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Original Article

Chemical Safety and Toxicology: A Comprehensive Review of Current Protocols and Principles

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Abstract

This comprehensive review examines the latest advances in chemical safety protocols and toxicological principles, synthesizing current research findings from 2020-2025. The review encompasses emerging non-animal testing methodologies (NAMs), and regulatory compliance requirements. Key findings reveal a paradigm shift toward integrated tiered assessment approaches that combine in silico, in vitro, and targeted in vivo methods, alongside structured control banding systems for workplace exposure management. The analysis demonstrates that contemporary chemical safety practice emphasizes source-control engineering, administrative procedures, and competency-based training, while toxicological assessment increasingly adopts adverse outcome pathways (AOPs) and read-across strategies to reduce animal testing. This review provides researchers, safety professionals, and regulatory bodies with an evidence-based synthesis of current best practices and emerging trends in chemical safety and toxicology.

Keywords: *Chemical safety, toxicology, NAMs*

Introduction

Chemical safety and toxicology represent critical disciplines at the intersection of public health, environmental protection, and industrial operations. The past five years (2020-2025) have witnessed significant evolution in both the scientific understanding of chemical hazards and the methodological approaches used to assess and manage risks [1, 6]. Traditional toxicological paradigms, which relied heavily on animal testing and conservative safety factors, are being complemented—and in some cases replaced by innovative new approach methodologies (NAMs) that integrate computational modelling, in vitro assays, and mechanistic understanding of adverse outcome pathways [6, 7].

The regulatory landscape has evolved in parallel, with frameworks such as REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) in the European Union and TSCA (Toxic Substances Control Act) in the United States increasingly accepting integrated testing strategies and grouping approaches [10]. These changes reflect both scientific advancement and societal pressure to reduce animal testing while maintaining or improving the quality of safety assessments.

Scope and Objectives

This review synthesizes current knowledge across two key domains:

1. Current chemical safety protocols and management systems employed in research and industrial settings
2. Modern toxicological principles and assessment methods, with emphasis on NAMs and tiered testing strategies

The Paradigm Shift in Chemical Safety

Contemporary chemical safety practice represents a fundamental shift from reactive hazard management to proactive, evidence-based risk assessment. This transformation is characterized by:

- Tiered risk management that matches the intensity of assessment to the level of concern and data availability [6]
- Control banding approaches that provide practical guidance even when quantitative exposure limits are unavailable [1]

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- Integration of NAMs to reduce reliance on animal testing while maintaining regulatory confidence [7, 8]
- Material-specific guidance for emerging substances such as nanomaterials and metal-organic frameworks [1, 3, 4]

The convergence of these trends reflects a maturing field that balances scientific rigor with practical implementation constraints.

Current Chemical Safety Protocols and Management Systems

Chemical safety programs in research and industry rely on structured risk-management tools that combine hazard banding, exposure evaluation, and prescribed control measures. Several sector-specific implementations illustrate these approaches, addressing diverse challenges from nanomaterial handling to process scale-up.

Control Banding for Nanomaterials

The **Nano Safe III** system exemplifies modern control banding methodology, implementing a three-step process for nanomaterial safety management [2]:

1. Hazard-band assignment based on material properties and toxicological data
2. Work exposure modelling considering handling procedures, quantities, and engineering controls
3. Control prescription specifying technical, organizational, and personal protective equipment (PPE) measures

This approach has been validated in laboratory and small facility settings, demonstrating that user-friendly safety management systems can effectively protect workers even when quantitative exposure data are limited [2]. The system uses hazard bands combined with work-exposure estimates and recommended occupational exposure limits (rOELs), applying additional safety factors to set workplace exposure tiers [1].

Laboratory Risk Implementation Framework

Academic and research laboratories face unique challenges due to the diversity of chemicals handled and the variability of procedures. A phased implementation framework has been developed and tested, comprising three sequential steps [2]:

- **Identification phase:** Cataloguing all chemicals, reviewing safety data sheets (SDSs), and documenting handling procedures
- **Evaluation phase:** Assessing exposure potential, hazard severity, and adequacy of existing controls
- **Classification phase:** Prioritizing risks and assigning control measures

Case study data from academic laboratory implementation revealed measurable risk distributions across domains: health hazards (9.3%), environmental hazards (35.2%), and safety hazards (20.4%) [2]. This quantitative approach enables evidence-based prioritization of safety interventions.

