The concept of risk assessment evaluations in the 21st Century: The speedy and slippery progress of science and its political stand

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The field of toxicological risk assessment (RA) is facing significant challenges as technological progress accelerates and societal needs continue to evolve. Traditional RA methods, which focus primarily on single stressors and high-dose evaluations, are increasingly inadequate in addressing the complexity of real-world exposures. Concepts such as the real-life risk simulation (RLRS) highlight forward-thinking frameworks that aim to bridge these gaps by integrating multiple chemical exposures, cumulative effects, and real-world scenarios[1]. However, the advancement of science and technology in this domain is not without its obstacles. Political influences, industry pressures, and the rapid pace of innovation contribute to the 'slippery' trajectory that complicates the adoption of comprehensive risk assessment approaches. Here, we reflect on these dynamics and the need for an updated RA framework that accurately addresses real-life exposures.

Speedy progress of science

In the 21st century, rapid advancements in fields such as biotechnology, artificial intelligence (AI), and genetic engineering have outpaced society's ability to fully evaluate their potential risks[2,3]. Often, innovations are introduced into the market, driven by short-term profits without adequate long-term risk assessments. This accelerated pace leaves little time for comprehensive evaluation, resulting in the release of technologies that are not fully vetted for their long-term impacts.

A significant consequence of this rapid development is the potential for unforeseen consequences, which may only become apparent after these technologies are widely adopted. Historical patterns show that societal unrest and regulatory backlash often follow technological revolutions when ethical and safety standards cannot keep up with innovation[4,5]. The disparity between fast-paced technological progress and the slower implementation of regulatory frameworks underscores the critical need for sustainable innovation, one that prioritizes real societal needs and minimizes risks through careful, preemptive evaluations.

Risk assessment frameworks

Current RA frameworks focus largely on evaluating single stressors (chemical, physical, or biological) at high doses to establish safety thresholds[6,7]. However, human exposure is far more complex. People are exposed to mixtures of chemicals and stressors over extended periods, rather than isolated, high-dose exposures.

Traditional RA methods overlook the cumulative and synergistic effects of these chemical mixtures. Studies fail to account for non-linear dose responses and the complex interactions between stressors that can amplify toxicity. For example, chemicals that are individually non-toxic at low doses can exhibit harmful effects when combined, known as synergistic toxicity. Additionally, the current regulatory standards are often influenced by industry sectors like pharmaceuticals, agrochemicals, and fossil fuels. The involvement of these industries in setting safety thresholds sometimes leads to regulatory frameworks that may downplay the risks of chemical exposures, particularly when industry-funded research contradicts independent studies.

This gap in RA calls for a paradigm shift, one that considers the cumulative and long-term effects of multiple, low-dose exposures to various chemicals – conditions that are more representative of real-world scenarios. Approaches like RLRS are examples of frameworks that can better reflect these complex interactions and improve the accuracy of risk assessments.

The RLRS paradigm story

Addressing the increasing complexity of toxicological challenges in the 21st century requires comprehensive approaches like the RLRS. Unlike traditional toxicological methods that focus on single-stressor, high-dose evaluations, RLRS offers a holistic approach that accounts for multiple exposures, cumulative effects, and the interplay of real-world environmental and lifestyle factors[8]. This paradigm provides a more accurate representation of human exposure scenarios, reflecting the low-dose, long-term interactions individuals face daily.

RLRS was initially developed to overcome the limitations of traditional risk assessment by simulating realistic, cumulative exposures across multiple chemicals. Advances in analytical sensitivity, allowing the detection of lower concentrations of compounds in biological samples, support RLRS by capturing long-term exposure patterns, such as those seen in hair-sample analyses. Observational data linking the rise in autoimmune and chronic diseases to continuous, low-level exposure to diverse chemicals further underscores the importance of RLRS. Experimental studies starting in 2015 have tested the effects of such combined exposures over extended periods, establishing RLRS as a transformative framework for assessing health risks in toxicology [9].

Methodological innovations in RLRS

The RLRS framework incorporates refined methodologies to assess cumulative exposures effectively, across various biological systems. Methodologies within RLRS, such as the enhanced hazard quotient (HQ) and hazard index (HI) models, include source-related HQ and adversity-specific hazard index (HIA), which allow for a nuanced understanding of mixture effects by accounting for aggregate exposures and specific adverse effects[10]. These advancements underscore the need for risk models that integrate both chemical and non-chemical stressors, providing a more holistic view of health risks under realistic conditions. By aligning toxicological evaluations with real-world complexities, RLRS facilitates regulatory frameworks that are better equipped to protect public health from the nuanced threats posed by contemporary environmental and lifestyle factors[11].

