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Original Paper

Human Health Risk Assessment of Complexly Contaminated Sites: Limitations of Additive Risk Models and the Challenge of Complex Environmental Mixtures

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Abstract

Human health risk assessment (HHRA) has become a central regulatory framework for evaluating contaminated soils and groundwater impacted by industrial activities, petroleum releases, hazardous waste disposal, and urban development. Contemporary cumulative HHRA methodologies commonly estimate carcinogenic and noncarcinogenic risks through additive aggregation of individual contaminant risks across multiple exposure pathways. Although these approaches provide practical and conservative tools for environmental regulation, they also rely on substantial assumptions regarding toxicological additivity, contaminant independence, and dose response behavior. Real-world contaminated sites frequently contain complex mixtures such as hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), chlorinated solvents, metals, and transformation products which interactions remain incompletely understood. This review critically examines the conceptual and scientific limitations associated with additive cumulative HHRA frameworks for complexly contaminated sites. Particular attention is given to unresolved mixture toxicology, toxicokinetic and toxicodynamic interactions, exposure heterogeneity, and the distinction between regulatory screening thresholds and actual biological disease probability. Total petroleum hydrocarbons (TPH) are discussed as a representative example of unresolved environmental mixtures that challenge conventional fraction-based assessment methodologies. The paper argues that current cumulative HHRA models should be interpreted primarily as operational regulatory approximations designed to provide conservative protection rather than comprehensive mechanistic representations of human carcinogenesis under mixed environmental exposure conditions. Emerging advances in systems toxicology, exposomics, physiologically based pharmacokinetic modeling, and high-resolution analytical chemistry may support development of more biologically informed future risk assessment

frameworks.

Keywords

Human health risk assessment, Multi contaminant mixtures, Additive risk models, Cumulative risk, Total petroleum hydrocarbons, Complex mixtures, Systems toxicology

1. Introduction

Human health risk assessment (HHRA) has become a central regulatory framework for evaluating contaminated soils and groundwater impacted by industrial activities, petroleum releases, hazardous waste disposal, and urban development worldwide. The core process of HHRA including hazard identification, dose-response assessment, exposure assessment, and risk characterization provides a systematic, though simplified, approach to managing chemical risks (Greim & Snyder, 2008). Exposure to multiple chemical contaminants may occur through direct soil contact, inhalation of contaminated vapors, groundwater ingestion, vapor intrusion into buildings, and indirect food chain transfer. Consequently, complexly contaminated sites represent a major focus of environmental regulation and risk management (Mahammedi et al., 2020). Unlike the single chemical toxicity studies that form the empirical basis of most regulatory thresholds, real-world contaminated sites almost invariably contain multiple cooccurring contaminants - legacy industrial pollutants, degradation byproducts, and unrelated chemicals from different source terms. Current HHRA frameworks typically address this complexity through additive cumulative risk models, which sum individual contaminant hazard quotients or cancer risks under the assumption of dose additivity (U.S. EPA, 1989; U.S. EPA, 2000). This additive approach is operationally practical and often conservative, but it carries substantial scientific uncertainty: chemical mixtures may exhibit synergistic toxicity exceeding additive predictions, antagonistic interactions that reduce net effects, or complex dose ratio dependencies that invalidate simple summation.

Total petroleum hydrocarbons (TPH) provide a representative example of the limitations of additive and fraction-based methodologies. Unlike many conventional contaminants, petroleum does not exist as a single chemical but as a highly complex and chemically unresolved mixture of aliphatic, aromatic, cyclic, and heterocyclic compounds. The composition of petroleum contamination evolves continuously through weathering, biodegradation, and volatilization, further challenging assessment. Historically, petroleum contaminated sites were assessed using bulk TPH concentrations, but regulators increasingly recognized that bulk TPH lacks toxicological relevance because different fractions exhibit different mobility and health effects. Many agencies adopted fraction-based TPH methodologies that subdivide petroleum into generalized carbon ranges and assign surrogate toxicity criteria (MassDEP, 2002; ASTM, 2021). However, these fraction-based approaches, like broader additive cumulative models, rely on substantial simplifications regarding mixture composition, toxicological equivalence, and biological interactions.

