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From residue to cancer risk: How thirdhand smoke drives cancer hallmarks

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Abstract

Thirdhand smoke (THS) is a reservoir of toxic compounds that persist in indoor environments and on surfaces long after active smoking has ceased. Major THS chemicals, including nicotine, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and heavy metals, can induce DNA damage, epigenetic alterations, oxidative stress, and chronic inflammation. These biological changes contribute to one or more canonical hallmarks of cancer. In this minireview, we propose an integrated mechanistic framework that incorporates the hallmarks of cancer into environmental exposure risk assessment. This framework offers a system-level approach to carcinogenicity assessment that transcends the limitations of conventional single-endpoint toxicological assays. As a case application, we systematically analyze how THS chemicals disrupt specific cancer hallmarks and delineate the molecular and cellular mechanisms through which persistent tobacco smoke residues promote carcinogenesis. These insights establish a mechanistically grounded framework for assessing the environmental cancer hazard associated with THS.

Key Words: Environmental carcinogenesis; Thirdhand smoke; Cancer hallmarks; Nicotine-derived tobacco-specific nitrosamines; Polycyclic aromatic hydrocarbons; Heavy metals; Risk assessment

Core Tip: Thirdhand smoke (THS) represents a persistent and underrecognized environmental carcinogen whose complex chemical mixture drives cancer-relevant biological processes beyond the window of active smoking. By integrating THS-induced molecular and cellular perturbations, such as DNA damage, epigenetic reprogramming, oxidative stress, and chronic inflammation, within the framework of the hallmarks of cancer, a systems-level paradigm for carcinogenic risk assessment emerges. This approach moves beyond traditional single-endpoint toxicology to capture the cumulative, multi-pathway impact of chronic low-dose exposures. Applying this framework to THS reveals how residual tobacco toxicants synergistically disrupt multiple cancer hallmarks, providing a mechanistically grounded basis for evaluating long-term cancer risk and informing environmental health policy.

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INTRODUCTION

Tobacco smoke is a well-recognized human carcinogen and continues to rank among the leading causes of preventable cancer-related mortality[1,2]. Beyond active smoking and secondhand smoke (SHS), growing evidence over the past 15 years has identified thirdhand smoke (THS) as a distinct and enduring category of tobacco-related exposure[3-7]. THS refers to the residual tobacco smoke constituents that deposit onto indoor surfaces, accumulate in household dust, and adhere to clothing and furnishings, where they can remain for months to years after smoking has ceased[8,9]. THS is defined by the so-called “four Rs”: (1) Tobacco smoke constituents that remain in the indoor environment; (2) React with ambient oxidants to form secondary pollutant; (3) Re-emit back into the air; and (4) Become resuspended in indoor dust[8,9]. Through these interconnected processes, THS evolves into a chemically dynamic and continuously transforming mixture enriched in carcinogenic and toxic compounds[10], including nicotine-derived tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), reactive aldehydes, heavy metals, and secondary oxidants[11-15].

In contrast to SHS, which predominantly influences the respiratory tract through inhalation, THS leads to chronic, low-dose exposure through multiple routes, involving dermal absorption, ingestion and inhalation of contaminated particles [8]. Accumulating experimental evidence from *in vitro* systems, animal models, clinical trial studies, and chemical analyses demonstrates that THS exposure induces DNA damage[16], epigenetic alterations, oxidative stress, and sustained inflammatory signaling[17,18], all of which are central biological processes underlying carcinogenesis[4,6]. These findings underscore that THS should not be regarded merely as a residual odor or passive byproduct of smoking, but rather as an active and enduring source of carcinogenic exposure with significant implications for cancer risk.

Importantly, the health burden of THS exposure is likely to be disproportionately higher in vulnerable populations. Infants and young children are particularly at risk due to frequent hand-to-mouth behaviors[19], extensive contact with contaminated surfaces, and underdeveloped detoxification systems[20,21]. Likewise, elderly individuals and those with pre-existing cardiopulmonary or metabolic disorders may exhibit increased susceptibility due to reduced physiological resilience and elevated baseline levels of oxidative stress and inflammation[22,23]. In these groups, even low-level, chronic THS exposure may exacerbate underlying pathophysiological conditions, thereby intensifying processes such as sustained inflammation, impaired tissue repair, and genomic instability that contribute to carcinogenic progression.

