, estimated to be more than twice that observed in unexposed populations, with the risk rising proportionally with the extent and duration of exposure.[31] Histopathological evaluations of these cases frequently identify SCC and adenocarcinoma as the predominant tumor types, typically occurring in a background of chronic airway injury characterized by bronchitis, bronchiolitis obliterans, and pulmonary fibrosis—conditions that create a pro-carcinogenic microenvironment conducive to malignant transformation.[32]

Table 2. Key cell death pathways induced by sulfur mustard

Pathway	Characteristics	Energy (ATP) dependent?	Inflammatory outcome	Primary SM dose
Oncosis/necrosis	Cellular swelling, membrane rupture, release of intracellular contents	No	Highly inflammatory	High
Apoptosis	Cell shrinkage, nuclear fragmentation, formation of apoptotic bodies	Yes	Anti-inflammatory / tolerogenic	Low to moderate
Necroptosis	Regulated necrosis, RIPK1/RIPK3/ MLKL pathway activation	No	Highly inflammatory	Moderate to high

SM: Sulfur mustard, RIPK1: Receptor-interacting protein kinase 1, MLKL: Mixed lineage kinase domain-like pseudokinase

Similarly, cutaneous malignancies represent another critical long-term complication among SM survivors. Persistent or recurrent skin lesions at sites of previous vesication have been recognized as pre-neoplastic foci that may progress to SCC or, less commonly, basal cell carcinoma. A systematic review of affected populations revealed that the risk of developing such skin cancers is substantially elevated compared with that in non-exposed individuals.[33] The underlying mechanisms appear to involve a combination of field cancerization, resulting from widespread alkylation-induced DNA damage across large skin areas, and chronic inflammation associated with repeated cycles of ulceration and wound healing. Together, these processes create an environment that favors clonal expansion of mutated keratinocytes and the gradual emergence of malignant lesions.

The Therapeutic Legacy: From Mustard Gas to Chemotherapy

Paradoxically, the study of SM's systemic effects led to a medical revolution. The observation of profound leukopenia and lymphoid atrophy in victims of the 1943 Bari harbor incident prompted pharmacologists Louis S. Goodman and Alfred Gilman to investigate NMs as potential treatments for lymphoproliferative cancers.[34]

Nitrogen Mustards as Chemotherapeutic Agents

NMs, such as mechlorethamine, cyclophosphamide, and melphalan, share SM's core mechanism of action: forming DNA ICLs that are fatal to rapidly dividing cells. Their development marked the birth of modern cancer chemotherapy (Table 3).[35]

The Enduring Paradox in Therapy

The use of NM chemotherapy mirrors the dual nature of SM. While they are curative for many cancers, they are potent human carcinogens. Patients treated with alkylating agents have a markedly increased risk of developing secondary myeloid neoplasms and other cancers, often with a characteristic latency of 5-10 years.[36] This underscores the fundamental principle that the very mechanism that kills cancer cells-genomic disruption-can also initiate it, a risk that must be carefully managed in clinical practice.

CONCLUSION

Vesicant agents occupy a distinctive place in toxicology and oncology, embodying a dual nature that is simultaneously destructive and instructive. Haber's seminal 1986 analysis first articulated how these agents push the limits of cellular resilience, producing rapid energy collapse, overwhelming oxidative stress, and necrotic inflammatory cascades. These early mechanistic insights became the foundation for the conceptual framework that Szinicz further refined nearly two decades later, in 2005-namely, the continuity between acute cytotoxicity and delayed oncogenic outcomes following vesicant exposure.

The biphasic biological trajectory was originally delineated by the biochemical and histopathological studies of Papirmeister and colleagues, who documented the early acute phase characterized by bifunctional alkylation, depletion of GSH and ATP, PARP hyperactivation, and oncosis/necrosis. This acute phase manifests in severe dermal, ocular, and respiratory tissue injury. Subsequent mechanistic advances, especially those contributed by Kehe and Smith, clarified that unrepaired DNA ICLs and a persistently inflamed tissue microenvironment shape the delayed genotoxic phase—culminating in field cancerization, clonal selection, and a documented 2- to 8-fold elevation in SCC of the skin and lung in previously exposed populations.