This issue becomes particularly important for aged complexly contaminated sites containing highly

weathered, decades old unresolved complex mixtures (UCMs) that no longer correspond to the fresh petroleum compositions used in original toxicological studies. Moreover, the same additive logic is applied to mixtures of unrelated contaminants (e.g., PAHs + chlorinated solvents + metals), despite limited mechanistic understanding of long term interaction effects (NRC, 2009). The fundamental principles of mixture toxicology, including the distinction between simple and complex mixtures and the categorization of joint actions (similar, dissimilar, and interactive), have been recognized for decades (Feron & Jonker, 2008), yet these concepts are rarely fully integrated into routine site specific risk assessments. This review critically evaluates the scientific foundations and limitations of additive cumulative risk frameworks for complexly contaminated sites, with emphasis on mixture toxicology, exposure heterogeneity, and the distinction between regulatory screening heuristics and true biological risk.

2. The Nature of Multi Contaminant Mixtures at Contaminated Sites

One of the central scientific challenges in assessing complexly contaminated sites arises from the fact that environmental contamination is rarely a single substance. Industrial sites, former gasworks, military facilities, and urban brownfields typically contain dozens or hundreds of individual chemical species belonging to multiple classes: volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), chlorinated solvents, pesticides, metals, and polar transformation products.

The U.S. EPA has formally recognized such mixtures as “complex mixtures” which individual constituents cannot always be completely identified or reproducibly quantified (U.S. EPA, 1986; U.S. EPA, 2000). Petroleum hydrocarbons provide an instructive case: crude oil and refined products contain heterogeneous mixtures of aliphatics, aromatics, and nonhydrocarbon compounds. Environmental weathering further complicates characterization (Peters et al., 2005). Following release, lighter monoaromatic compounds (BTEX) may volatilize rapidly, soluble compounds migrate into groundwater, and biodegradable linear alkanes are preferentially removed by soil microbes.

However, over decades, degradation slows drastically, leaving behind a highly recalcitrant residual mass, an Unresolved Complex Mixture (UCM), dominated by heavy, high molecular weight branched and cyclic aliphatics, PAHs, and newly formed oxygenated polar metabolites. (Mukherjee et al., 2022) recently reviewed the formation and enhanced toxicity of such transformation products in environmental mixtures. Thus, a decades old spill’s composition and toxicity profile are fundamentally different from the original “fresh” product. This dynamic behavior creates a major limitation for conventional additive risk models, because toxicity assumptions are frequently based on relatively fresh petroleum products or single surrogate chemicals, while the actual mixture has evolved into something toxicologically distinct.

In addition to the dynamic changes that individual mixtures undergo, a further conceptual challenge is the classification of mixtures themselves. Regulatory toxicology distinguishes between “simple mixtures” comprising a small, known number of chemicals and “complex mixtures,” which contain

tens to thousands of components that identities and concentrations may be only partially characterized (Feron & Jonker, 2008). Most aged contaminated sites fall squarely into the latter category. Furthermore, the type of joint toxic action exhibited by a mixture can vary: components may act by dose addition (similar action), response addition (dissimilar action), or interact toxicokinetically or toxicodynamically to produce synergistic or antagonistic effects. Standard cumulative risk assessments, however, nearly always default to dose addition, even when the underlying joint action is unknown, on the presumption that this provides a conservative estimate of risk. This conceptual framework highlights the gap between regulatory convenience and the real behavior of environmental mixtures.

Similar issues arise with nonpetroleum mixtures: co-disposal of industrial solvents and metals can lead to novel complexation products; microbial transformation of chlorinated ethenes produces vinyl chloride; and weathering of pesticide mixtures yields unknown metabolites. In all cases, the assumption that cumulative risk can be adequately represented by summing individual surrogate based risks is scientifically tenuous.