Assessing the carcinogenic potential of environmental exposures remains inherently challenging due to difficulties in quantifying chronic, low-dose exposures, extended latency periods between exposure and disease onset, and the chemical complexity of mixed contaminants[24]. In this review, we introduce an integrated mechanistic framework that incorporates the hallmarks of cancer[25-27] into environmental exposure risk assessment, which offers a system-level strategy for evaluating carcinogenic potential. Conventional toxicology often focuses on discrete endpoints, such as DNA damage or oxidative stress, without accounting for how these biological perturbations interact and converge to promote tumor initiation and progression. In contrast, the hallmark framework encompasses the interconnected cellular, molecular, and microenvironmental programs that collectively drive carcinogenesis and provides a structured scaffold for mapping complex exposure-induced disruptions onto canonical oncogenic pathways. This framework is particularly well suited for emerging or low-dose exposures such as THS, where long-term epidemiological data remains limited but mechanistic evidence is increasingly compelling. By identifying which cancer hallmarks are initiated, reinforced, or reprogrammed by specific toxicants, researchers can more accurately characterize carcinogenic potential, uncover mechanistic points of convergence, and prioritize exposures for regulatory consideration. Ultimately, integrating the hallmarks of cancer into environmental health science establishes a predictive and mechanistically grounded paradigm for cancer risk assessment, especially in contexts where long-term human data are lacking. Applying this framework, we systematically examine how THS chemicals disrupt specific cancer hallmarks and delineate the molecular and cellular mechanisms through which persistent tobacco smoke residues contribute to carcinogenesis (Figure 1).