Material-Specific Guidance

Emerging materials such as carbon nanotubes (CNTs), graphene, and metal-organic frameworks (MOFs) present unique challenges due to limited toxicological data and novel exposure scenarios.

Engineered Nanomaterials

For CNTs and graphene products, safety guidance emphasizes [1, 3]:

- **Installation controls:** Enclosed handling systems and local exhaust ventilation (LEV) for processes generating aerosols
- **Maintenance protocols:** Regular inspection and validation of engineering controls
- **PPE selection:** Material-specific respiratory protection and protective clothing based on worst-case exposure scenarios
- **Personnel training:** Competency-based programs addressing nano-specific hazards rather than generic chemical safety

This tailored approach recognizes that standard SDSs often lack nano-specific information, necessitating precautionary measures informed by emerging toxicological evidence [3].

Process Scale-Up Reviews

The scale-up of laboratory syntheses to pilot or production scale introduces new exposure scenarios and hazard potentials. A documented case study of metal-organic framework (MOF) synthesis demonstrates best practices [4]:

1. Step-by-step documentation of all laboratory procedures
2. Exposure identification at each process stage (weighing, mixing, heating, isolation, drying)
3. Control verification ensuring that existing laboratory safety protocols remain adequate at increased scale
4. Hazard communication to all personnel involved in scale-up operations

This systematic approach prevents the common pitfall of assuming that laboratory-scale controls will automatically translate to larger operations.

Industrial Action Planning

In industrial settings, comprehensive chemical management tools enable systematic hazard mapping and preventive action prioritization. The SEIRICH system, applied in petroleum production facilities, illustrates this approach [5]:

- Chemical inventory mapping across all units (production, laboratory, storage)
- Hazard level assessment using standardized classification criteria
- Prioritized action planning focusing resources on highest-risk chemicals and inadequate storage conditions
- Unit-specific interventions tailored to the operational context of each facility area

Case study implementation in an Algerian oil and gas company demonstrated the system's effectiveness in identifying disposal deficiencies and prioritizing preventive actions for storage and laboratory units [5].

Modern Toxicological Principles and Assessment Methods

Contemporary toxicology is undergoing a fundamental transformation, shifting from exclusive reliance on animal testing to integrated approaches that combine computational predictions, in vitro assays, and mechanistic

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understanding. This section examines the scientific foundations and practical implementations of these new approach methodologies (NAMs).

Tiered NAM Frameworks

The integration of NAMs into regulatory toxicology requires structured frameworks that maintain scientific rigor while reducing animal use. A comprehensive tiered approach has been developed to meet REACH-style decision needs [6]:

In Silico Assessment

- Structure-activity relationship (SAR) analysis
- Quantitative structure-activity relationship (QSAR) modelling
- Read-across from structurally similar chemicals
- Threshold of toxicological concern (TTC) evaluation

Tier 2: In Vitro Testing

- High-throughput screening (HTS) assays
- Organ-on-chip systems
- 3D tissue models
- Mechanistic pathway interrogation

Tier 3: Targeted In Vivo Studies

- Focused studies to address specific data gaps
- Abbreviated protocols guided by lower-tier results
- Emphasis on mechanistic endpoints rather than apical toxicity

This sequential approach produces classification categories, safe doses, and risk assessments while allowing conservative outputs with substantially lower resource use than traditional testing batteries [6]. The framework explicitly addresses regulatory needs for hazard classification, dose-response characterization, and uncertainty quantification.

Non-Animal Repeated-Dose Strategies

Systemic toxicity assessment has traditionally relied on chronic animal bioassays (e.g., 90-day or 2-year studies). Emerging strategies exploit mechanistic understanding to predict repeated-dose effects without routine long-term studies [7]:

Threshold of Toxicological Concern (TTC)

The TTC approach establishes exposure thresholds below which adverse effects are unlikely, based on empirical databases of known toxicants. This method is particularly valuable for substances with limited data, enabling risk-based prioritization without immediate testing [7].

