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GENOTOXIC EFFECTS OF PESTICIDE EXPOSURE IN BRAZIL: A MULTI-TIER EVIDENCE SYNTHESIS

EFECTOS GENOTÓXICOS DE LA EXPOSICIÓN A PESTICIDAS EN BRASIL: UNA SÍNTESIS DE EVIDENCIA EN MÚLTIPLES NIVELES

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RESUMEN

Brasil se encuentra entre los mayores consumidores de plaguicidas del mundo, con 907.564 toneladas de ingredientes activos comercializados en 2024. Sin embargo, las implicaciones de esta exposición generalizada sobre la inestabilidad genómica siguen siendo insuficientemente abordadas en los sistemas de vigilancia de la salud pública. Esta revisión narrativa integra evidencias de nuestro programa de investigación multiinstitucional y de la literatura científica disponible, combinando datos in vitro, in vivo y de biomonitoreo humano para caracterizar el riesgo de inestabilidad genómica asociado con la exposición a agroquímicos en Brasil. Los estudios in vitro muestran que las formulaciones comerciales de plaguicidas son más genotóxicas que los ingredientes activos aislados, mientras que las mezclas de herbicidas, particularmente glifosato con 2,4-D o atrazina, inducen daño al ADN supra-aditivo. Los estudios in vivo también demuestran un aumento de la frecuencia de micronúcleos y del daño al ADN en múltiples tejidos incluso a exposiciones sub-tóxicas, principalmente mediados por estrés oxidativo y alteraciones en los mecanismos de reparación del ADN. Los estudios de biomonitoreo humano informan consistentemente un aumento de biomarcadores de inestabilidad genómica en poblaciones expuestas, incluyendo roturas de las cadenas de ADN, micronúcleos, acortamiento de los telómeros y alteraciones epigenéticas. Estos efectos están influenciados por la duración de la exposición, el uso inadecuado de equipos de protección personal y la susceptibilidad genética. La exposición ambiental a través del agua, los alimentos y la deriva de plaguicidas extiende estos riesgos más allá de los entornos ocupacionales. La evidencia meta-analítica confirma un aumento significativo del daño al ADN en trabajadores expuestos (DME = 2,02; IC del 95 %: 1,69–2,35). En conjunto, estos hallazgos indican que la exposición a agroquímicos actúa como un factor determinante de la inestabilidad genómica y ponen de manifiesto las limitaciones de los marcos regulatorios basados en compuestos individuales. La evidencia respalda la integración del biomonitoreo genético en los sistemas de salud pública y la adopción de enfoques de evaluación de riesgos que consideren las exposiciones a mezclas en condiciones reales.

Palabras clave: agroquímicos, genotoxicidad, daño al ADN, biomonitoreo, plaguicidas

ABSTRACT

Brazil ranks among the world's largest consumers of pesticides, with 907,564 tons of active ingredients sold in 2024. However, the implications of this widespread exposure for genomic instability remain insufficiently addressed in public health surveillance systems. This narrative review integrates evidence from our multi-institutional research program and the broader literature, combining in vitro, in vivo, and human biomonitoring data to characterize the genomic instability risk associated with agrochemical exposure in Brazil. In vitro studies show that commercial pesticide formulations are more genotoxic than isolated active ingredients, while herbicide mixtures, particularly glyphosate with 2,4-D or atrazine, induce supra-additive DNA damage. In vivo studies further demonstrate increased micronucleus frequency and DNA damage across multiple tissues at sub-toxic exposures, largely mediated by oxidative stress and impaired DNA repair. Human biomonitoring studies consistently report elevated biomarkers of genomic instability in exposed populations, including DNA strand breaks, micronuclei, telomere shortening, and epigenetic alterations. These effects are influenced by exposure duration, inadequate use of personal protective equipment, and genetic susceptibility. Environmental exposure through water, food, and pesticide drift extends these risks beyond occupational settings. Meta-analytical evidence confirms significantly increased DNA damage in exposed workers (SMD = 2.02; 95% CI: 1.69–2.35). Collectively, these findings indicate that agrochemical exposure acts as a driver of genomic instability and highlight the limitations of compound-based regulatory frameworks. The evidence supports the integration of genetic biomonitoring into public health systems and the adoption of risk assessment approaches that consider real-world mixture exposures.

Key words: agrochemicals, genotoxicity, dna damage, biomonitoring, pesticides

INTRODUCTION

Agriculture constitutes a fundamental pillar of the global economy, underpinning food security and socioeconomic development (Pawlak and Kołodziejczak, 2020). The Brazilian agricultural model exemplifies this dynamic through high productivity, extensive land use, and intensive agrochemical application, positioning the country among the world's largest consumers of these substances (Almeida et al., 2017; Bombardi, 2017; Gaboardi et al., 2023). Globally, pesticide use has more than doubled since 1990, reaching 3.7 million tons in 2023, with the Americas accounting for approximately 49% of total consumption (FAO, 2024). Brazil alone registered 0.8 million tons in 2023 and a record 907,564 tons in 2024, representing a substantial share of global use (FAO, 2024; IBAMA, 2025).

This intensive use is historically rooted in the Green Revolution and further consolidated with the widespread adoption of glyphosate-resistant cultivars, which markedly increased herbicide application rates in large-scale commodity production systems (Almeida et al., 2017; Pignati et al., 2017). In parallel, regulatory frameworks in Brazil have diverged from those of other jurisdictions, permitting the continued use of active ingredients restricted or banned elsewhere, raising concerns regarding the adequacy of current safety thresholds (Bombardi, 2017; Brasil, 2023; Abrasco, 2024).

Pesticide exposure in Brazil occurs through multiple interconnected pathways, including occupational handling, environmental dispersion, and dietary intake. Rural workers are disproportionately affected due to direct contact with complex chemical mixtures under variable safety conditions, while contamination of water, soil, and food systems extends exposure to surrounding populations (Egger et al., 2021; Panis et al., 2022). Importantly, these exposures are rarely limited to single compounds but instead involve mixtures whose cumulative and interactive effects remain insufficiently addressed in conventional risk assessment frameworks. The toxicological significance of this multi-pathway exposure is compounded by its cumulative character: even at sub-threshold individual doses, prolonged contact with agrochemical mixtures has been associated with epigenetic alterations, telomere shortening, and broader genomic instability (Arbo et al., 2022; Kahl et al., 2018b; Flesch et al., 2025).