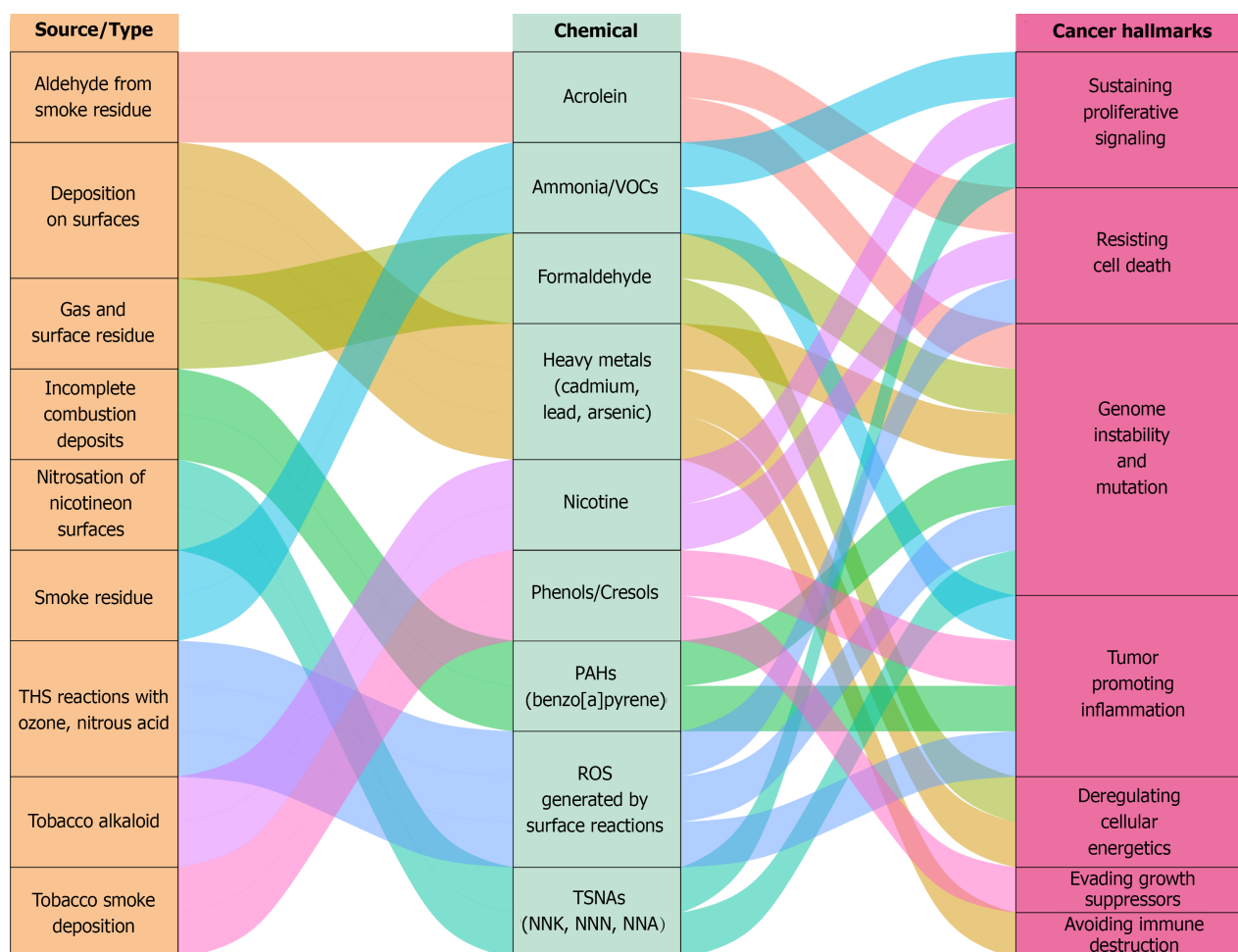


Figure 1 Thirdhand smoke chemicals and the hallmarks of cancer. This schematic illustrates the relationships between major thirdhand smoke (THS) constituents and key cancer hallmarks. Left panel: Sources and categories of THS exposure. Middle panel: Principal chemical components of THS and their transformation processes in indoor environments. Right panel: Mechanistic links between THS constituents and hallmark processes, including sustaining proliferative signaling, resisting cell death, genome instability and mutation, tumor-promoting inflammation, deregulating cellular energetics, evading growth suppressors, and avoiding immune destruction. NNA: 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanal; NNK: 4-(methylnitrosamino)-4-(3-pyridyl)-butanal; NNN: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PAHs: Polycyclic aromatic hydrocarbons; ROS: Reactive oxygen species; TSNAs: Tobacco-specific nitrosamines; VOCs: Volatile organic compounds.

CHEMICAL COMPONENTS AND FORMATION PATHWAYS OF THS

The deposition of tobacco smoke residues onto indoor surfaces, furnishings, and settled dust establishes persistent THS reservoirs largely enriched in nicotine and semi-volatile organic compounds. Once bound to surfaces, these constituents undergo chemical aging, reacting with indoor nitrous acid to form TSNAs such as 4-(methylnitrosamino)-4-(3-pyridyl)-butanal and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and with ozone and other oxidants to produce aldehydes, ketones, and reactive oxygen species (ROS) (Figure 1 left and middle panel). To date, THS has been characterized as a complex mixture containing more than 250 chemicals, many of which possess known toxic or carcinogenic properties[10-14].

Major classes of constituents include: (1) Alkaloids: Nicotine, the most prominent compound, which provides a large reservoir for further reactions with indoor air to form more dangerous substances; (2) TSNAs: Established carcinogens such as 4-(methylnitrosamino)-4-(3-pyridyl)-butanal and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, found in both fresh smoke and aged residue; and 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanal, which is unique to THS and formed *via* nicotine nitrosation with nitrous acid; (3) Volatile organic compounds: Formaldehyde and acetaldehyde, both carcinogenic, acrolein, a potent respiratory toxicant, and benzene and toluene, toxic solvents frequently detected in dust from smokers' homes; (4) PAHs: Persistent compounds such as benzo(a)pyrene and naphthalene that accumulate in carpets and settled dust; (5) Heavy metals: Lead, arsenic, and cadmium, transported *via* smoke and retained in indoor matrices; (6) Radioactive substances: Trace levels of polonium-210, a known carcinogen, that can persist indoors; and (7) Other: Ammonia, phenols, cresols, styrene, pyridine, 3-ethenylpyridine.