Adverse Outcome Pathways (AOPs)

AOPs provide structured frameworks linking molecular initiating events to adverse outcomes through key events at cellular, tissue, and organ levels. AOP-informed assessment enables [7, 8]:

- Mechanistic hypothesis generation about potential toxicity
- Targeted assay selection to interrogate specific pathways
- Human relevance determination by comparing pathway conservation across species
- Evidence integration from diverse data sources into coherent assessments

Read-Across and Chemical Grouping

Read-across infers properties of a target substance from data on structurally or mechanistically similar source substances. Ten principles for defensible grouping have been articulated [10]

1. **Transparency of purpose:** Clearly state the regulatory endpoint and decision context
2. **Adequate justification:** Provide scientific rationale for grouping hypothesis
3. **Structural similarity:** Document shared molecular features
4. **Toxicological congruence:** Demonstrate similar toxicity profiles or mechanisms
5. **Exposure relevance:** Consider bioavailability and metabolic activation
6. **Data adequacy:** Ensure source data meet quality standards
7. **Uncertainty characterization:** Explicitly address limitations and gaps
8. **Consistency evaluation:** Verify that all group members behave similarly
9. **Documentation completeness:** Provide reproducible methodology
10. **Regulatory acceptance:** Align with jurisdiction-specific guidance

These principles enable expedited risk prioritization while maintaining scientific credibility under both EU-REACH and US-TSCA paradigms [10].

Carcinogenicity Assessment

Cancer hazard assessment represents a particularly challenging domain due to the complexity of carcinogenic mechanisms and the high stakes of classification decisions. Recent expert workshops have recommended integrated decision frameworks [8]:

Problem Formulation

Structured problem formulation defines:

- The specific carcinogenicity question (hazard identification vs. dose-response)
- Relevant exposure scenarios and populations
- Available data sources and their quality
- Decision criteria and acceptable uncertainty levels

Mode-of-Action (MOA) Analysis

MOA analysis determines whether carcinogenicity proceeds through:

- **Genotoxic mechanisms:** Direct DNA damage, chromosomal aberrations
- **Non-genotoxic mechanisms:** Receptor-mediated effects, chronic inflammation, hormonal disruption
- **Mixed mechanisms:** Multiple contributing pathways
- This distinction profoundly affects dose-response modelling and risk characterization, with genotoxic carcinogens typically assessed using linear low-dose extrapolation and non-genotoxic carcinogens often exhibiting thresholds [8].

Integration of NAMs

Decision matrices have been proposed to incorporate NAMs into carcinogenicity assessment [8]:

- **In silico alerts:** Structural features associated with carcinogenicity

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- **In vitro genotoxicity:** Battery of mutagenicity and clastogenicity assays
- **Mechanistic assays:** Tests interrogating specific carcinogenic pathways
- **Short-term in vivo studies:** Targeted investigations of key events

The AOP framework is particularly valuable for organizing evidence and supporting human relevance determinations, enabling assessors to weight mechanistic data appropriately [8].

Dose Selection and Its Impact

An often-underappreciated aspect of toxicity testing is the selection of dose levels, which profoundly influences hazard characterization and subsequent risk management [9]. Key considerations include:

- **Maximum tolerated dose (MTD):** Traditionally used as the high dose in chronic studies, but may induce toxicity through overload mechanisms irrelevant to environmental exposures
- **Pharmacokinetic saturation:** Doses exceeding metabolic capacity may produce artifacts
- **Relevance to human exposure:** Testing at doses orders of magnitude above realistic exposures may detect effects of questionable relevance

Transparent dose-selection rationale is essential for defensible hazard assessment, particularly when extrapolating from high-dose animal studies to low-dose human exposures [9].

Conclusions

This comprehensive review of chemical safety and toxicology has synthesized current knowledge across safety protocols, toxicological assessment methods, risk frameworks, laboratory practices, and regulatory systems, with emphasis on developments from 2020-2025. Several overarching conclusions emerge:

Key Findings

Paradigm Shift Toward Integrated

Assessment: Chemical safety practice is transitioning from siloed approaches (separate hazard identification, exposure assessment, and risk management) to integrated frameworks that combine mechanistic understanding, tiered testing strategies, and practical control measures. This shift is evident in tiered NAM frameworks [6], control banding systems [1, 2], and material-specific guidance [3, 4].

NAM Integration Is Accelerating: New approach methodologies are moving from research concepts to regulatory practice, with defined approaches now accepted for several endpoints and frameworks developed for REACH-compatible assessment [6]. While challenges remain for complex endpoints such as chronic toxicity and carcinogenicity [7, 8], the trajectory toward reduced animal testing is clear.