Genotoxicity assessment represents a critical component of pesticide risk evaluation, enabling detection of early biological effects such as DNA strand breaks, chromosomal aberrations, and micronucleus (MN) formation that precede clinical disease and reflect underlying genomic instability (Silva Pinto et al., 2020). The comet assay and MN test are widely applied as complementary biomarkers of DNA and chromosomal damage, respectively, providing a robust framework for human biomonitoring studies (Rohr et al., 2020; da Silva, 2016). A recent systematic review and meta-analysis of 80 biomonitoring studies (66 eligible for quantitative synthesis) confirmed a significant increase in DNA strand breaks among pesticide-exposed workers (standardized mean difference = 2.02; 95% CI: 1.69–2.35), with higher effect sizes observed in middle-income countries (Gerić et al., 2025).

Despite this growing body of evidence, systematic genetic monitoring remains largely absent from national public health surveillance systems in Brazil. A comprehensive review of occupational health studies identified agrochemicals as the leading class of toxic exposures, while highlighting the lack of standardized biomonitoring strategies capable of capturing cumulative genetic damage at the population level (Arbo et al., 2022). This gap is particularly relevant in the Brazilian context, where high-intensity agrochemical use intersects with heterogeneous exposure conditions and limited integration of molecular biomarkers into health policy.

This narrative review aims to delineate a genotoxic risk profile for Brazil by synthesizing evidence from *in vitro*, *in vivo*, and human biomonitoring studies, with emphasis on data generated by our multi-institutional research program. By integrating multi-tier evidence, this review seeks to highlight the disconnect between extensive agrochemical use and current surveillance frameworks, and to support the incorporation of genetic biomonitoring into public health strategies.

AGROCHEMICAL EXPOSURE BY AGRICULTURAL CROP

Brazil's high pesticide consumption is closely linked to large-scale commodity production concentrated in a small number of dominant crops. According to IBAMA (2025), commercial sales of active ingredients reached a record 907,564 tons in 2024, with glyphosate and its salts as the most widely sold molecule, followed by 2,4-D, atrazine, mancozeb, acephate, chlorothalonil, diquat, glufosinate-ammonium, chlorpyrifos, and methomyl. Soybean cultivation, occupying over 44 million hectares (USDA, 2023), is the primary driver of herbicide consumption, particularly glyphosate-based formulations. The near-universal adoption of glyphosate-tolerant genetically modified seeds (97% of planted area) has consolidated a model of chemical dependency with substantially increased herbicide application rates (USDA, 2023; Almeida et al., 2017; Pignati et al., 2017). Soybean production additionally relies on 2,4-D, atrazine, insecticides (imidacloprid, thiamethoxam, lambda-cyhalothrin), and fungicides (azoxystrobin, trifloxystrobin, epoxiconazole) to

control soybean rust and pest complexes (Pignati et al., 2017; Bombardi, 2017).

Maize cultivation presents a similarly intensive chemical profile, with atrazine, mesotrione, and nicosulfuron for weed control, alongside neonicotinoid seed treatments and insecticides targeting fall armyworm (Pignati et al., 2017; Bombardi, 2017). Cotton production exhibits one of the highest pesticide application rates per hectare, with herbicides, insecticides, and growth regulators applied in spray calendars exceeding 20 applications per season (Bombardi, 2017; Pignati et al., 2017).

Sugarcane cultivation, concentrated in São Paulo, relies on herbicides (ametryn, diuron, hexazinone, tebuthiuron, 2,4-D) and insecticides (fipronil, thiamethoxam), with aerial spraying contributing to environmental dispersion (Pignati et al., 2017; Egger et al., 2021). Coffee production employs fungicides, organophosphate and neonicotinoid insecticides, and herbicides such as glyphosate and paraquat (Pignati et al., 2017). The horticultural sector, despite smaller area, shows high application rates and frequent exceedance of maximum residue limits (MRLs) (Lopes and Albuquerque, 2021). Environmental contamination is evidenced in the Sinos River Basin, where pesticide residues and genotoxic effects were detected (Bianchi et al., 2017; Egger et al., 2021).

A defining feature of agrochemical exposure in Brazil is mixture exposure. Agricultural practices commonly involve tank mixes combining herbicides, insecticides, and fungicides (Pignati et al., 2017; Hernández et al., 2017). In soybean systems, mixtures may include multiple active ingredients simultaneously, while cotton systems may involve up to seven compounds plus adjuvants (Defarge et al., 2018).

This has critical implications for genotoxic risk assessment. Pesticide mixtures can produce synergistic effects exceeding additive predictions (Hernández et al., 2017). Combinations such as glyphosate with atrazine or 2,4-D induce greater DNA damage than individual compounds (Tsatsakis et al., 2017), and commercial formulations containing co-formulants (e.g., POEA) are more cytotoxic and genotoxic than pure active ingredients (Defarge et al., 2018). Biomonitoring studies confirm DNA damage and epigenetic alterations in exposed workers (de Oliveira et al., 2019; Benedetti et al., 2018).

Regional agricultural specialization creates distinct exposure patterns. The Midwest (Centro-Oeste) concentrates the highest pesticide use, with Mato Grosso alone accounting for ~20% of national consumption and extensive aerial spraying contributing to environmental drift (Pignati et al., 2017; Bombardi, 2017; Skidmore et al., 2023). In the South, large-scale agriculture coexists with tobacco farming, a high-exposure scenario involving pesticides, nicotine absorption, and tobacco-specific nitrosamines (TSNAs), generating complex multi-agent exposure (da Silva et al., 2012a; Dalberto et al., 2023; da Silva et al., 2014). Experimental and *in vitro* studies confirm the genotoxic potential of these combined exposures (Dalberto et al., 2021; Borges et al., 2025; Jaeger et al., 2026). The Northeast presents a distinct profile linked to irrigated fruit production, with pesticide use associated with environmental contamination and adverse health outcomes (Egger et al., 2021).

