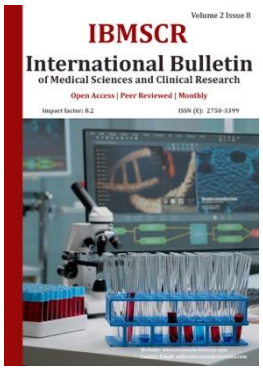


# SYSTEMATIC REVIEW OF HEPATIC SINUSOIDAL DILATATION IN RODENT FEEDING STUDIES OF GLYPHOSATE-TOLERANT GM CROPS AND ITS TRANSLATIONAL IMPLICATIONS FOR HUMAN LIVER MICROVASCULAR HEALTH

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https://doi.org/10.5281/zenodo.19496203

**Abstract**

Hepatic sinusoidal dilatation (HSD) is a histopathological alteration characterized by the widening of hepatic sinusoids and is associated with a range of physiological and pathological conditions, including toxic injury and vascular disturbances. This systematic review evaluates the occurrence of HSD in rodent feeding studies involving glyphosate-tolerant genetically modified (GM) crops and examines its translational relevance for human liver microvascular health. A comprehensive analysis of experimental and regulatory studies reveals that while sinusoidal dilatation has been reported in some rodent models, its frequency, severity, and reproducibility remain inconsistent across studies; in most cases, HSD appears as a mild and isolated finding without clear dose–response relationships or accompanying biochemical evidence of hepatotoxicity, suggesting a predominantly adaptive or incidental nature.

The review further explores the structural and functional characteristics of hepatic sinusoids, underlying mechanisms of sinusoidal alterations, and the challenges in distinguishing adaptive responses from toxicologically significant changes. Importantly, interspecies differences in hepatic microarchitecture, metabolic rate, and regenerative capacity limit direct extrapolation of rodent findings to humans. Current evidence supports a weight-of-evidence approach integrating histopathological, biochemical, and mechanistic data for accurate risk assessment.

Although existing data do not indicate a clear adverse effect of glyphosate-tolerant GM crops on liver microvasculature, the potential role of sinusoidal endothelial injury as an early marker of hepatic dysfunction warrants further investigation, and future research incorporating standardized histological criteria and advanced human-relevant models is essential to enhance translational value and ensure robust safety evaluation.

**Keywords:** hepatic sinusoidal dilatation; glyphosate-tolerant crops; genetically modified organisms; rodent feeding studies; liver microvascular health; translational toxicology; sinusoidal endothelial cells; food safety assessment; histopathology; oxidative stress.

**Introduction**. Hepatic sinusoidal dilatation (HSD) is a histopathological finding characterized by abnormal widening of hepatic sinusoids, the specialized microvascular channels responsible for exchange between hepatocytes and systemic circulation (DeLeve, 2013). Although sinusoidal dilatation may occur as a transient adaptive response, it is also associated with toxic injury, vascular congestion, inflammatory states, and drug-induced liver damage (Rubbia-Brandt, 2010).

In recent decades, safety assessments of glyphosate-tolerant genetically modified (GM) crops have included long-term rodent feeding studies designed to evaluate potential metabolic and histopathological effects (EFSA, 2011). While the majority of regulatory reviews report

substantial equivalence between approved GM crops and conventional counterparts, some experimental studies have described hepatic findings such as sinusoidal dilatation, hepatocellular hypertrophy, or mild inflammatory changes (Domingo & Bordonaba, 2011). However, the reproducibility and toxicological relevance of these observations remain controversial.

The hepatic sinusoidal network plays a critical role in maintaining liver microvascular homeostasis. Structural alterations of sinusoidal architecture may affect oxygen diffusion, immune cell trafficking, and metabolic exchange (Poisson et al., 2017). In humans, persistent sinusoidal injury is linked to conditions such as sinusoidal obstruction syndrome, drug-induced liver injury, and chronic inflammatory liver diseases (DeLeve, 2013). Nevertheless, extrapolating rodent findings to humans requires caution due to interspecies differences in liver architecture, regenerative capacity, and microvascular dynamics (Treuting et al., 2018).

Understanding whether sinusoidal dilatation observed in rodent feeding studies represents an adaptive vascular response or a marker of toxic injury is essential for accurate risk assessment. The aim of this review is to evaluate reports of hepatic sinusoidal dilatation in rodent feeding studies involving glyphosate-tolerant GM crops and to assess their translational relevance for human liver microvascular health.