Several chemical "markers" have been proposed to quantify and track THS contamination in indoor environments[15, 28]. These include 3-ethenylpyridine, a robust indicator of tobacco smoke residues; myosmine, a tobacco alkaloid elevated in dust from smokers' homes; and tris(2-chloroethyl) phosphate, a toxic flame retardant and suspected carcinogen detected in both tobacco smoke and settled dust from smoking environments.

In summary, the chemical composition of THS demonstrates that it is not a passive or inert residue, but rather a dynamic, reactive mixture that continues to generate harmful secondary toxicants over time. This ongoing transformation confers toxicological risks that differ from, and potentially exceed, those associated with SHS. These insights emphasize the importance of sustained investigation and the development of targeted strategies to mitigate THS-related exposure.

THS CHEMICALS AND HALLMARKS OF CANCER

Exposure to the THS, which includes hazardous substances like nicotine, TSNA, PAHs, aldehydes, and heavy metals, triggers harmful biological processes such as DNA damage, epigenetic shifts, oxidative stress, and chronic inflammation [4,6]. These cellular disruptions are foundational drivers of several canonical hallmarks of cancer (Figure 1 right panel). The key links between THS chemicals and individual hallmarks are summarized below.

Sustaining proliferative signaling

Nicotine drives mitogenic signaling primarily through activation of nicotinic acetylcholine receptors (nAChRs) [29], particularly $\alpha 7$ -nAChR, on epithelial and transformed cells [30–34]. This receptor engagement amplifies canonical growth pathways, including PI3K/Akt and MAPK/ERK [29,32,34], which promote cell cycle progression, protein synthesis, and resistance to growth-limiting cues. Crosstalk with receptor tyrosine kinases such as epidermal growth factor receptor further reinforces these proliferative circuits and sustains responsiveness to both endogenous and exogenous growth signals [35,36].

In parallel, non-nicotine components of tobacco residues, including aldehydes and phenolic compounds, act indirectly by elevating intracellular oxidative stress [37–40]. ROS function as signaling intermediates that activate transcriptional regulators such as nuclear factor kappa B and activator protein-1, which coordinately induce genes involved in proliferation, survival, and inflammatory signaling [41,42]. Chronic oxidative stress additionally promotes epigenetic alterations and signaling plasticity, which locks cells into a persistently activated growth state. Overall, receptor-driven and redox-mediated mechanisms converge to maintain continuous proliferative signaling independent of normal regulatory constraints.

Resisting cell death

Tobacco-associated toxicants confer a survival advantage by broadly suppressing apoptotic responses. Nicotine-mediated signaling through nAChRs activates downstream kinase pathways that shift the balance toward anti-apoptotic programs by enhancing the expression and stability of BCL-2 family proteins while functionally inhibiting pro-apoptotic mediators [43]. This signaling context reduces cellular sensitivity to intrinsic and extrinsic death cues.

Aldehydes such as acrolein further impair apoptosis by directly modifying proteins involved in DNA damage sensing and stress responses by weakening checkpoint activation [44]. Concurrent oxidative stress sustains transcriptional programs that reinforce survival and suppress caspase activation. At the organelle level, mitochondrial integrity is preserved despite damage, which limits cytochrome c release and prevents execution of the intrinsic apoptotic pathway. Disruption of endoplasmic reticulum stress signaling further diminishes programmed cell death under proteotoxic conditions. Overall, these effects allow genetically or metabolically compromised cells to persist, facilitating clonal expansion and increasing the likelihood of malignant progression.

Genome instability and mutation

Tobacco-derived carcinogens, particularly TSNA and PAHs, are potent inducers of DNA damage [16,45]. After metabolic activation, these compounds form bulky DNA adducts that distort the DNA helix and introduce replication errors if left unrepaired. In addition, they induce DNA double-strand breaks, promoting chromosomal rearrangements and structural alterations.