The genotoxic potential of agrochemical exposure in Brazilian agriculture can be inferred from the mutagenic profiles of the most widely used active ingredients. Glyphosate, classified by the International Agency for Research on Cancer (IARC) as "probably carcinogenic to humans" (Group 2A, Monograph 112), has been consistently associated with oxidative stress, DNA strand breaks, chromosomal aberrations, and micronucleus induction across multiple experimental systems (IARC, 2017), as well as with a 41% increased risk of non-Hodgkin lymphoma in the highest exposure category in a meta-analysis of epidemiological studies (Zhang et al., 2019). Similarly, 2,4-D has been classified as "possibly carcinogenic" (Group 2B, IARC Monograph 113, 2018) and has been linked to clastogenic activity and chromosomal instability (IARC, 2018). Atrazine, recently reclassified by IARC from Group 3 to Group 2A ("probably carcinogenic to humans", Monograph 140), based on epidemiological associations with non-Hodgkin lymphoma and robust mechanistic evidence, including endocrine disruption and oxidative DNA damage, now joins glyphosate and 2,4-D as an herbicide of elevated carcinogenic concern (IARC, 2025; Hernández et al., 2017). Among insecticides, organophosphates such as chlorpyrifos and acephate exert their toxic effects primarily through acetylcholinesterase inhibition and the induction of oxidative stress-mediated DNA damage and chromosomal aberrations (Mostafalou and Abdollahi, 2017).

When combined in complex mixtures characteristic of real-world agricultural practice, these genotoxic effects may be substantially amplified through converging mechanisms. Oxidative stress emerges as a central pathway: the simultaneous generation of reactive oxygen species (ROS) by multiple compounds can overwhelm cellular antioxidant defenses, resulting in oxidative DNA base modifications (e.g., 8-oxo-7,8-dihydroguanine; 8-oxoG), single- and double-strand breaks, and lipid peroxidation products capable of forming mutagenic DNA adducts (Mostafalou and Abdollahi, 2017). In parallel, inhibition of DNA repair pathways by specific pesticide components may further compromise genomic integrity by preventing the resolution of DNA lesions, thereby converting transient damage into permanent mutations and chromosomal aberrations. Emerging evidence also indicates that chronic exposure

to pesticide mixtures induces epigenetic dysregulation, including global DNA methylation changes (Flesch et al., 2025; Sherif et al., 2026), contributing to genomic instability even in the absence of overt DNA lesions.

EXPERIMENTAL EVIDENCE FROM *IN VITRO* AND *IN VIVO* MODELS

Experimental models provide mechanistic support for understanding the genotoxic effects of agrochemical exposure observed in human populations. *In vitro* systems represent a first tier of genotoxicological assessment, offering controlled and mechanistically informative platforms. Commonly used cell lines in pesticide research include Chinese Hamster Ovary (CHO-K1) cells for chromosomal aberration and MN assays, and V79 cells for mutagenicity testing via the hypoxanthine-guanine phosphoribosyltransferase (HPRT) assay (OECD, 2016; Kirkland et al., 2019). However, the limited metabolic capacity of these rodent-derived lines may underestimate the genotoxicity of compounds requiring metabolic activation.

Human-derived models, particularly HepG2 cells, address this limitation by retaining cytochrome P450 and phase II enzyme activity, enabling detection of promutagens without exogenous metabolic systems (Shah et al., 2018). Human peripheral blood lymphocytes are widely used in the cytokinesis-block micronucleus (CBMN) cytome assay to assess chromosomal damage, nucleoplasmic bridges (NPBs), and nuclear buds (NBUDs), while the buccal micronucleus cytome (BMCyt) assay has emerged as a non-invasive alternative for biomonitoring in exposed populations (Fenech, 2020; Fenech et al., 2024).

Detection of genetic damage relies on a battery of complementary assays targeting distinct endpoints. The alkaline comet assay quantifies DNA strand breaks and alkali-labile sites at the single-cell level, with enzyme-modified variants (FPG, Endo III) enabling detection of oxidized purines and pyrimidines (Collins et al., 2014). The CBMN cytome assay simultaneously evaluates MN, NPBs, and NBUDs, integrating cytotoxicity and cytostasis endpoints (Fenech, 2020). Chromosomal aberration analysis remains a regulatory requirement under OECD Test Guideline 473 (OECD, 2016a), while cytotoxicity assays such as MTT, neutral red uptake, and trypan blue exclusion ensure that observed genotoxicity occurs at sub-cytotoxic concentrations (OECD, 2016).

Our group has contributed extensively to *in vitro* genotoxicity assessment of agrochemicals and related exposures. Thiel et al. (2024) demonstrated in glioblastoma cell lines that a glyphosate-based formulation induced greater cytotoxicity and DNA damage than pure glyphosate, with p53 playing a central role in the response. Dalberto et al. (2021) showed that aqueous extracts of dried Nicotiana tabacum leaves induced significant DNA damage, increased MN frequency, and NBUD formation in V79 cells. Borges et al. (2025), using HepG2 cells, confirmed concentration-dependent genotoxicity of nicotine, tobacco-specific nitrosamines (NNN and NNK), and dried tobacco leaf extracts. Additional studies by our group have extended these approaches to environmental matrices, including industrial effluents and treated wastewater, and incorporated Daphnia magna as a sensitive bioindicator of toxicity (Alderete et al., 2021). Environmental monitoring in the Sinos River Basin further demonstrated cytotoxic and genotoxic effects in HEp-2 cells associated with pesticide residues (including 2,4-D) and hydrocarbons (Bianchi et al., 2017).

