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# FROM EXPOSURE INDICES TO CELLULAR DAMAGE: A REVIEW ON INTEGRATED FRAMEWORK FOR GENOTOXICITY-INFORMED HEAVY METAL RISK ASSESSMENT

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**ABSTRACT**
The heavy metal contamination of water, food, and soil is a widely recognized global problem. Yet the strategies commonly used to evaluate the impact of heavy metal contamination on human health typically do not account for the metabolic pathways of metals in living cells. Exposure metrics like Estimated Daily Intake, Hazard Quotient, Hazard Index, and Cancer Risk are simple and inexpensive, and easy to compare to regulatory limits, but they do not provide much information about underlying biological mechanisms: they assume metals are absorbed at a constant rate, do not consider the effects of metal mixtures, and disregard the non-linear cellular damage increasingly shown in in vitro genotoxicity studies. In vitro assays, however, directly demonstrate damage to DNA and chromosomes, and consistently implicate oxidative stress as a common mechanism through which cadmium, arsenic and chromium act; and these assays are seldom connected to actual dietary or drinking water exposures. This review combines the two methods, using contamination data from high-risk environments and data from occupational and environmental biomonitoring studies, which already demonstrate a measurable relationship between exposure and cellular damage. This type of integration is now feasible using newer tools such as physiologically based pharmacokinetic modeling, adverse outcome pathways, and omics-based biomarkers. Building on these, the review proposes a concentration-response approach for assessing heavy metal risk in food. This approach moves beyond a purely statistical exercise and offers a biologically grounded model with real-world implications for the setting and harmonization of international food safety standards. It is based on bioaccessibility-corrected exposure estimates and in vitro-to-in vivo extrapolation.

## INTRODUCTION

Pollution of soils, surface water, ground water and food with heavy metals is a major food safety issue worldwide. High levels of arsenic, cadmium, lead, chromium, and mercury have been detected repeatedly in river floodplains in Nigeria (Nkwunonwo et al., 2020), Bangladesh (Rakib et al., 2024), and across South Asia (Bangladesh, India, and Pakistan). These metals are found in drinking water, soil and crop samples. Angon et al. (2024) and Khan et al. (2015) attribute these high concentrations to effluents from industries and mining operations, and application of agrochemicals, respectively. These increase the levels of metals in irrigation water and soil. The metals are then mobilized to the crops and subsequently enter into the human food chain. The issue is not limited to a specific medium or location. Similar results have been observed in rice fields (Sharma et al., 2021), aquatic food webs (Rakib et al., 2024), the Arctic food chain (Van Oostdam et al., 2005), and antimony contaminated areas (Bolan et al., 2022). This emphasises the worldwide nature of the problem. This is well exemplified in the floodplain of the river Yamuna in Delhi, where industrial/urban pollution merges with intensive vegetable cultivation near the city.

While there is vast data available on contamination, most health risk assessments are based on indices that are exposure-based (e.g., Daily Intake of metal (EDI), Non-carcinogenic risk factors (HQ, HI) and Cancer Risk (CR) (Schaefer et al., 2020; Tariq et al., 2024)) rather than on measures of actual biological harm. The indices are widely used because they are easy to calculate and require only concentration and consumption data. However, they do not show the changes in cells that happen when cells are exposed to metals, such as DNA damage, cell death, especially when laboratory doses do not reflect the doses that are found in the real world. Though such holistic approaches are rare, Reytor-González et al. (2025) link these areas in their review of gastric cancer risk.

This is a crucial gap; at present, there are no consistent methods for converting estimated dietary or water intake in a population into the genotoxic thresholds observed in living cells. Exposure scientists and cellular toxicologists commonly operate independently rather than collaboratively. Risk assessments based on the EDI, HQ, or CR alone may therefore not accurately reflect the actual genotoxic risk, as these do not account for factors such as bioavailability, metal uptake, or the non-linear dose-response observed in laboratory studies.

The purpose of this review is two-fold. First, it brings to the forefront what is known about dietary and water exposure assessment and in vitro genotoxicity testing for heavy metals. Second, it suggests a framework for connecting population-

level exposure estimates to genotoxic thresholds measured in the lab. The goal is to shift the field toward a more mechanistic, rather than statistical, approach to evaluating the health risk of heavy metals.