3. Development of Cumulative Additive Risk Frameworks

Recognition of the limitations associated with single contaminant thresholds led to the development of cumulative risk methodologies. For petroleum, this took the form of fraction-based assessment, largely pioneered by the TPH Criteria Working Group (TPHCWG) (Edwards et al., 1997). A representative example is the Texas Commission on Environmental Quality's TRRP27 guidance (TCEQ, 2010), which establishes protective concentration levels for TPH mixtures by assigning surrogate toxicity factors to 13 aliphatic/aromatic boiling point ranges and calculating a mixture hazard index via inverse weighted averaging. Fractionbased methodologies separate hydrocarbons into aliphatic and aromatic fractions across carbon ranges (e.g., C5-C8 aliphatics, C9-C18 aliphatics). Each fraction is assigned a surrogate toxicity value, typically a well characterized indicator compound (e.g., n-hexane for light aliphatics, benzo[a]pyrene for heavy aromatics).

For general complexly contaminated sites, cumulative risk is calculated using the hazard index (HI) for noncarcinogens:

$HI = \Sigma(HQ_i)$ where $HQ_i = \text{exposure}_i / \text{reference dose}_i$

and the cumulative cancer risk:

$CR_{total} = \Sigma(R_i)$ where $R_i = \text{exposure}_i \times \text{slope factor}_i$

These equations embody the assumption of dose additivity, which, as outlined in the classic mixture toxicology framework, is one of several possible joint action types (Feron & Jonker, 2008). In the broader context of HHRA, the toxicological evaluation process itself, from acute to chronic studies, relies on the identification of NOAELs for single chemicals, which are then extrapolated to acceptable human exposures using default uncertainty factors (Greim & Snyder, 2008). This single chemical paradigm is fundamentally challenged when multiple agents act on the same target organ or system, even at individually subthreshold doses.

Although these frameworks improved consistency, they rely on several strong assumptions: (1) dose additivity holds across all mixture components; (2) no toxicokinetic or toxicodynamic interactions occur; (3) the surrogate chemical adequately represents the entire fraction or class; and (4) exposure pathways are independent and additive. Each of these assumptions can be violated in real-world complexly contaminated sites.

For example, individual compounds within a given carbon fraction differ considerably in toxicity, bioavailability, and carcinogenic potential (Pinedo et al., 2014). Using a single surrogate thus produces generalized approximations rather than direct measurements of actual mixture toxicity. Moreover, unidentified constituents, such as oxygenated metabolites in weathered petroleum, may contribute to toxicity without being incorporated into the risk calculation.

4. Toxicological Uncertainty and Mixture Interactions: A Quantitative Paradox

One of the most significant scientific limitations of current cumulative HHRA is the limited understanding of chronic mixture toxicology. Beyond the general concerns, additive models can produce counterintuitive and potentially misleading risk rankings, as shown below.

4.1 Illustrative Scenario: Two Contaminants Below Limits vs. One Above

Consider a realistic scenario involving two common polycyclic aromatic hydrocarbons (PAHs) at a contaminated industrial site. Table 1 summarizes the concentrations, regulatory limits, and hazard quotients.

Table 1. Illustrative Cumulative Risk Paradox for two PAHs below Individual Limits vs. one PAH above its Limit

Parameter	Scenario A (Mixture)	Scenario B (Single)
Contaminant 1	Benzo[a]pyrene	Benzo[a]pyrene
Concentration (mg/kg)	0.5	0.6
Regulatory limit (mg/kg)	0.55	0.55
Cancer Risk (CR_1)	9.15E-07	1.10E-06
Contaminant 2	Benzo[b]fluoranthene	-
Concentration (mg/kg)	5.0	-
Regulatory limit (mg/kg)	5.5	-
Cancer Risk (CR2)	9.15E-07	-
Cumulative Cancer Risk	1.83E-06	1.10E-06
Exceeds CR threshold of 1E-06?	Yes	Yes
Need Reaction under Regulations?	No	Yes

Regulatory limits based on Soil environmental quality - Risk control standard for soil contamination of

development land (MEE, GB36600-2018) Screening Levels (residential soil, 1E-06 cancer risk): benzo[a]pyrene = 0.55 mg/kg; benzo[b]fluoranthene = 5.5 mg/kg. The paradox holds for any two substances with comparable hazard indices.

Interpretation: Under standard additive HHRA logic, Scenario A - where neither contaminant individually exceeds its regulatory limit - yields a cumulative CR of 1.83E-06, exceeding the threshold of 1E-06, however requires no reaction under current regulations. Scenario B, a single contaminant just exceeds its limit, at CR of 1.10E-6, would be classified as requiring remediation.