These findings align with a broader body of *in vitro* evidence. Commercial pesticide formulations containing co-formulants such as polyethoxylated tallow amine (POEA) have been shown to be more genotoxic than isolated active ingredients (Defarge et al., 2018; Woźniak et al., 2018). Binary and ternary mixtures of glyphosate, 2,4-D, and atrazine produce synergistic increases in DNA damage, exceeding additive expectations (Hernández et al., 2017; Tsatsakis et al., 2017). Additional compounds widely used in Brazilian agriculture, including chlorpyrifos and fipronil, induce micronucleus formation and chromosomal aberrations via oxidative stress mechanisms, while mancozeb and its metabolite ethylenethiourea (ETU) produce genotoxic and cytotoxic effects in HepG2 cells (Mostafalou and Abdollahi, 2017; Lori et al., 2021; Laborde et al., 2020).

Experimental animal models complement *in vitro* findings by incorporating systemic processes such as absorption, distribution, metabolism, and tissue-specific responses (OECD, 2016; Arbo et al., 2022). Genotoxicity *in vivo* is commonly evaluated using the bone marrow micronucleus assay (OECD Test Guideline 474) and the comet assay across multiple tissues (OECD Test Guideline 489), enabling detection of both chromosomal damage and DNA strand breaks (OECD, 2016b; OECD, 2016c). Oxidative stress biomarkers, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA), provide additional mechanistic insight (Mostafalou and Abdollahi, 2017).

In vivo studies conducted in Brazil and internationally have reported increased DNA damage and micronucleus frequency following exposure to glyphosate-based herbicides, organophosphates, and their mixtures, even at environmentally relevant concentrations (Mostafalou and Abdollahi, 2017). Odetti et al. (2020) demonstrated that embryonic exposure of *Caiman latirostris* to glyphosate-, cypermethrin-, and chlorpyrifos-based formulations, alone and in mixtures, resulted in significant genotoxic and oxidative DNA damage.

These findings are consistent with international evidence and with the IARC Monograph 112 conclusion of strong mechanistic evidence for glyphosate-induced genotoxicity (IARC, 2017).

Some discrepancies persist between experimental and regulatory studies. Investigations conducted under Good Laboratory Practice (GLP) conditions often report negative results, particularly when using pure active ingredients and standard endpoints. Differences in formulation type, exposure conditions, and assay sensitivity are likely to explain these inconsistencies (IARC, 2017; Benbrook, 2019). Studies employing commercial formulations, environmentally relevant concentrations, multi-tissue designs, and sensitive endpoints such as the FPG-modified comet assay provide a more realistic assessment of genotoxic risk (Collins et al., 2014; Defarge et al., 2018).

Overall, experimental evidence supports two key conclusions: (i) commercial pesticide formulations are more genotoxic than their isolated active ingredients, and (ii) mixtures produce synergistic effects that are not captured by single-compound risk assessment frameworks. These findings have direct implications for human health, as real-world exposures in agricultural settings involve complex mixtures and commercial products rather than single active ingredients. The mechanistic pathways consistently identified in experimental systems, particularly oxidative stress, DNA strand breaks, chromosomal instability, and epigenetic alterations, are the same endpoints evaluated in human biomonitoring studies. Thus, experimental data provide biological plausibility and mechanistic support for the patterns of genomic instability observed in occupationally and environmentally exposed populations, reinforcing the importance of integrating in vitro and in vivo evidence with human data in the assessment of agrochemical-associated health risks. In this context, the following section examines human biomonitoring evidence, providing direct insight into the magnitude and biological relevance of genotoxic effects in exposed populations.

HUMAN ASSESSMENTS

Human biomonitoring studies represent a direct and epidemiologically relevant approach for assessing the genotoxic consequences of agrochemical exposure, providing evidence of biological effects under real-world conditions that integrate the complexity of mixed exposures, individual genetic susceptibility, nutritional status, and co-exposures. As summarized in Table 1, our research group, in collaboration with partner institutions, has conducted a series of cross-sectional biomonitoring studies targeting populations with distinct exposure profiles across Brazilian agricultural regions. Primary study populations have included farmworkers directly involved in pesticide application in soybean, tobacco, and vineyard production systems in Rio Grande do Sul, as well as soybean growers in Mato Grosso (Benedetti et al., 2013, 2018; da Silva et al., 2008; de Oliveira et al., 2019; Kahl et al., 2018a; Toniasso et al., 2025). The scope of these evaluations has been further expanded by comparative analyses across occupational groups exposed to different classes of genotoxins, including pesticides, tannery chemicals, and coal dust, highlighting the systemic burden of environmental exposures (Kvitko et al., 2012).

In addition to occupational cohorts, biomonitoring studies have included residents of rural communities located near intensive agricultural areas, who experience indirect but chronic environmental exposure through contaminated drinking water, atmospheric drift from aerial and ground spraying, and dietary intake of locally produced food (Panis et al., 2022; Egger et al., 2021). These populations are particularly relevant for risk assessment because they include vulnerable subgroups, children, pregnant women, and the elderly, who may exhibit increased susceptibility due to differences in metabolism, DNA repair capacity, and critical developmental windows (Fenech et al., 2024; Sherif et al., 2026). Control groups were selected from unexposed populations (organic farmers or urban residents) and matched for key demographic variables to minimize confounding (de Oliveira et al., 2019; Toniasso et al., 2025).

The methodological framework of these studies is based on a multi-biomarker strategy integrating complementary endpoints to assess genetic damage, cytotoxicity, and susceptibility. The alkaline comet assay, performed in peripheral blood lymphocytes, serves as a primary biomarker of effect, detecting DNA strand breaks, alkali-labile sites, and incomplete excision repair intermediates (Collins et al., 2014). Results were expressed using multiple parameters, damage index (DI), damage frequency (DF), and percentage of tail DNA, to ensure comparability across studies (Collins et al., 2014).