**Determine the level of exposure to heavy metals from diet and environment**

Researchers typically use a standard method to evaluate health risks from heavy metals. They determine the amount of metal in the food or water and then apply information on metal consumption and body weight to estimate the amount of metal consumed per day (Estimated Daily Intake, or EDI). The EDI is then compared with agencies' permissible limits, such as the US EPA's. This method is very simple and requires only metal concentration and food consumption data, so it has been widely used in various contexts such as vegetables in Bangladesh (Chowdhury et al., 2024), infant food in Ghana (Amarh et al., 2023), spices in Bangladesh (Islam et al., 2023), eggs in China (Zhao et al., 2021), milk (Alinezhad et al., 2024), herbal medicines (Zuo et al., 2020), beer in Tanzania (Eliaza et al., 2024), high-altitude vegetables (Giri et al., 2022), aquatic products in China (Wang et al., 2020), and hand-sanitizer gels (Gnonsoro et al., 2022). The calculation is essentially the same across these studies, with the main differences in the assumptions about consumption and body weight.

Three main risk indices come from the EDI. The Hazard Quotient (HQ) is used to compare estimated intake to a safe reference dose for non-cancer effects, and an HQ above 1 generally indicates substantial health risk. Studies on milk (Alinezhad et al., 2024), spices (Islam et al., 2023), food baskets (Jain et al., 2023), and beer (Eliaza et al., 2024) have shown that the cumulative Hazard Quotient (∑HQ) can be used to estimate the combined non-carcinogenic risk of several metals. The Carcinogenic Risk (CR) is derived from the EDI and a cancer slope factor for each metal and is used to estimate the lifetime cancer risk for metals such as arsenic, cadmium, and chromium. These indices are collectively the primary tools employed in food safety and environmental monitoring studies for heavy metals.

The exposure-only approach is widely used, but it has certain disadvantages. It assumes that metals are absorbed equally, whether from leafy vegetables or from fish or herbal medicine, though they are not. This approach also does not directly quantify biological or cellular effects. Rather, it relies on reference doses and slope factors derived from older animal or population studies, typically not containing new cell-based genotoxicity data. Most studies also do not account for bioaccessibility, or the amount of metal released and available for absorption during digestion in the human body. The adjustment is not always applied or even done when bioaccessibility is taken into account.

In general, EDI, HQ, HI, and CR have been found to be useful for initial screening purposes but cannot be used to determine whether a population is at increased genotoxic risk. The next sections will look at this gap using in vitro and bridging analyses.

**In Vitro Genotoxicity of Heavy Metals**

In vitro genotoxicity testing is more direct than exposure indices, as it asks whether a particular metal at a specific concentration is genotoxic (causing damage to DNA or chromosomes) in living cells. The most commonly used cell lines include human blood cells for biomonitoring; liver (HepG2), lung (A549), and bone-derived cell lines that represent specific target organs. This methodology has been demonstrated to be useful in practice by Nersesyan et al. (2016), who used the micronucleus assay in individuals occupationally or environmentally exposed to mercury, lead, and cadmium, combining laboratory and field evidence in a single study.

A limited number of fundamental assays are generally deployed in this domain. The review and meta-analysis of cadmium genotoxicity conducted by Nagaraju et al. (2022) is based on the comet assay, which quantifies DNA strand breaks, and summarizes findings from multiple studies demonstrating a clear, dose-dependent effect on DNA damage. Nersesyan et al. (2016) detected chromosome-level damage by using the micronucleus assay, which is suitable for human biomonitoring. The tool kit is supplemented by chromosomal aberration tests, gene-expression or epigenetic marker panels. Iyer et al. (2023) for example identified epigenetic changes after chromium exposure by gene expression analysis.

Mechanism of cell damage is different for each metal. It has been reported by Tam et al. (2020) that arsenic primarily interferes with cellular DNA repair mechanisms, leading to increased damage from other contaminants rather than direct DNA damage. It has also been reported to disrupt DNA methylation, an epigenetic process (Chakraborty et al., 2022). Sadiku & Rodríguez-Seijo (2022) and Thakur et al. (2021) explain the metabolism and nervous system (neurotoxicity), and genome (genotoxicity) effects of arsenic and lead, respectively. Unlike arsenic, chromium does not inhibit repair enzymes, but reacts directly with cell DNA. The best characterized is hexavalent chromium (Cr (VI)). Inside a cell, it forms reactive intermediates that bind to DNA, resulting in DNA strand breaks and disruption of chromosome structure (Meaza et al., 2024). Alur et al. (2024) show that, apart from the nuclear effects, mitochondrial damage is a significant factor in the carcinogenicity of chromium, and Zablon et al. (2019) report that chromium can affect gene activity without directly mutating them. In the case of inhalation exposure, Proctor et al. (2014) review the evidence of cell damage in the lungs following exposure to Cr (VI) and show that this has been used to guide at least one large-scale regulatory risk assessment that has not yet been fully integrated by research into dietary and waterborne exposures.