Hair as a biomarker in RLRS

Hair serves as a critical biomarker in the RLRS framework, allowing for long-term monitoring of various environmental contaminants, including endocrine disruptors and pesticides. Hair analysis can effectively capture cumulative exposure to substances such as bisphenol A (BPA), triclosan, and organophosphate metabolites, which are challenging to assess accurately with blood or urine due to their short-lived presence in these matrices[12]. Studies demonstrate that hair analysis can detect persistent organic pollutants like DDTs and PCBs, even in vulnerable groups such as pregnant women and children, highlighting its effectiveness in evaluating chronic exposure scenarios[13]. Additionally, hair provides a unique advantage in assessing lifestyle-related exposures, as observed with smoking and its impact on metal and metalloid accumulation, further supporting the role of hair as an integrative biomarker of both environmental and behavioral factors[14]. The use of hair in RLRS thus enables more realistic toxicological assessments by capturing cumulative, low-dose exposures over time, aligning toxicological practices with real-world exposure complexities.

Telomeres as biomarkers in RLRS

Telomeres are increasingly recognized as significant biomarkers within the RLRS framework, due to their ability to reflect cumulative genetic, environmental, and behavioral factors over an individual's lifespan. These DNA-protein complexes protect chromosome ends, but progressively shorten with each cell division and in response to environmental and lifestyle stressors, including exposure to xenobiotics and oxidative stress. This shortening, particularly when telomeres reach critically short lengths, is linked to cellular senescence or apoptosis, processes associated with aging and a heightened risk of chronic diseases, including cancer[15].

Within RLRS, telomere length (TL) serves as a valuable indicator because it captures the effects of real-world exposures, which often involve low-dose, long-term interactions with multiple chemicals. This sensitivity allows TL to function as an early biomarker for disease onset, revealing the impacts of both genetic predispositions and modifiable environmental factors. Studies indicate that diet, exposure to toxins, and behavioral factors like stress significantly influence telomere attrition rates, making TL a comprehensive measure of biological aging and disease susceptibility[16].

Moreover, as a biomarker within the RLRS framework, telomere length offers a personalized insight into health risk by integrating these complex influences. This comprehensive approach advances toxicological assessments, facilitating more accurate risk predictions that reflect real-life conditions and support tailored healthcare interventions.

Influence of driving forces of economic progress

One of the significant obstacles to advancing new RA methodologies is the influence of politics and industry on scientific research and regulatory processes. Political priorities often dictate the allocation of research funding, and regulatory bodies are subject to political pressures when making decisions related to public health and safety[17]. As a result, important studies demonstrating the negative impacts of certain compounds are sometimes excluded from regulatory consideration, especially when their findings conflict with industrial interests.

For example, in the case of endocrine-disrupting chemicals (EDCs), industry-funded studies frequently contradict independent research, leading to regulatory delays and weaker safety standards[18-21]. Similarly, chemical regulations in sectors such as agrochemicals, fossil fuels, and pharmaceuticals are heavily influenced by industry lobbying[22-26]. These pressures often result in delayed or weakened regulations, obstructing progress in protecting public health[2].

The political influence extends beyond chemical safety to broader scientific issues, such as climate change and vaccine safety, where public perception is shaped by media narratives and political debates that can diverge from scientific consensus. To ensure sound regulatory decisions, it is essential to promote independent research that is free from political and industrial biases, ensuring that public health remains the primary focus.

The way forward

To pave the way forward in modernizing risk assessment, regulatory practices must evolve to incorporate holistic approaches like RLRS, ensuring that real-world exposures and their complexities are adequately addressed[27]. Moreover, mandating mixture studies is essential for regulatory bodies to update their guidelines, moving beyond the assessment of single substances. This ensures that the combined effects of multiple exposures, particularly at low doses, are considered where traditional assessments might overlook significant risks. To support the integration of holistic approaches like RLRS, standardized testing protocols must also be developed. These protocols should evaluate chemical mixtures across various exposure routes (oral, dermal, inhalation) and durations (acute, chronic), while incorporating sensitive populations and environmental factors.

While holistic frameworks like RLRS are important advancements in toxicological risk assessment (RA), they must be accompanied by broader systemic changes in regulatory oversight and academic engagement. These overarching needs go beyond any single framework, ensuring RA keeps pace with modern scientific and societal demands.

Strengthening regulatory oversight is crucial. Robust enforcement mechanisms must ensure compliance with new regulations that integrate comprehensive RA frameworks. Regulatory bodies need the authority and resources to enforce regulations addressing the complexities of real-world exposures. Transparency in the regulatory process is also vital, offering public access to risk assessment data and methodologies to foster trust and accountability.

Independent risk assessment and the role of academia

Enhancing the role of academia is equally important. Academic institutions should be empowered to play a more prominent role in shaping RA methodologies and providing independent research. Increased funding for independent academic research will enable academia to contribute unbiased, high-quality data to inform policymaking, free from industrial or political pressures. Academia's independence and dedication to scientific integrity make it a crucial player in advancing RA methods that reflect real-world complexities.

Conclusion

By providing more comprehensive frameworks that account for the real-world complexity of chemical exposures, RLRS and similar holistic approaches have the potential to significantly improve public health outcomes. However, their integration into regulatory practices will require overcoming challenges such as political and industrial influence, outdated regulatory protocols, and the need for standardized testing methodologies. At the same time, broader reforms to regulatory oversight and academic engagement are necessary to create a robust, transparent, and scientifically sound RA system that can meet the demands of the 21st century.

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