The CBMN cytome assay provided a complementary cytogenetic evaluation, quantifying micronuclei (MNi), nucleoplasmic bridges (NPBs), and nuclear buds (NBUDs) (Fenech, 2020). These endpoints, validated by the HUMN project, have demonstrated predictive value for cancer risk, with meta-analyses reporting mean MN frequency ratios of approximately 1.7 in lymphocytes and 2.6 in buccal cells when comparing cancer cases to controls (Bonassi and Fenech, 2021). In selected studies, the buccal micronucleus cytome (BMCyt) assay was employed as a non-invasive alternative, enabling the assessment of genotoxic and cytotoxic effects in epithelial tissue directly exposed to ingested contaminants (Fenech et al., 2024).

Biomarkers of exposure included erythrocyte acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity for organophosphate and carbamate exposure, urinary ETU for mancozeb, and structured questionnaires detailing pesticide use patterns (de Oliveira et al., 2019; Toniasso et al., 2025). Biomarkers of susceptibility included polymorphisms in xenobiotic metabolism genes (GSTM1, GSTT1, CYP2D6) and DNA repair genes (XRCC1, OGG1), enabling evaluation of gene–environment interactions (Silva Pinto et al., 2020; Kahl et al., 2018c). Specific interactions were described by Rohr et al. (2011), demonstrating increased DNA damage in individuals carrying the OGG1 Cys variant, and protective effects of XRCC1 Arg/Trp in individuals with poor PON1 metabolism. Similar modulation of cytogenetic damage was observed in tobacco farmers (Kahl et al., 2018d).

According to the studies summarized in Table 1, exposed populations consistently exhibited elevated DNA damage compared to controls. In farmworkers from Rio Grande do Sul, comet assay analyses showed increased DNA damage, particularly in higher damage classes (Alves et al., 2020; Dalberto et al., 2022; da Silva et al., 2012a; Kahl et al., 2018a; Toniasso et al., 2025). Altered antioxidant profiles were also observed, with SOD activity and MN frequencies influenced by PON1 polymorphisms (Alves et al., 2016). Nutritional factors further modulated responses: deficiencies in folate, vitamin B6, and B12 were associated with increased DNA damage, although no association with MTHFR C677T polymorphism was detected (Fernandes et al., 2018).

Soybean workers in Mato Grosso showed increased frequencies of MNs, binucleated cells, NBUDs, and cell death markers in buccal cells (de Oliveira et al., 2019), consistent with findings in southern Brazil (Benedetti et al., 2013; da Silva et al., 2008). Elemental analysis further revealed elevated bromine, rubidium, and lead levels, with the XRCC1 Arg/Arg genotype conferring partial protection (de Oliveira et al., 2019).

Meta-analytical evidence reinforces these findings. Nascimento et al. (2021), analyzing 42 studies, reported significantly increased DNA damage in exposed workers (SMD = 4.63), although with high heterogeneity (I^2 = 98.4%). A more recent analysis by Gerić et al. (2025) reported a lower but robust effect size (SMD = 2.02), confirming consistent increases in DNA damage despite methodological variability. Together, these studies support a clear direction of effect across populations.

Elevated MN frequencies were consistently reported across cohorts (da Silva et al., 2012b; Benedetti et al., 2013; de Oliveira et al., 2019; Toniasso et al., 2025). Determinants of damage included duration of exposure, number of pesticides handled, PPE use, and prior intoxication (Silva Pinto et al., 2020). PPE reduced but did not eliminate damage, indicating partial protection.

Additional cytogenetic endpoints revealed increased NBUDs and apoptotic markers (Fenech et al., 2024; Toniasso et al., 2025). Telomere and epigenetic analyses further demonstrated genomic instability, including telomere shortening and altered DNA methylation (Benedetti et al., 2018; Flesch et al., 2025; Kahl et al., 2018b). Mechanistic studies linked telomere shortening to UPS-mediated degradation of hTERT (Kahl et al., 2016a, 2016b), with further confirmation in tobacco exposure scenarios (Dalberto et al., 2023). These findings align with broader occupational evidence (de Souza et al., 2018; Passos et al., 2022; Kahl and da Silva, 2021).

Importantly, these molecular alterations are not only biomarkers of exposure but also predictors of disease. Elevated MN frequencies predict cancer risk (Bonassi and Fenech, 2021), and comet assay data have been associated with increased mortality (Bonassi et al., 2021). Epidemiological findings on glyphosate remain mixed (Zhang et al., 2019; Andreotti et al., 2018), but ecological studies in Brazil show associations between pesticide exposure and cancer incidence (Panis et al., 2022; Skidmore et al., 2023). Beyond cancer, telomere shortening and epigenetic dysregulation are linked to ageing and chronic diseases (Mostafalou and Abdollahi, 2017; Sherif et al., 2026), reinforcing the systemic impact of agrochemical exposure.

The consistency of findings across studies, as summarized in Table 1, together with mechanistic plausibility and validated biomarkers, provides strong evidence linking agrochemical exposure to genotoxicity in Brazilian populations (Arbo et al., 2022). Standardization efforts (Rojas et al., 2026; Rohr et al., 2020) further strengthen data reliability.

Nonetheless, key limitations remain, including the predominance of cross-sectional designs, limited internal exposure quantification, and insufficient evaluation of sex-specific effects (Nascimento et al., 2021; Gerić et al., 2025; Evenden et al., 2024). Additionally, disentangling mixture effects remains a major challenge in human populations.

IMPLICATIONS FOR PUBLIC HEALTH AND THE ENVIRONMENT

A consistent finding across the human biomonitoring studies summarized in Table 1 is the presence of elevated genotoxicity biomarkers in populations occupationally and environmentally exposed to agrochemicals. These alterations, DNA strand breaks, chromosomal instability, telomere disruption, and epigenetic changes, are not merely indicators of exposure but represent early biological events with established predictive value for cancer and other chronic diseases. As such, they constitute a measurable early-warning signal linking real-world pesticide exposure to long-term health risk, thereby providing a critical bridge between mechanistic evidence and population-level outcomes.