Although the mechanisms differ for each metal, they all share a common mechanism of action: the production of reactive oxygen species (ROS). Metal ions readily undergo Fenton-type reactions, generating oxidative stress that can damage DNA bases and cell membranes. If the damage exceeds the cell's repair mechanisms, then cell death is initiated by p53. The oxidative pathway of stress is common across the three environmental factors discussed (cadmium, arsenic, and chromium) and is probably the most important biological pathway connecting environmental exposure to the population-level genotoxic markers discussed in the next section.

**Linking Exposure Estimates to Genotoxic Thresholds**

To link environmental exposure estimates to in vitro genotoxicity thresholds, it is necessary to convert an EDI value (mg/kg bw/day) to a concentration comparable to those typically used in cellular studies. One of the more recent and

rigorous attempts at this problem is that of Beal et al. (2023), who developed a quantitative in vitro-to-in vivo extrapolation (IVIVE) approach for genotoxicity data, taking explicit account of the amount of substance absorbed, the distribution in the body, and the rate of clearance. This type of reasoning is more typical for drug studies than environmental toxicology, and this review suggests that the process should be modified specifically for dietary and waterborne exposures to metals.
The best available example of this type of exposure-to-cell linkage is the study of occupational exposure of communities to metals for which exposure levels are known, by measuring genotoxic markers directly in humans with known exposure levels. Maeng et al. (2004) identified a clear association between chromium exposure and chromosome damage and lipid oxidation markers in the exposed workers, which was the first time a level of exposure was measured and a cellular damage marker was linked directly to that exposure. On this, Garcia-Leston et al. (2012) built on the concept of lead, demonstrating that genetic variation among individuals also influences the metabolism and repair of lead in the body, and that any exposure-to-cell bridge will ultimately have to consider individual differences. Additional support is provided by Meng et al. (2021), who find associations between occupational lead exposure and changes in ratios of immune cells and genotoxicity markers; by Cao et al. (2020), who employ a sensitive mutation assay to assess lead-exposed workers; and by Hu et al. (2022) who report associations between blood chromium levels, immune markers, and genetic damage in chromate-exposed populations. Lope et al. (2010) identified measurable genetic effects in newborns and their parents in an urban setting with high pollution, indicating that pollution levels outside the workplace can be studied in this way as well.
Very few studies, however, have tried to systematically rank or compare several genotoxic and cancer-causing contaminants within a single food-safety framework. An exception is Vromman et al. (2014), who came up with a risk ranking method for food contaminants that may cause cancer and damage the genetic material. This method explicitly takes the margin of exposure as a comparative risk measure, which is the ratio between a point of departure derived from the laboratory and an estimated human exposure. In principle, this margin-of-exposure approach is the type of tool that the bridging framework proposed in this review is designed to develop for heavy metals, allowing consideration of both population exposure estimates and in vitro or in vivo genotoxic thresholds. In general, the progress of genotoxicity testing methods has been reviewed by Turkez et al. (2017), who state that such integration is one of the unmet needs in the field, and this was also observed by Lauwerys et al. (1995) in their early call for biological markers that could correlate long-term chemical exposure with measurable health risk.
The occupational biomonitoring literature as a whole indicates that, in principle, it is possible to link exposure to cellular effects. It should, however, be systematically expanded to include other forms of dietary and waterborne heavy-metal exposure in the general population.