This paradox exposes a fundamental limitation: it is difficult to determine which scenario is more harmful to human health. Additive models imply that two “safe” concentrations can combine to become “unsafe,” while a single “unsafe” concentration may produce a lower cumulative CR. Regulators relying solely on individual contaminant exceedances would systematically underestimate risk at sites with diverse, low-level mixture contamination, exactly the conditions that characterize most aged industrial sites, including weathered petroleum spills with complex UCMs and sites with multiple unrelated contaminants.

4.2 Mechanistic Limitations of Additive Assumptions

Beyond the quantitative paradox, chemical mixtures, including petroleum, PAHs, chlorinated solvents, and metals, may interact biologically through multiple mechanisms that additive models cannot capture:

Metabolic competition: Aliphatic hydrocarbons may competitively inhibit cytochrome P450 enzymes required for detoxification of more toxic PAHs, leading to higher effective doses (ATSDR, 2004; Feron et al., 1998).

Bioavailability alteration: Certain hydrocarbons act as solvents, increasing the intestinal absorption of co-administered contaminants.

Oxidative stress synergy: Multiple contaminants may induce oxidative stress through different pathways, potentially producing more than additive cellular damage (Cedergreen, 2014).

Receptor crosstalk: Mixtures may simultaneously activate the aryl hydrocarbon receptor (AhR) and other nuclear receptors, resulting in complex gene expression responses not predictable from individual compounds.

These interaction mechanisms have been comprehensively reviewed in the context of mixed environmental contaminants (Mukherjee et al., 2022). Importantly, such interactions can be toxicokinetic (e.g., altered absorption, distribution, metabolism, or excretion) or toxicodynamic (e.g., effects at the same or different target sites), and their net result may be greaterthanadditive or lessthanadditive (Feron & Jonker, 2008). For example, enzyme induction by one mixture component can accelerate the bioactivation of a co-occurring procarcinogen, a scenario that cannot be captured by simply summing individual hazard quotients. The real-world implication is that the CR of 1.83E-06 in Scenario A could be an underestimate if synergistic metabolic activation occurs, or an overestimate if antagonistic receptor binding predominates. Default additive assumptions inevitably obscure these

possibilities, leaving risk managers with an illusion of precision that is not supported by mechanistic toxicology.

5. Exposure Pathway Complexity and Environmental Heterogeneity

Exposure assessment for complexly contaminated sites involves substantial environmental and behavioral variability. Soil ingestion, dermal contact, inhalation of vapors, and vapor intrusion may all contribute to cumulative exposure depending on site conditions (Fryer et al., 2006). Different contaminant classes dominate different pathways: volatile hydrocarbons (e.g., benzene) are associated primarily with inhalation, while heavy PAHs and metals contribute more significantly to dermal and ingestion pathways.

The modeling of these pathways, particularly vapor intrusion using the Johnson and Ettinger approach (Johnson & Ettinger, 1991), relies on subsurface assumptions where small parameter changes can drastically alter predicted risks When multiple contaminants with different physicochemical properties are present, the additive assumption becomes even more tenuous because exposure pathways may not be independent.

Furthermore, the bioavailability of many contaminants decreases over time due to aging and sorption processes. Laboratory extraction methods using aggressive solvents may overestimate the fraction actually available for human absorption. This issue is highly relevant for decade sold weathered soils where tightly bound heavy hydrocarbons or metals may exhibit reduced biological accessibility despite high analytical concentrations. Additive models that assume 100% bioavailability from measured concentrations thus may overestimate risk for aged contaminants while potentially underestimating risk for more bioavailable freshly released compounds.

Furthermore, the joint action of mixture components may change with the exposure matrix. For instance, sorption of hydrophobic contaminants to soil organic matter reduces their bioavailability, but cooccurring surfactants or dissolved organic carbon can mobilise these compounds, increasing both exposure and the potential for interactive effects at target tissues. The simple additive framework, which treats each chemical's exposure pathway independently, cannot accommodate such matrix dependent interactions.

6. Emerging Directions in Multi Contaminant Risk Assessment

Advances in analytical chemistry and computational toxicology offer opportunities to overcome the limitations of additive cumulative HHRA.