From a public health perspective, these findings support the integration of genotoxicity biomonitoring into the Brazilian Unified Health System (SUS) as a tool for early detection and prevention (Arbo et al., 2022). Currently, national surveillance of pesticide-related illness relies predominantly on the reporting of acute intoxication cases through the Notifiable Diseases Information System (SINAN), an approach that fails to capture subclinical and cumulative genetic damage that may precede disease onset by years or decades. The incorporation of validated biomarkers, such as the comet assay and micronucleus (MN) test, into occupational health programs would enable identification of high-risk populations, support exposure stratification, and guide preventive interventions (Fenech et al., 2024; Nascimento et al., 2021).

The environmental dimension of agrochemical genotoxicity extends these concerns beyond occupational settings. Contamination of surface and groundwater with pesticide residues, documented across multiple Brazilian regions, constitutes a pathway for chronic, low-dose exposure affecting entire communities, including urban populations reliant on these water sources (Egger et al., 2021; Panis et al., 2022). In parallel, genotoxic effects have been reported in non-target organisms across aquatic ecosystems, including fish, amphibians, and invertebrates, with potential consequences for biodiversity and ecosystem services (Odetti et al., 2020). A comprehensive review by Picinini-Zambelli et al. (2025) further highlights emerging pollutants, including pesticides, pharmaceuticals, and microplastics, as drivers of oxidative stress, endocrine disruption, and genotoxicity in aquatic environments, reinforcing the need for integrated environmental biomonitoring strategies.

These converging lines of evidence have direct regulatory implications. A significant disparity persists between Brazilian pesticide standards and those of other major economies, with several active ingredients currently authorized in Brazil being banned or severely restricted in the European Union (Bombardi, 2017). This issue is further intensified by the enactment of Lei nº 14.785/2023, which streamlined pesticide registration processes and introduced the criterion of "unacceptable risk," raising concerns regarding the adequacy of safety thresholds under simplified evaluation frameworks (Brasil, 2023; Abrasco, 2024). In this context, the incorporation of genotoxicity data, particularly from mixture exposures and real-world biomonitoring, into regulatory decision-making is essential. A more protective framework should consider cumulative and aggregate exposures across occupational, dietary, and environmental pathways, while applying the precautionary principle in the presence of mechanistic evidence of harm.

FUTURE PERSPECTIVES

Despite the advances outlined in this review, significant scientific and methodological challenges remain. A central issue concerns the assessment of chemical mixtures, as real-world agricultural exposure involves simultaneous contact with multiple compounds whose interactive effects are not adequately captured by current risk assessment frameworks (Hernández et al., 2017). Experimental and analytical approaches, including combination index (CI) methods, isobolographic analysis, and whole-mixture testing strategies, are needed to better characterize synergistic and potentiating genotoxic effects (Tsatsakis et al., 2017).

Longitudinal cohort studies represent another priority. While cross-sectional biomonitoring studies consistently demonstrate elevated genotoxicity in exposed populations, prospective designs are required to determine whether these biomarkers predict the development of cancer and other chronic diseases over time (Bonassi and Fenech, 2021; Nascimento et al., 2021).

Methodological standardization across laboratories also remains a critical need. Only a small proportion of studies included in recent systematic reviews have been classified as low risk of bias (Gerić et al., 2025), underscoring the importance of adopting harmonized protocols such as the Minimum Information for Reporting Comet Assay (MIRCA) guidelines and standardized BMCyt methodologies (Møller et al., 2020; Rohr et al., 2020; Rojas et al., 2026). These frameworks are essential for ensuring data comparability and enabling robust meta-analytical synthesis.

The integration of multi-omics technologies—including genomics, transcriptomics, proteomics, metabolomics, and epigenomics—offers new opportunities to elucidate the molecular mechanisms underlying pesticide-induced genotoxicity and to identify novel biomarkers of exposure, effect, and susceptibility (Froetschl et al., 2025; Labib et al., 2017). Epigenomic analyses have revealed persistent alterations associated with chronic and early-life exposure (Flesch et al., 2025; Sherif et al., 2026). Although a recent meta-analysis reported extremely large effect sizes for early-life exposure (Cohen's d = 4.85), this estimate likely reflects methodological heterogeneity and publication bias rather than a precise population-level effect. Nonetheless, the consistency of directional findings supports the biological plausibility of early-life susceptibility to genotoxic and epigenetic disruption (Sherif et al., 2026).

Advances in New Approach Methodologies (NAMs), including organ-on-a-chip systems, three-dimensional cultures, and adverse outcome pathway (AOP) frameworks, may further enhance the mechanistic

Table 1. Summary of human biomonitoring studies on Brazilian agricultural populations exposed to agrochemicals.