**Current approaches: Their strengths and limitations**

A comparative overview of the two methodologies is provided in Table 1, but a major limitation is that it does not consider how each method handles multi-metal real-world exposures. The one-chemical, one-route paradigm is no longer valid, as real populations are exposed to mixtures of metals and other contaminants, in which the combined exposure may be additive, synergistic, or antagonistic, as proposed by Domingo & Nadal (2026). Likewise, Cory-Slechta's (2005) criticism of single-chemical toxicity testing and Laskowski et al.'s (2010) study on chemical interactions with environmental matrices led to similar conclusions from different research perspectives. All these studies show that mixture and cumulative-risk effects are basic gaps in current practices.
MacGregor et al. (2015) summarise an international genotoxicity testing workshop that highlights the continued inconsistencies in how laboratories define and use reference doses. These inconsistencies make the translation of in vitro thresholds into benchmarks relevant for human populations more complicated. One often-overlooked limitation is bioaccessibility. Typically, in vitro genotoxicity tests are performed with metal salts in culture medium, and the amount of metal released from food or soil during human digestion may significantly differ from the amount measured in the food or soil. Bioaccessible fractions are often considerably lower than total concentrations, as demonstrated by Oomen et al. (2003) in an in vitro digestion model, and later for cadmium in rice (Yang et al., 2012) and for arsenic and zinc in contaminated soil (Fang et al., 2022). Thus, risk assessments that rely solely on total metal concentration, as is often done in EDI studies, could significantly overestimate actual cellular exposure in the body.
Both these research traditions are complementary rather than competitive. The EDI-based assessment is useful for population-level screening but is not mechanistically grounded and often does not account for mixture effects and bioaccessibility. In vitro genotoxicity testing, on the other hand, is useful for determining mechanistic interconnections but is subject to issues of extrapolation, dose relevance, and study consistency. Thus, an integrated dose-response paradigm, which incorporates bioaccessibility-corrected exposure estimates, takes into account mixtures of metals, and uses harmonized reference points to anchor genotoxic thresholds would overcome the limitations of both approaches.

**Table 1: Comparison of merits and limitations of population-level exposure indices and in vitro genotoxicity testing in heavy metal risk assessment**

| Dimension | EDI/ HQ/ HI/ CR based exposure assessment | In Vitro genotoxicity testing |
|---|---|---|
| Type of Evidence | Population-level, statistical/ probabilistic | Cellular/ mechanistic, direct biological damage |
| Data Requirements | Metal concentration, consumption and body-weight data | Cultured cells, defined metal concentrations, assay-specific protocols |

| | | |
|---|---|---|
| Output | EDI, HQ, HI and CR values compared to regulatory thresholds | DNA/ chromosomal damage endpoints (e.g. comet tail moment, micronucleus frequency) |
| Key Strengths | Standardized, low-cost, directly comparable to existing regulatory limits | Direct mechanistic evidence, captures oxidative stress and DNA repair-inhibition pathways |
| Key Limitations | Assumes uniform bioavailability, largely ignores metal mixtures, rarely incorporates bioaccessibilty correction | Poor extrapolation to real-world dose, inconsistent reference dose definitions across laboratories, typically uses metal salts rather bioaccessible fractions |
| Regulatory relevance | High thresholds map directly onto existing food-safety standards | Currently limited, lacks a standardized translation into population-relevant benchmarks |
| Representative studies | Chowdhury et al. (2024); Alinezhad et al. (2024); Jain et al. (2023) | Nersesyan et al. (2016); Nagaraju et al. (2022); Meaza et al. (2024) |

**Public Health and Regulatory Policy Implications**

The framework proposed here is integrated and has immediate application for human health risk assessment. It includes both mechanistic and genotoxic biomarkers, in addition to the classic EDI, HQ, and CR indices, and does not rely only on exposure measures. Biomarker-informed methodologies have already been used for some metals. Examples include the effects of cadmium on early biomarkers of toxicity reviewed by Fowler (2009) and the metabolic effects of chronic cadmium exposure analysed by Chen et al., (2022). These results provide a model for more sensitive, earlier monitoring of the population than relying on dietary intake calculations alone. Likewise, Ganie et al. (2023) review the origin, biological pathways, and mechanisms of arsenic toxicity, highlighting that a holistic understanding of the mechanisms can help interpret the exposure data in arsenic-affected areas.

The implications for vulnerable populations are particularly significant for farming communities in floodplain areas like the Yamuna floodplain, who are exposed multiple times over longer periods through various exposure pathways, as opposed to acute, high-dose exposures. The current efforts in the United States to prevent childhood lead poisoning provide a good example of how to use biomarker and exposure data to design effective public health interventions. In their review of more than five decades of U.S. policy, both the American Academy of Pediatrics Council on Environmental Health (2016) and Jacobs & Brown (2023) show that substantial decreases in population BLLs necessitated multiple reductions in acceptable BLELs, as new biomarker data emerged. This experience is directly applicable to the metals-in-food-basket theme of this review. Despite the presence of lead poisoning prevention policies in every state in the United States, Ruckart et al. (2024) note persistent differences across state policies, noting that even in a resource-rich country, state-level policies can vary. In addition, the assessment of deep groundwater development as an arsenic mitigation strategy in Bangladesh by Meyer et al. (2003) and Shibasaki et al. (2007) illustrates that effective interventions need to be tailored to the local context rather than simply transplanted from high-income countries.