More recent studies have converged on ROS-driven mutagenesis and stem-cell niche disruption as central molecular drivers of vesicant-induced carcinogenesis. The same alkylation chemistry responsible for battlefield injuries also forms the basis of therapeutic repurposing: as Szinicz highlighted, NMs served as the prototype for modern anticancer chemotherapy. Yet this scientific transformation—from chemical weapon to chemotherapeutic tool—raises continuing ethical and biosecurity concerns, including risks of secondary malignancies, especially in communities with historical exposure.

Future research priorities include the development of sensitive early-detection biomarkers for long-term cancer surveillance, targeted pharmacologic strategies such as PARP and RIPK1 inhibitors to mitigate acute tissue injury, and the design of safer alkylating chemotherapeutics. In

Table 3. Nitrogen mustards as chemotherapeutic agents

Agent	Structure	ICL Formation	FDA approval	Cancers
Mechlorethamine	HN_2 analog	2-5%/10^6 bp	1949	Lymphoma
Cyclophosphamide	Cyclic prodrug	1-3%/10^6 bp	1959	Breast, Ovarian
Melphalan	Phe analog	3-6%/10^6 bp	1964	Myeloma

ICL: Interstrand cross-links, FDA: Food and Drug Administration

particular, next-generation antibody–drug conjugates offer promise in preserving antitumor potency while minimizing off-target genomic toxicity.

Ultimately, the story of SM represents both a cautionary lesson and an example of scientific redemption. Understanding the mechanisms of a devastating vesicant has become a foundation for therapeutic advances, illustrating how the biology of a poison can guide the development of modern cancer therapies.