Study	Region	Population	n (exp/ ctrl)	Primary exposure	Biomarker(s)	Key finding(s)
da Silva et al. (2008)	RS	Vineyard workers (Caxias do Sul)	108/65	Mixed pesticides	Comet; MN (binucleated lymphocytes); metabolizing gene polymorphisms (GSTT1, GSTM1, GSTP1, CYP1A1, CYP2E1, PON)	MN and DI significantly increased; PON polymorphism modulates MN frequency; associations suggested for GSTM1, GSTT1, and CYP2E1
Rohr et al. (2011)	RS	Vineyard workers	108/65	Multiple pesticides	Comet; MN; BER gene polymorphisms (OGG1 Ser326Cys, XRCC1 Arg194Trp, PON1 Gln192Arg)	DI significantly increased; OGG1 Cys variant - higher DNA damage; PON1 Gln/Gln - higher MN; XRCC1 Arg/Trp protective in poor PON1 metabolizers
da Silva et al. (2012a)	RS	Tobacco farmers	111/56	Multiple pesticides + nicotine	Comet; BMCyt; AChE/BChE; urinary ETU; metabolizing gene polymorphisms (GSTT1, GSTM1, GSTP1, CYP2A6, PON1, OGG1, XRCC1, XRCC4)	DI significantly increased; ETU detected; GSTM1 null and CYP2A6*9 associated with MN frequency
da Silva et al. (2012b)	RS	Tobacco farmers	106/53	Multiple pesticides	BMCyt; PON1Gln192Arg; CYP2A6*9	MN significantly increased; PON1Gln192Arg and CYP2A6*9 associated with DNA damage and cell death
Kvitko et al. (2012)	RS	Tobacco farmers (Venâncio Aires)	56/57	Multiple pesticides; tobacco harvest	Comet (DI, DF); PCR-RFLP; nutritional assessment (folate, B12)	DI and DF significantly increased; folate and B12 deficiency associated with higher MN frequency in lymphocytes
Benedetti et al. (2013)	RS	Soybean farmers	81/46	Complex pesticide mixture	Comet; BMCyt (MN, NBUDs)	DI, MN, and NBUDs all significantly increased
da Silva et al. (2014)	RS	Tobacco farmers (temporal)	30/30	Multiple pesticides; seasonal	Comet; MDA (lipid peroxidation)	DNA damage peaks at harvest; remains elevated in off-season
Alves et al. (2016)	RS	Agricultural workers	77/60	Multiple pesticides	Comet (DI); SOD activity; MN	SOD activity and MN frequency modulated by PON1 polymorphism
Kahl et al. (2016a)	RS	Tobacco farmers	62/62	Mixed pesticides + nicotine	Absolute telomere length (aTL); oxidative stress (TBARS, TEAC)	aTL significantly decreased in exposed; oxidative stress significantly increased
Kahl et al. (2016b)	RS	Tobacco farmers	62/62	Mixed pesticides + nicotine	Systems biology; telomere length; UPS pathway analysis	UPS inhibition and hTERT degradation identified as molecular mechanism of telomere shortening
Fernandes et al. (2018)	RS	Tobacco farmers	110/0	Multiple pesticides	Comet; MN; dietary micronutrients	DI significantly increased; inadequate folate/B6/B12 intake associated with higher DNA damage
Kahl et al. (2018a)	RS	Tobacco farmers	56/74	Mixed pesticides + nicotine	Comet; telomere length (qPCR); global DNA methylation; oxidative stress (TBARS, TEAC)	DI significantly increased; telomere length significantly decreased; global DNA hypomethylation; p16 hypermethylation; lipid peroxidation significantly increased
Kahl et al. (2018b)	RS	Tobacco farmers	40/40	Mixed pesticides	CBMN-Cyt; global DNA methylation; nutritional biomarkers	Genomic and epigenetic instability; global DNA hypomethylation
Kahl et al. (2018c)	RS	Tobacco farmers	121/121	Multiple pesticides	BMCyt; comet; telomere length; inorganic elements; PON1 Gln192Arg, SOD2 Val16Ala, OGG1 Ser326Cys, XRCC1 Arg194Trp, XRCC4 Ile401Val polymorphisms	MN, NBUDs significantly increased; PON1 Gln/Gln - significantly increased MN; SOD2 Val/Val - significantly increased MN and significantly increased BUD; XRCC1 Arg/Arg protective for MN and TL; OGG1 Cys/- influences TL
Kahl et al. (2018d)	RS	Tobacco farmers	129/91	Multiple pesticides	CBMN-Cyt; inflammatory markers (IL-6, TNF-α, CD4+/CD8+); OGG1 Ser326Cys, XRCC1 Arg194Trp, PON1 Gln192Arg polymorphisms; inorganic elements (S, Cl, K)	MN, NPBs, NBUDs significantly increased; IL-6 and TNF-α significantly increased; OGG1 Cys/- significantly increased NPBs; PON1 Arg/- + XRCC1 Arg/Arg - significantly increased NPBs; necrosis significantly increased in combined PON1/XRCC1 genotypes
Benedetti et al. (2018)	RS	Soybean farmers	137/83	Complex pesticide mixture	Comet; MN; global DNA methylation	DI significantly increased; MN significantly increased; global DNA hypermethylation correlated with MN frequency; epigenetic instability documented

Table 1 (continues). Summary of human biomonitoring studies on Brazilian agricultural populations exposed to agrochemicals.

Study	Region	Population	n (exp/ ctrl)	Primary exposure	Biomarker(s)	Key finding(s)
de Oliveira et al. (2019)	MT	Soybean farmers	76/72	Mixed pesticides (OP, herbicides)	BMCyt; PIXE; XRCC1/PON1 polymorphisms; in silico	MN, NBUDs significantly increased; Br, Rb, Pb significantly increased; XRCC1 Arg/Arg genotype protective
Alves et al. (2020)	RS	Tobacco farmers with GTS	40/40	Nicotine (dermal absorption; GTS)	Comet; cotinine; TBARS; TEAC	DI ~3× controls; GTS symptoms associated with higher DNA damage
dos Santos et al. (2022)	SP	Family farmers	81/81	Mixed (cypermethrin; abamectin)	BMCyt; telomere length (qPCR)	MN, cell death markers significantly increased; cypermethrin – TL significantly decreased; abamectin - TL significantly increased
Dalberto et al. (2022)	RS	Tobacco farmers (harvest + grading)	241 (3 groups)	Seasonal: harvest vs. dry grading	Comet; BMCyt; TBARS; cotinine; nitrates	DI and MN significantly increased in both seasons; oxidative stress highest at harvest
Dalberto et al. (2023)	RS	Dry tobacco graders	44/42	TSNAs; nicotine; inorganic elements (Br, Rb)	Comet; CBMN-Cyt; telomere length	DI significantly increased; telomere disruption; Br and Rb associated with genotoxicity
Dalberto et al. (2025)	RS	Dry tobacco workers	44/42	Dry tobacco (TSNAs, nicotine, inorganic elements)	Comet; MN; NPBs; NBUDs; inflammatory markers (TNF-α, IL-6, IL-1β, MCP-1, IL-18)	DNA damage significantly increased; inflammatory markers significantly increased; IL-1β correlates with DNA damage; TNF-α correlates with NPBs; sex-specific inflammatory responses
Flesch et al. (2025)	RS	Farmers (intensive vs. non-intensive agrochemical handling)	44/68	Multiple agrochemicals	BMCyt; telomere length; global DNA methylation; PIXE	Trace elements (As, Cr, Ni, V) significantly increased; epigenetic and cytogenetic damage correlated with exposure intensity
Toniasso et al. (2025)	RS	Viticulture workers (mancozeb)	50/44	Mancozeb (dithiocarbamate fungicide; ≥5 years exposure)	Comet; CBMN; biochemical (ChE, oxidative markers; haematological parameters)	DI significantly increased; oxidative stress biomarkers significantly increased; consistent with mancozeb genotoxicity