*In summary, the safety of glyphosate-tolerant GM crops remains a subject of ongoing scientific inquiry, with hepatic sinusoidal dilatation emerging as a histopathological finding of uncertain significance. This review aims to critically evaluate the available evidence and assess its relevance for human liver microvascular health.*

**Hepatic Sinusoidal Architecture and Function**

*Structure of Hepatic Sinusoids*

The hepatic sinusoidal network represents a unique microvascular system specialized for efficient exchange between hepatocytes and the systemic circulation. Unlike typical capillaries, hepatic sinusoids are lined by fenestrated endothelial cells lacking a continuous basement membrane, allowing direct interaction between blood plasma and hepatocyte surfaces within the space of Disse (Braet & Wisse, 2002). This structural specialization supports high metabolic activity and rapid molecular transport, which are essential for detoxification, lipid metabolism, and immune surveillance.

*Role in Microcirculation and Metabolism*

Hepatic sinusoids play a central role in regulating intrahepatic blood flow and maintaining liver microcirculatory homeostasis. Their function is modulated by sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells, which collectively regulate vascular tone, inflammatory signaling, and extracellular matrix turnover (Poisson et al., 2017). Under physiological conditions, sinusoidal diameter dynamically adapts to metabolic demands and hemodynamic changes, reflecting the liver's remarkable vascular plasticity.

*Physiological vs. Pathological Dilatation*

Sinusoidal dilatation refers to abnormal widening of sinusoidal spaces and may occur as either an adaptive or pathological phenomenon. Transient dilatation can arise in response to increased portal flow, regenerative processes, or reversible toxic exposure. However, persistent sinusoidal expansion may reflect endothelial injury, altered vascular permeability, or disruption of hepatic microvascular integrity (DeLeve, 2013). Histologically, sinusoidal dilatation is characterized by expanded vascular channels filled with erythrocytes, often

without overt hepatocellular necrosis. The biological significance of sinusoidal dilatation therefore depends on its duration, severity, and association with additional structural or functional abnormalities (Rubbia-Brandt, 2010).

*In summary, hepatic sinusoids constitute a highly specialized microvascular system whose structural and functional integrity is essential for liver homeostasis. The distinction between physiological adaptation and pathological dilatation depends on duration, severity, and co-occurring abnormalities, making contextual assessment critical in toxicological evaluation.*

**Causes of Hepatic Sinusoidal Dilatation**

*Toxic and Drug-Induced Injury*

Sinusoidal dilatation is a well-recognized consequence of various hepatotoxic exposures. Chemotherapeutic agents such as oxaliplatin have been shown to induce sinusoidal obstruction syndrome through direct endothelial damage, leading to sinusoidal widening, perisinusoidal fibrosis, and eventual vascular occlusion (Rubbia-Brandt, 2010). Similarly, oral contraceptives and anabolic steroids have been associated with hepatic peliosis, a severe form of sinusoidal dilatation involving blood-filled cavities within the parenchyma. In toxicological contexts, hepatotoxicants may act through reactive metabolite formation, oxidative stress, and disruption of endothelial cell junctions, thereby compromising sinusoidal structural integrity (Mesnage & Antoniou, 2017).

*Vascular Congestion and Inflammation*

Sinusoidal dilatation may also result from hemodynamic disturbances such as venous outflow obstruction, right-sided heart failure, or portal hypertension. In these conditions, elevated sinusoidal pressure leads to passive congestion and mechanical widening of sinusoidal lumina (Poisson et al., 2017). Inflammatory processes involving activation of Kupffer cells and infiltration of immune cells into sinusoidal spaces further contribute to sinusoidal remodeling through cytokine-mediated endothelial activation and increased vascular permeability. Understanding these diverse etiologies is essential for distinguishing compound-specific toxicity from background hemodynamic variation in experimental studies.

*In summary, hepatic sinusoidal dilatation arises from diverse etiologies, including direct toxic injury, drug-induced endothelial damage, and hemodynamic disturbances. Recognizing these varied causes is fundamental to differentiating compound-specific toxicity from incidental or background histological variation in experimental settings.*

**Rodent Feeding Studies of Glyphosate-Tolerant GM Crops**

*Design of Safety Feeding Trials*

Regulatory safety assessments of GM crops typically rely on 90-day subchronic rodent feeding studies conducted under OECD Test Guideline 408 (OECD, 2016). These studies evaluate potential adverse effects by comparing treated and control groups using dietary inclusion rates up to the highest tolerable percentage. Endpoints include body weight, organ weight, hematological and biochemical parameters, and comprehensive histopathological examination. However, study designs vary significantly among investigators, with differences in animal strain, group size, feeding duration, and statistical methodology complicating cross-study comparisons (EFSA, 2011).