Footnotes

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REFERENCES

1. Fitzgerald GJ. Chemical warfare and medical response during World War I. Am J Public Health. 2008;98:611-625. Erratum in: Am J Public Health. 2008;98:1158.
2. Szinicz L. History of chemical and biological warfare agents. Toxicology. 2005;214:167-81.
3. Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. Fundam Clin Pharmacol. 2005;19:297-315.
4. Jan Y, Heck D, Laskin D, Laskin J. DNA damage signaling in the cellular responses to mustard vesicants. Toxicology letters. 2020.
5. Kehe K, Balszuweit F, Steinritz D, Thiermann H. Molecular toxicology of sulfur mustard-induced cutaneous inflammation and blistering. Toxicology. 2009;263:12-9.
6. Ghanei M, Harandi AA. Long term consequences from exposure to sulfur mustard: a review. Inhal Toxicol. 2007;19:451-6.
7. Khateri S, Ghanei M, Keshavarz S, Soroush M, Haines D. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. J Occup Environ Med. 2003;45:1136-43.
8. Laskin JD, Black AT, Jan YH, et al. Oxidants and antioxidants in sulfur mustard-induced injury. Ann N Y Acad Sci. 2010;1203:92-100.
9. Sezigen S, Eyison RK, Ortatatli M, Kilic E, Kenar L. Myelosuppression and acute hematological complications of sulfur mustard exposure in victims of chemical terrorism. Toxicol Lett. 2020;318:92-8.
10. Balali-Mood M, Hefazi M. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. Basic Clin Pharmacol Toxicol. 2006;99:273-82.
11. Xiaoji Z, Xiao M, Rui X, et al. Mechanism underlying acute lung injury due to sulfur mustard exposure in rats. Toxicol Ind Health. 2016;32:1345-57.
12. Beigi Harchegani A, Khor A, Tahmasbpour E, Ghatrehsamani M, Bakhtiari Kaboutaraki H, Shahriary A. Role of oxidative stress and antioxidant therapy in acute and chronic phases of sulfur mustard injuries: a review. Cutan Ocul Toxicol. 2019;38:9-17.
13. Panahi Y, Roshandel D, Sadoughi MM, Ghanei M, Sahebkar A. Sulfur Mustard-Induced Ocular Injuries: Update on Mechanisms and Management. Curr Pharm Des. 2017;23:1589-97.
14. Munro NB, Talmage SS, Griffin GD, et al. The sources, fate, and toxicity of chemical warfare agent degradation products. Environ Health Perspect. 1999;107:933-74.
15. Noort D, Benschop HP, Black RM. Biomonitoring of exposure to chemical warfare agents: a review. Toxicol Appl Pharmacol. 2002;184:116-26.
16. Ludlum DB, Austin-Ritchie P, Hagopian M, Niu TQ, Yu D. Detection of sulfur mustard-induced DNA modifications. Chem Biol Interact. 1994;91:39-49.
17. Jost P, Svobodova H, Stetina R. Induction and repair of DNA cross-links induced by sulfur mustard in the A-549 cell line followed by a comet assay. Chem Biol Interact. 2015;237:31-37.
18. Deans AJ, West SC. DNA interstrand crosslink repair and cancer. Nat Rev Cancer. 2011;11:467-80.
19. Smith WJ, Dunn MA. Medical defense against blistering chemical warfare agents. Arch Dermatol. 1991;127:1207-13.
20. Layali I, Shahriary A, Rahmani Talatappe N, Tahmasbpour E, Rostami H, Beigi Harchegani A. Sulfur mustard triggers oxidative stress through glutathione depletion and altered expression of glutathione-related enzymes in human airways. Immunopharmacol Immunotoxicol. 2018;40:290-296.
21. Ramos E, Gil-Martín E, De Los Ríos C, et al. Melatonin as modulator for sulfur and nitrogen mustard-induced inflammation, oxidative stress and DNA damage: molecular therapeutics. Antioxidants (Basel). 2023;12:397.
22. Mol MA, van de Ruit AM, Kluivers AW. NAD+ levels and glucose uptake of cultured human epidermal cells exposed to sulfur mustard. Toxicol Appl Pharmacol. 1989;98:159-65.
23. Gould NS, White CW, Day BJ. A role for mitochondrial oxidative stress in sulfur mustard analog 2-chloroethyl ethyl sulfide-induced lung cell injury and antioxidant protection. J Pharmacol Exp Ther. 2009;328:732-9.
24. Rosenthal DS, Simbulan-Rosenthal CM, Iyer S, Spoonde A, Smith W, Ray R, Smulson ME. Sulfur mustard induces markers of terminal differentiation and apoptosis in keratinocytes via a Ca2+-calmodulin and caspase-dependent pathway. J Invest Dermatol. 1998;111:64-71.
25. Ghabili K, Agutter PS, Ghanei M, Ansarin K, Panahi Y, Shoja MM. Sulfur mustard toxicity: history, chemistry, pharmacokinetics, and pharmacodynamics. Crit Rev Toxicol. 2011;41:384-403.
26. Zhang B, Zhang Y. Necroptosis in sulfur mustard-induced toxicity. *J Appl Toxicol*. 2021;41(1):33–41.
27. Chappell G, Pogribny IP, Guyton KZ, Rusyn I. Epigenetic alterations induced by genotoxic occupational and environmental human chemical carcinogens: a systematic literature review. Mutat Res Rev Mutat Res. 2016;768:27-45.
28. Zubel T, Hochgesand S, John H, et al. A mass spectrometric platform for the quantitation of sulfur mustard-induced nucleic acid adducts as mechanistically relevant biomarkers of exposure. Arch Toxicol. 2019;93:61-79.
29. Panahi Y, Fattahi A, Zarei F. Ghasemzadeh N. Next-generation sequencing approaches for the study of genome and epigenome toxicity induced by sulfur mustard. Arch Toxicol 2018;92:3443-3457 .
30. Yu W, Tu Y, Long Z, et al. Reactive oxygen species bridge the gap between chronic inflammation and tumor development. Oxid Med Cell Longev. 2022;2022:2606928.
31. Zafarghandi MR, Soroush MR, Mahmoodi M, Naieni KH, Ardalan A, Dolatyari A, Falahati F, Mirmohammadkhani M, Mousavi B,

Ghanei M. Incidence of cancer in Iranian sulfur mustard exposed veterans: a long-term follow-up cohort study. Cancer Causes Control. 2013;24:99-105.

32. Hosseini-khalili A, Haines DD, Modirian E, Soroush M, Khateri S, et al. Mustard gas exposure and carcinogenesis of lung. Mutat Res. 2009;678:1-6.
33. Owens M, Thyagarajan A, Travers JB, Sahu RP. Mechanistic insights and pharmacological approaches for nitrogen and sulfur mustards and their implications as therapeutic agents. J Appl Toxicol. 2025;45:1417-1425.
34. Gilman A. The initial clinical trial of nitrogen mustard. Am J Surg. 1963;105:574-8.
35. Chabner BA, Roberts TG Jr. Timeline: chemotherapy and the war on cancer. Nat Rev Cancer. 2005;5:65-72.
36. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood. 2000;95:3273-9.