Oxidative stress acts as a major amplifier of this damage. Elevated ROS levels generate oxidative DNA lesions and replication stress, increasing the frequency of strand breaks and mutagenic repair events [46]. Simultaneously, heavy metals such as cadmium, arsenic, and nickel compromise multiple DNA repair pathways, reducing repair fidelity and favoring error-prone mechanisms [47]. Aldehydes add further burden by inducing DNA-protein crosslinks and replication-blocking lesions [44].

The convergence of persistent DNA damage and impaired repair capacity results in a high mutational load and chromosomal instability, which provides a substrate for oncogenic transformation and intratumoral heterogeneity.

Tumor-promoting inflammation

Chronic exposure to THS toxicants sustains a low-grade inflammatory state driven by continuous ROS production and cytokine induction [7,17,48]. Activation of redox-sensitive transcription factors leads to persistent expression of pro-inflammatory mediators, which establishes a tissue environment characterized by ongoing stress and incomplete resolution. This milieu promotes recruitment and functional reprogramming of immune cells. Macrophages and other myeloid populations adopt tumor-supportive phenotypes by secreting growth factors, matrix-remodeling enzymes, and additional cytokines that reinforce local signaling loops. These processes not only enhance epithelial cell survival and proliferation but also increase oxidative damage and genomic stress. Sustained inflammation also reshapes stromal and epigenetic landscapes, promoting fibroblast activation and reinforcing aberrant cell-cell communication. Over time, this chronic inflammatory niche supports malignant transformation, tissue remodeling, and progression toward a tumor-

permissive microenvironment. These processes are consistent with broader observations from experimental and clinical studies of toxin-induced oxidative stress, inflammation, and tissue remodeling across multiple organ systems[49-52].

Deregulating cellular energetics

THS-associated aldehydes and PAHs disrupt mitochondrial function through oxidative and electrophilic damage to mitochondrial DNA, lipids, and respiratory chain components[53,54]. This impairs oxidative phosphorylation and reduces energetic efficiency, while simultaneously increasing ROS production. To compensate, cells undergo metabolic reprogramming characterized by increased reliance on aerobic glycolysis and alternative nutrient utilization. This shift supports biosynthetic demands and redox balance rather than maximal adenosine triphosphate production. Mitochondrial quality control mechanisms, including mitophagy and dynamic remodeling, help maintain a partially functional organelle pool under stress conditions. In parallel, stress-responsive signaling pathways enhance antioxidant defenses and metabolic flexibility, which enables cells to adapt to fluctuating energy and redox states. This metabolic plasticity provides a selective advantage, allowing damaged or premalignant cells to survive and proliferate under conditions that would otherwise be prohibitive.

Evading growth suppressors

Tobacco toxicants disrupt growth-inhibitory pathways primarily through epigenetic reprogramming. Heavy metals alter the activity of DNA methylation and histone modification machinery, leading to stable silencing of tumor suppressor genes involved in cell cycle control, DNA repair, and senescence[47,55-57]. This reduces cellular responsiveness to anti-proliferative signals and checkpoint activation. Nicotine-derived signaling further reinforces this effect by modulating transcriptional and post-translational regulation of tumor suppressors, functionally diminishing their activity[58]. Alterations in non-coding RNA networks add an additional regulatory layer, stabilizing the suppression of growth-inhibitory pathways. These combined mechanisms enable cells to bypass senescence and proliferate despite genomic damage and environmental stress.

Avoiding immune destruction

Tobacco-associated exposures promote immune evasion by altering both tumor cell immunogenicity and the surrounding immune landscape[59]. Epigenetic silencing of genes involved in antigen presentation and interferon signaling reduces recognition by cytotoxic immune cells, weakening immune surveillance. At the same time, nicotine and related compounds modulate immune cell function, favoring immunosuppressive phenotypes[60]. Myeloid cells and regulatory lymphocyte populations expand or become functionally dominant, producing anti-inflammatory cytokines and suppressing effective anti-tumor responses. Induction of immune checkpoint molecules further limits T cell activation and promotes tolerance. These changes are reinforced by alterations in cytokine and chemokine networks, which reshape immune cell recruitment and function within the tissue microenvironment. Together, they establish a permissive niche in which emerging malignant cells can evade immune-mediated elimination and continue to evolve.