Analysis at the policy-making and regulatory level by El Hawari et al. (2024) and Gawalko et al. (2009) shows that national and regional maximum limits (MLs) for metals in food continue to vary internationally, often for reasons other than toxicological evidence. It underscores the case for a genotoxicity-based, internationally harmonized approach. Together, these examples point to the direct relevance of the integrated framework proposed here. It is relevant to exposure monitoring, the protection of vulnerable populations, and the harmonization of food safety standards.

**Future Research Directions**

The use of standardized exposure-to-cellular approaches, as recommended in this review, is becoming more feasible in recent years. Physiologically based pharmacokinetic (PBPK) modeling can provide a direct pathway to link an external dose to cellular concentrations by simulating absorption, distribution, metabolism, and excretion to predict tissue-level concentrations from estimates of external intake. Chou & Lin (2023) discuss how machine learning and artificial intelligence techniques can be incorporated into PBPK modeling, thereby accelerating parameter fitting and enhancing predictive power. These advancements can significantly reduce technical hurdles to applying PBPK approaches to heavy metals, particularly in resource-constrained research environments.

A second complementary approach are adverse outcome pathway (AOP) frameworks. Recently, Pamanji (2026) suggested the use of AOP frameworks for dietary contaminants, which is in line with the bridging framework described here. Wang et al. (2024) and He et al. (2025) provide examples of how AOP-based reasoning can be applied to multi-metal co-exposure and cadmium-induced cardiovascular and kidney effects, respectively. These studies demonstrate that AOPs can be used to model the complexity of mixtures and multi-organ effects that estimated daily intake (EDI) based models, as discussed in Section 5, are generally incapable of capturing.

A third method for validating laboratory-derived thresholds is to use emerging omics and biomarker-based approaches in real-world applications. DNA methylation-based biomarkers of environmental exposure in the human population are reviewed by Nwanaji-Enwerem & Colicino (2020), and chromium-specific epigenetic toxicity by Iyer et al. (2023). Both studies suggest that epigenetic signatures are potential intermediate endpoints that are closer to the genotoxic mechanism than symptom-based clinical endpoints, yet can still be measured noninvasively in population studies. Based on this, Sille et al. (2025) suggest that the MPS, organ-on-chip, and other in vitro systems should be integrated into the Human

Exposome Project at large. Kopanska & Rimann (2022) state that more realistic in vitro models are increasingly adopted across industries, and that genotoxicity testing in such systems could soon be available to directly address the extrapolation concerns discussed in Section 5.

In combination, these advances, and the recommendations of Schmeisser et al. (2023) to move from debating the adoption of new methods to determining how to implement them, indicate that toxicology is moving toward the standardized exposure-to-cellular integration that was identified in this review as being lacking for toxic metals in food and water.

## CONCLUSION

This review covers two methodologically advanced and historically different traditions in heavy metal toxicology: exposure-based risk assessment, which is currently used worldwide for food, water and non-food matrices and is based on the estimated daily intake (EDI), hazard quotient (HQ), hazard index (HI) and cancer risk (CR) framework; and in vitro genotoxicity testing, which has led to a detailed understanding of how specific metals damage DNA and chromosomal material in cultured cells. Each tradition alone only deals with a part of the risk assessment problem. Exposure indices provide population-level policy-relevant estimates and are based on assumptions of uniform bioavailability and do not consider cellular mechanisms. On the other hand, in vitro genotoxicity data can provide direct evidence of the mechanism but have difficulty with dose relevance and extrapolation to real-life exposure situations.

The proposed concentration-response bridging framework based on bioaccessibility-corrected exposure estimates, quantitative in vitro to in vivo extrapolation, and adverse outcome pathway reasoning is a comprehensive approach for addressing this disconnect. Occupational and environmental biomonitoring studies suggest that it is possible to correlate exposure with cellular events; but more studies are needed to apply this to dietary and waterborne heavy metal exposure in the general population. This gap, the main focus of this review, is especially critical for the Yamuna floodplain and other similarly polluted areas worldwide. With the development of mechanistic, omics-based, and computational toxicology, it is increasingly possible to shift heavy metal health risk assessment from mostly statistical to evidence-based approaches grounded in mechanistic understanding.

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