High-resolution mass spectrometry (HRMS) and comprehensive two-dimensional gas chromatography now allow detailed characterization of unresolved complex mixtures and their polar transformation products (e.g., oxygenated PAHs, chlorinated transformation products); see also (Mukherjee et al., 2022) for a discussion of analytical and computational approaches to complex mixtures. These technologies bypass the limitations of broad carbon range groupings by enabling identification of specific,

toxicologically active metabolites.

Systems toxicology and exposomics provide a more realistic framework for lifetime environmental exposures (Vineis & Wild, 2014). Rather than summing individual risks, systems approaches model biological network responses to mixtures, potentially identifying synergistic interaction nodes.

Physiologically based pharmacokinetic (PBPK) models can be extended to mixtures, physically tracking how co-exposure alters metabolic absorption, distribution, and elimination (Haddad et al., 2001). With sufficient data, PBPK models can predict internal doses of multiple contaminants and their metabolites, providing a mechanistic basis for cumulative risk estimation.

Machine learning and high through put screening are increasingly used to predict mixture toxicity from chemical structures and in vitro assays, reducing reliance on default additivity. However, real-world contamination, whether from petroleum or other industrial sources, continues to exceed the complexity currently achievable in standard experimental toxicology. Integration of these emerging tools into regulatory frameworks will require validation, standardization, and acceptance by risk management agencies.

In addition to these analytical and computational advances, the evolution of regulatory thinking itself points toward a more mechanistic integration of mixture science. The traditional “whole mixture” or “component based” approaches to safety evaluation (Feron & Jonker, 2008) are increasingly being supplemented by frameworks that require explicit consideration of mode of action and joint action. For example, the Hazard Index/Weight of Evidence (HI/WOE) method adjusts the HI by an uncertainty factor for interactions, based on a systematic evaluation of the likelihood of synergism or antagonism among mixture constituents. While still reliant on expert judgement and limited data, such approaches represent a conceptual advance over unqualified additivity.

Moreover, the incorporation of time dependent and dose dependent toxicokinetic data into PBPK models can elucidate the conditions under which metabolic interactions become significant, thereby refining the range of exposures over which additivity can be assumed. The ultimate goal is a risk assessment paradigm that is “biologically based” rather than “default driven” (Greim & Snyder, 2008), one that can distinguish between exposure scenarios where additive assumptions are adequately protective and those where they may lead to significant underestimation or overestimation of risk.

7. Conclusions

Complexly contaminated sites exemplify a broader challenge in environmental health science: real-world contaminant mixtures do not behave as simple sums of their parts. Current cumulative HHRA frameworks, including petroleum fraction-based methodologies and general additive hazard index models, have historically provided highly practical and operationally necessary tools for site management. However, as demonstrated throughout this review, they rely on profound scientific simplifications regarding mixture composition, toxicological equivalence, and most critically, the absence of biological interactions among cooccurring contaminants.

The conceptual framework of mixture toxicology, which distinguishes between simple and complex mixtures and among dissimilar, similar, and interactive joint actions (Feron & Jonker, 2008), highlights the inherent limitations of default additive approaches. The quantitative paradox presented in Section 4, combined with the lack of mechanistic validation for dose additivity across most environmental mixtures, indicates that current cumulative HHRA models should be interpreted primarily as regulatory screening heuristics designed to ensure a conservative margin of safety, rather than exact mechanistic predictors of human disease.

The distinction is not merely academic: overreliance on additive risk estimates can lead to misallocation of remediation resources (e.g., cleaning up a single marginally exceeding contaminant while ignoring a mixture of several below threshold contaminants that sum to a higher cumulative risk). Conversely, conservative additive assumptions may overestimate risk at sites where antagonistic interactions dominate, leading to unnecessary remediation.

Continued advances in higher-solution analytical chemistry, systems toxicology, exposomics, and PBPK modelling offer promising pathways to bridge the gap between regulatory approximations and the reality of complex environmental exposures. Future HHRA frameworks should move toward mechanistically informed cumulative risk assessment that incorporates, where possible, mixture interaction data, bioavailability corrections, and pathway-based biological modeling. Until then, regulators and risk assessors must explicitly acknowledge the uncertainties embedded in additive models and avoid conflating regulatory convenience with biological truth.

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