IMPLICATIONS FOR RISK ASSESSMENT, REGULATION, AND REMEDIATION

Integrating hallmark-based mechanistic insights with exposure science offers a pathway toward more refined risk assessment and regulatory frameworks. Mechanistic endpoints, such as oxidative DNA damage, activation of inflammatory signaling pathways, and metabolic reprogramming, can serve as sensitive early indicators of biological effect, which complements conventional toxicological measures. At the same time, biomonitoring markers, including cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and indices of oxidative stress, provide quantifiable links between environmental contamination and internal doses. Although precise dose-response relationships remain to be fully established, the incorporation of these exposure metrics enhances the biological plausibility of the mechanisms discussed and highlights the potential cumulative impact of chronic, low-level THS exposure.

Importantly, this integrative framework can also inform the prioritization of high-risk environments, such as multi-unit housing, vehicles, and hospitality settings, for targeted interventions. In addition, it underscores the need for remediation strategies that address not only airborne pollutants but also persistent surface-bound chemical reservoirs that serve as ongoing sources of exposure. From a risk communication standpoint, presenting THS exposure as a cumulative, multi-route biological burden may improve public understanding and support behavioral and policy-level efforts to reduce exposure.

CONCLUDING REMARKS AND PERSPECTIVES

Integrating the cancer hallmarks framework into THS risk assessment enables mechanistic inference grounded in the modular biology of tumorigenesis. The complex mixture of THS constituents, including surface-derived TSNAs, carbonyls formed through heterogeneous oxidation, and ROS-generating PAH derivatives, interfaces with key molecular networks governing genome maintenance, mitogenic signaling, programmed cell death, metabolic regulation, and stromal-immune communication[4,6]. Multi-omics studies reveal that THS exposure induces distributed perturbations across these interconnected systems: (1) Transcriptional activation of stress-response pathways; (2) Adduct-mediated disruption of replication fidelity; (3) Mitochondrial redox imbalance; (4) Cytokine-driven inflammatory amplification;

and (5) Remodeling of extracellular matrix and immune surveillance circuits[61-63]. Aligning these molecular and cellular perturbations with hallmark-specific signaling architectures facilitates reconstruction of plausible mechanistic trajectories linking THS exposure to pro-tumorigenic phenotypes. This mechanistic triangulation provides a biologically principled strategy for predicting cancer risk in the absence of long-latency epidemiological data and supports recognition of THS as a consequential environmental source of carcinogenic exposure.

Future mechanistic investigations on THS should progress beyond descriptive toxicology toward systematic interrogation of the molecular, cellular, and systems-level pathways through which chronic, low-dose exposure promotes carcinogenesis. High-resolution chemical profiling is required to define the dynamic aging, transformation, and recombination of THS constituents under realistic indoor conditions, including the formation of secondary carcinogens such as TSNA and reactive carbonyls[64]. At the biological level, integrated multi-omics strategies, encompassing genomics, epigenomics, transcriptomics, proteomics, and metabolomics, should be deployed to map exposure-response relationships across the cancer hallmarks and to identify early mechanistic biomarkers indicative of carcinogenic potential [65]. Advanced model systems, including organoids, air-liquid interface cultures, and humanized animal models, are essential for capturing tissue-specific dynamics and microenvironmental interactions that are not adequately modeled in traditional cell monocultures. Additionally, future research must quantify how THS interacts with other environmental stressors, such as particulate matter, microbial communities, endogenous metabolic states to produce synergistic or nonlinear carcinogenic effects. Finally, longitudinal human exposure and biomonitoring studies will be critical for validating mechanistic findings, determining biologically effective doses, and informing evidence-based risk assessment. Collectively, these efforts will establish a mechanistically anchored, predictive framework for evaluating cancer risk associated with THS exposure.

CONCLUSION

THS is not an inert residue but an active carcinogen that engages multiple Hallmarks of Cancer. Integrating THS into tobacco control and cancer prevention links mechanistic toxicology with evidence-based policy. Continued research will clarify its role in carcinogenesis and guide interventions for vulnerable populations, while cancer hallmark-based frameworks will strengthen risk assessment for THS and other complex environmental exposures.

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