*Reported Hepatic Histological Findings*

Several independent studies have reported hepatic histopathological alterations in rodents fed glyphosate-tolerant GM crops. Séralini et al. (2014) conducted a two-year feeding

study in Sprague-Dawley rats using NK603 Roundup-tolerant maize with and without Roundup herbicide application, reporting hepatic congestion, sinusoidal dilatation, and areas of necrosis in treated animals. Hammond et al. (2004) performed 90-day feeding studies of Roundup Ready soybeans in Sprague-Dawley rats and reported minimal hepatocellular changes that were considered within the range of normal biological variation. Mesnage et al. (2015) analyzed previously obtained regulatory datasets using multivariate statistical approaches and identified signs of hepatorenal toxicity in rats fed Roundup-tolerant maize, including elevated liver enzyme activity and histological indicators of oxidative stress.

However, regulatory authorities such as the European Food Safety Authority have generally concluded that observed hepatic changes in these studies do not represent treatment-related adverse effects, citing insufficient dose-response relationships, absence of functional correlates, and limitations in study design as reasons for this interpretation (EFSA, 2011).

*Frequency and Significance of Sinusoidal Alterations*

Sinusoidal dilatation has been reported in a subset of rodent GM feeding studies, but its frequency and severity vary considerably across experimental conditions. In studies where sinusoidal dilatation has been observed, it is often described as mild to moderate and not consistently associated with biochemical evidence of hepatotoxicity (Galli & Marinovich, 2020). The inconsistency of these findings across studies using similar GM varieties raises questions about whether sinusoidal dilatation in this context represents a compound-specific effect, a consequence of dietary composition, or a normal histological variant.

*In summary, rodent feeding studies of glyphosate-tolerant GM crops have yielded heterogeneous hepatic findings, with sinusoidal dilatation reported inconsistently and generally characterized as mild. The lack of reproducible dose-response relationships and the absence of robust biochemical correlates suggest that these observations may not represent treatment-related adverse effects.*

**Interpretation of Sinusoidal Changes in Rodents**

Distinguishing adaptive microvascular responses from toxicologically significant findings remains a central challenge in interpreting hepatic histopathology from feeding studies. Sinusoidal dilatation occurring in isolation—without accompanying hepatocellular degeneration, fibrosis, or inflammatory infiltration—is generally considered a nonspecific finding of uncertain biological relevance (Treuting et al., 2018). Adaptive changes may arise from increased metabolic demand, dietary shifts, or minor hemodynamic variation and do not necessarily indicate hepatotoxicity.

However, when sinusoidal dilatation is accompanied by elevated hepatic biomarkers (such as alanine aminotransferase or aspartate aminotransferase), oxidative stress indicators, or ultrastructural evidence of endothelial injury, its toxicological significance increases considerably (Mesnage et al., 2015). A weight-of-evidence approach integrating morphological, biochemical, and mechanistic data is therefore essential for accurate interpretation. The absence of standardized grading criteria for sinusoidal dilatation across toxicological studies further complicates comparison and meta-analysis of existing data.

*In summary, the interpretation of sinusoidal dilatation in rodent studies requires integration of histopathological, biochemical, and mechanistic evidence. Isolated sinusoidal changes without functional correlates are generally considered nonspecific, whereas findings*

*accompanied by hepatic biomarker elevations or endothelial injury carry greater toxicological weight.*

**Species Differences: Rodents vs. Humans**

*Hepatic Microvascular Differences*

Although the fundamental architecture of hepatic sinusoids is conserved across mammals, important species-specific differences exist that affect translational interpretation. Rodent hepatic sinusoids demonstrate a higher degree of fenestration and a more permeable endothelial lining compared to human sinusoids, which may influence the sensitivity of rodent livers to microvascular perturbation (Braet & Wisse, 2002). Additionally, differences in sinusoidal cell populations—including variations in Kupffer cell density and stellate cell activation thresholds—may modulate species-specific responses to dietary or chemical exposures.

*Metabolic Rate and Regenerative Capacity*

Rodents possess substantially higher basal metabolic rates and hepatic regenerative capacities compared to humans, which affects both the kinetics and the reversibility of hepatotoxic responses (Treuting et al., 2018). Findings that are reversible or adaptive in rodents may have different temporal dynamics in humans, where hepatic regenerative responses are slower and sinusoidal repair mechanisms may be less efficient. These differences underscore the need for caution when extrapolating rodent-derived histopathological findings to human health risk assessment.

*In summary, fundamental differences in hepatic sinusoidal architecture, metabolic rate, and regenerative capacity between rodents and humans limit direct extrapolation of rodent histopathological findings. These interspecies differences necessitate cautious interpretation and highlight the importance of human-relevant models in safety assessment.*

**Mechanistic Considerations**

Several molecular and cellular mechanisms have been proposed to underlie sinusoidal dilatation in the context of xenobiotic exposure. Endothelial cell dysfunction, characterized by loss of fenestration and alterations in nitric oxide signaling, represents a primary pathway through which sinusoidal architecture may be disrupted (DeLeve, 2013). Oxidative stress, mediated by reactive oxygen species generated during xenobiotic metabolism, can damage sinusoidal endothelial cells and activate inflammatory cascades involving Kupffer cell-derived cytokines (Mesnage & Antoniou, 2017).