Mechanistic Understanding Drives Innovation: Adverse outcome pathway frameworks [7, 8] provide structured methods for organizing toxicological evidence and assessing human relevance. This mechanistic foundation enables more confident extrapolation from in vitro and computational models to human health outcomes, supporting both NAM development and read-across approaches [10].

Emerging Materials Require Adaptive

Approaches: Nanomaterials [1, 2, 3] and other emerging substances demonstrate the need for adaptive risk management frameworks that balance precaution with innovation. Control banding, recommended exposure limits, and iterative refinement as data accumulate provide templates for managing uncertainty.

Dose Selection Matters: The choice of dose levels in toxicity testing profoundly influences hazard characterization and risk management decisions [9]. Transparent dose-selection rationale and mechanistic investigation of observed effects are essential for defensible risk assessment.

Implications for Practice

These findings have concrete implications for various stakeholders:

For Researchers:

- Prioritize mechanistic investigation and AOP development to support NAM validation and human relevance assessment
- Develop and validate in vitro models using human-derived cells and tissues
- Contribute to computational toxicology through QSAR development and machine learning applications
- Publish negative results and comparative studies (NAM vs. traditional methods) to build the evidence base

For Safety Professionals:

- Implement tiered risk assessment frameworks matched to organizational resources and decision needs
- Utilize available tools (control banding, risk matrices) to systematize hazard evaluation and control selection
- Emphasize engineering controls and administrative measures over reliance on PPE
- Develop competency-based training programs that go beyond compliance to foster safety culture

For Industrial Practitioners:

- Engage early with regulatory agencies regarding NAM use and grouping strategies
- Document dose-selection rationale and mode-of-action analysis to support defensible risk assessments
- Invest in green chemistry and safer-by-design approaches to reduce downstream hazard management burden
- Share lessons learned and best practices across the industry to accelerate collective improvement

For Regulators:

- Provide clear guidance on NAM acceptance criteria and defined approaches for specific endpoints
- Develop case studies demonstrating successful NAM-based regulatory decisions to build confidence
- Engage in international harmonization efforts to reduce redundant testing and compliance fragmentation
- Balance encouragement of innovation with maintenance of health protection standards

For Educators:

- Integrate NAMs, AOPs, and computational toxicology into curricula alongside traditional methods
- Emphasize mechanistic thinking and weight-of-evidence approaches over rote memorization
- Provide hands-on experience with risk assessment tools and frameworks
- Foster interdisciplinary perspectives combining toxicology, chemistry, engineering, and data science

Future Directions

Several priorities emerge for advancing chemical safety and toxicology:

Endpoint-Specific NAM Development: Sustained effort is needed to develop and validate NAMs for chronic toxicity, reproductive toxicity, and carcinogenicity endpoints that currently lack well-established alternatives to animal testing [7, 8].

Quantitative AOP Models: Moving beyond qualitative pathway descriptions to quantitative dose-response models along AOPs will enable more confident prediction of apical outcomes from key event measurements [7].

Exposure Science Integration: Risk assessment quality is limited by exposure assessment quality. Improved exposure modelling, biomonitoring, and sensor technologies are needed to characterize real-world exposures accurately.

Mixture Assessment: Most human exposures involve chemical mixtures, yet risk assessment typically addresses single substances. Frameworks for mixture assessment that are both scientifically sound and practically implementable require development [6].

Sensitive Population Protection: Standard toxicity testing uses healthy adult organisms, potentially missing effects in sensitive subpopulations. Developing models and approaches that explicitly address variability in susceptibility is a priority.

Computational Toxicology Advancement: Machine learning, artificial intelligence, and big data analytics offer substantial promise for toxicity prediction and mechanism elucidation. Continued investment in these approaches, with attention to model interpretability and validation, is warranted [6].

Green Chemistry Integration: The most effective hazard management is hazard elimination through safer molecular design. Deeper integration of toxicological principles into chemical innovation processes can prevent problems rather than managing them after the fact.

Global Capacity Building: Chemical safety capacity varies dramatically across countries and regions. International collaboration, knowledge sharing, and capacity building are essential for global health protection.

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Conflicts of interest

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