RS, Rio Grande do Sul; MT, Mato Grosso; SP, São Paulo; DI, damage index; MN, micronuclei; NPBs, nucleoplasmic bridges; NBUDs, nuclear buds; GTS, green tobacco sickness; TL, telomere length; aTL, absolute telomere length; OP, organophosphate; TSNAs, tobacco-specific nitrosamines; PIXE, particle-induced X-ray emission; TBARS, thiobarbituric acid reactive substances; TEAC, trolox equivalent antioxidant capacity; ChE, cholinesterase; UPS, ubiquitin-proteasome system; hTERT, human telomerase reverse transcriptase; SOD, superoxide dismutase; ETU, ethylenethiourea.

relevance of genotoxicity testing while reducing reliance on animal models (OECD, 2016; Collins et al., 2014). These approaches are particularly relevant for mixture toxicity, where conventional testing strategies are insufficient.

Finally, the establishment of large-scale, multicenter biomonitoring networks across Latin America represents a key strategic priority. A regional registry of genetic biomonitoring data, analogous to the HUMN project, would enable standardized data collection, facilitate inter-regional comparisons, and support identification of high-risk populations (Fenech, 2020; Bonassi and Fenech, 2021). Existing collaborative platforms, including ALAMCTA and SBMuCT, provide a foundation for such initiatives. Strengthening the interface between research and regulatory agencies, including ANVISA and IBAMA, will be essential to translate scientific evidence into policies that effectively protect human health and environmental integrity.

CONCLUSIONS

This narrative review synthesizes evidence from our multi-institutional research program and the broader national and international literature to define agrochemical exposure in Brazil as a driver of genomic instability across biological scales. Integrating *in vitro*, *in vivo*, and human biomonitoring evidence, a consistent and biologically coherent pattern emerges: commercial pesticide formulations exhibit greater genotoxic potential than isolated active ingredients, and their combinations at environmentally relevant concentrations induce synergistic effects that amplify DNA damage beyond additive expectations. These findings expose a critical limitation of current compound-by-compound regulatory frameworks, which fail to capture the complexity of real-world mixture exposures.

At the mechanistic level, genomic instability arises through converging pathways dominated by oxidative

stress, with excess reactive oxygen species (ROS) promoting DNA strand breaks, oxidative base lesions, chromosomal aberrations, and impaired DNA repair capacity. Experimental evidence further demonstrates that these effects extend beyond direct DNA damage to include telomere attrition and epigenetic dysregulation, reinforcing the concept of genomic instability as a multifactorial and cumulative process rather than a single-event outcome. In vivo studies corroborate these mechanisms at the organismal level, revealing multi-tissue genotoxicity and systemic oxidative imbalance under exposure conditions that reflect agricultural practices.

Human biomonitoring studies provide direct evidence that these mechanistic processes translate into measurable biological effects in exposed populations. Agricultural workers and environmentally exposed communities in Brazil consistently exhibit elevated biomarkers of genomic instability, including increased DNA strand breaks, micronucleus formation, chromosomal instability, telomere shortening, and alterations in DNA methylation patterns. These biomarkers are of relevance because they represent early and predictive indicators of disease risk, linking chronic agrochemical exposure to carcinogenesis, cardiovascular disease, and other non-communicable conditions. Although meta-analytical estimates confirm the robustness of these associations, substantial methodological heterogeneity highlights the need for harmonized protocols and cautious interpretation of effect magnitudes.

Importantly, genomic instability in this context is not restricted to occupational settings but reflects a broader environmental phenomenon. The widespread dispersion of pesticide residues across water, soil, and food systems establishes continuous low-dose exposure scenarios affecting entire populations, including vulnerable groups such as children and the elderly. This reinforces the characterization of agrochemical-induced genomic instability as a population-level risk with both public health and ecological dimensions.

Within the Latin American context, these findings acquire urgency. Brazil's high-volume pesticide use, combined with intensive monoculture systems, permissive regulatory thresholds, and limited implementation of genetic surveillance, creates conditions conducive to the accumulation of genomic damage at scale. The convergence of mechanistic, experimental, and human evidence supports the recognition of genomic instability as a central endpoint for risk assessment and public health action.

Accordingly, this body of evidence supports: (i) the integration of genomic instability biomarkers, such as comet assay and micronucleus endpoints, into occupational and environmental health surveillance systems; (ii) the adoption of regulatory frameworks that explicitly account for commercial formulations and mixture effects; and (iii) the application of the precautionary principle in the face of consistent mechanistic and epidemiological evidence of harm. Future advances will depend on longitudinal human studies, methodological standardization, and the incorporation of emerging approaches, including multi-omics and new approach methodologies (NAMs), to further elucidate the pathways linking exposure to genomic instability and disease.

Ultimately, framing pesticides exposure through the lens of genomic instability provides a unifying conceptual and translational framework that connects molecular damage to population-level health outcomes, supporting more effective prevention strategies in pesticide-intensive regions.

AUTHOR CONTRIBUTIONS

Conceptualization: J.d.S.; Writing, original draft: J.d.S., G.P.-P., A.L.G., B.M., M.S.B., R.D.S.F., F.R.d.S.; Writing, review & editing: J.d.S., G.P.-P., A.L.G., B.M., M.S.B., R.D.S.F., F.R.d.S.; Supervision: J.d.S.; Funding acquisition: J.d.S. All authors have read and agreed to the published version of the manuscript.

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ETHICS STATEMENT

No new data collection involving human participants or animals was conducted for this study; therefore, no additional ethics approval was required.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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