Glyphosate, the active ingredient in herbicide formulations used on tolerant GM crops, has been shown in in vitro studies to induce oxidative stress and mitochondrial dysfunction in hepatic cell lines at high concentrations (Mesnage et al., 2015). However, whether dietary exposure to glyphosate residues at levels present in GM crops achieves sufficient hepatic concentrations to induce such effects in vivo remains uncertain. The distinction between direct glyphosate toxicity and potential combinatorial effects of GM crop matrices, including altered nutritional composition or unintended metabolites, requires further mechanistic investigation (Galli & Marinovich, 2020).

*In summary, the mechanistic basis of sinusoidal dilatation involves endothelial dysfunction, oxidative stress, and inflammatory signaling pathways. While glyphosate has demonstrated hepatotoxic potential in vitro at high concentrations, the relevance of these mechanisms at dietary exposure levels encountered through GM crop consumption remains to be conclusively established.*

**Implications for Human Risk Assessment**

Regulatory frameworks for GM crop safety assessment generally adopt a weight-of-evidence approach, integrating data from compositional analysis, animal feeding studies, and post-market surveillance (OECD, 2016). Under this framework, isolated histopathological findings such as sinusoidal dilatation in the absence of dose-response relationships and functional hepatic impairment are typically not considered adverse effects requiring regulatory action (EFSA, 2011).

Nevertheless, the clinical relevance of rodent sinusoidal findings deserves continued attention. In human hepatology, sinusoidal dilatation is recognized as an early morphological manifestation of several clinically significant conditions, including sinusoidal obstruction syndrome, nodular regenerative hyperplasia, and chemotherapy-associated steatohepatitis (Rubbia-Brandt, 2010). While the exposure scenarios differ substantially between controlled rodent feeding studies and human dietary patterns, the identification of sinusoidal dilatation in experimental models warrants mechanistic follow-up to determine whether comparable pathways of endothelial injury could be relevant in humans exposed chronically to low-level glyphosate residues.

A precautionary approach that integrates advanced histological assessment, hepatic biomarker panels, and mechanistic endpoint analysis would strengthen the translational value of rodent feeding studies and improve confidence in human safety conclusions.

*In summary, current regulatory frameworks do not classify isolated sinusoidal dilatation as an adverse effect in the absence of dose-response relationships and functional impairment. Nevertheless, the clinical significance of sinusoidal injury in human hepatology warrants continued vigilance and mechanistic follow-up to ensure comprehensive safety evaluation.*

**Future Research Directions**

Several research priorities emerge from this review. First, there is a need for standardized histopathological grading criteria for sinusoidal dilatation in toxicological studies, as current variability in reporting limits cross-study comparison and meta-analysis. Second, application of advanced imaging techniques such as intravital microscopy and scanning electron microscopy of sinusoidal fenestration would provide functional and ultrastructural resolution beyond conventional light microscopy (Braet & Wisse, 2002).

Third, integration of omics-based approaches—including transcriptomics, proteomics, and metabolomics—into feeding study designs would enable identification of molecular signatures associated with sinusoidal remodeling and distinguish adaptive from pathological responses at the gene expression level. Finally, development of humanized liver models and organ-on-chip platforms incorporating human sinusoidal endothelial cells would improve translational predictivity and reduce reliance on interspecies extrapolation (Poisson et al., 2017).

*In summary, advancing the translational value of GM crop safety studies requires standardized histopathological criteria, integration of omics-based molecular profiling, and development of human-relevant in vitro models. These approaches will enable more precise differentiation between adaptive and pathological responses and strengthen confidence in human safety conclusions.*

**Conclusion**

Hepatic sinusoidal dilatation has been reported in a number of rodent feeding studies evaluating glyphosate-tolerant GM crops, although its frequency, severity, and reproducibility vary considerably across experimental conditions. Current evidence suggests that isolated sinusoidal dilatation, in the absence of accompanying hepatocellular injury or biochemical abnormalities, is most likely an adaptive or incidental finding of limited toxicological significance. However, the potential for sinusoidal endothelial injury to serve as an early indicator of hepatic microvascular compromise warrants continued mechanistic investigation.

Translational interpretation of rodent sinusoidal findings is complicated by species differences in hepatic architecture, regenerative capacity, and xenobiotic metabolism. A comprehensive weight-of-evidence approach integrating histopathological, biochemical, and molecular data—combined with advances in human-relevant in vitro models—will be essential for strengthening the translational relevance of rodent feeding studies and ensuring robust safety assessment of glyphosate-tolerant GM crops for human consumption.

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