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COMPARATIVE ANALYSIS OF GABAPENTSAL AND GABAPENTIN INDUCED HISTOLOGICAL CHANGES IN LIVER AND KIDNEY TISSUES OF A MURINE EXPERIMENTAL MODEL

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ABSTRACT

BACKGROUND: Chronic use of Gabapentin has been associated with hepatic and renal toxicity in some studies. Gabapentsal, a Schiff base derivative of gabapentin, has demonstrated diverse biological activities and possesses a comparatively lower toxicity profile.

OBJECTIVE : To compare the histological effects of gabapentin and gabapentsal on liver and kidney tissues in a murine model.

METHODOLOGY This experimental study was conducted at the Institute of Pathology and Diagnostic Medicine, Khyber Medical University, in collaboration with the Centre for Interdisciplinary Research in Basic Sciences, International Islamic University, Islamabad, and the Department of Pharmacy, Comsats University, Abbottabad, Pakistan. Thirty BALB/c mice were randomly divided into five groups (n = 6). Group I served as the control and received normal saline. Groups II and III were administered gabapentin at doses of 2.5 mg/kg and 5 mg/kg, respectively, while Groups IV and V received gabapentsal at the same doses. Histological evaluation of liver and kidney tissues was performed using a semi-quantitative scoring system assessing inflammatory cell infiltration, vascular dilatation, architectural distortion, and cellular degeneration on a scale of 0–3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Scoring was carried out by two independent blinded observers. Statistical analysis was performed using one-way ANOVA following assessment of data normality, with $p < 0.05$ considered statistically significant.

RESULTS :Gabapentin-treated groups demonstrated significantly reduced hepatocyte counts (Group II: 91.6 ± SD; Group III: 68.6 ± SD vs control: 138 ± SD; $p < 0.001$) and increased central vein diameter and granulocyte infiltration ($p < 0.001$). In contrast, gabapentsal-treated groups showed only mild histological alterations with significantly lower inflammatory scores and preserved tissue architecture ($p < 0.05$ vs control). Similar trends were observed in renal tissues, where gabapentin induced marked glomerular enlargement and vascular dilatation, while gabapentsal produced comparatively minimal changes.

CONCLUSION: Histological findings suggest that gabapentsal induces fewer toxic effects on liver and kidney tissues compared to gabapentin, suggesting a safer toxicity profile

KEYWORDS :Neuropathic Pain; Gabapentin; Schiff Bases; Histology; Hepatotoxicity; Nephrotoxicity

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INTRODUCTION

Neuropathic pain is estimated to affect 7 to 8 percent of the general population and significantly impacts quality of life.[1, 2] It is generally more challenging to treat than many other forms of chronic pain.[3-5] This pain commonly occurs in conditions such as diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, and central neuropathies.[6]

Gabapentin, an anticonvulsant medication, is commonly prescribed for neuropathic pain. It is also used in the management of partial seizures and restless legs syndrome.[7] In neuropathic pain management, gabapentin functions as an effective analgesic and is available in a wide dosage range, from 100 to 800 mg. However, its clinical efficacy in treating cisplatin-induced neuropathic pain appears limited. Long-term therapy is often necessary for effective management of neuropathic pain. This is an increasing concern due to the adverse effects associated with prolonged use of such drugs. Several studies have reported its potential to induce hepatic damage even in patients without pre-existing liver disease.[8,9]

Chronic administration of gabapentin has been shown in various studies to change liver and renal homeostasis; however, its exact mechanisms are not fully investigated.[10] Similar to gabapentin, even other anticonvulsants like pregabalin are reported to cause inflammatory cell infiltration and congestion of the central veins.[11] The presence of mononuclear inflammatory cells in the sinusoids and periportal regions are reported in some studies indicating that leukocyte infiltration is a significant response of liver tissue, which may result in tissue damage.[9,12]

Extensive Schiff base derivatives of gabapentin have attracted much interest because many of these drugs showed diversified pharmacological activities with favorable safety profiles. A recent study by Ahmad et al. demonstrated that gabapentsal, a Schiff

base derivative of gabapentin, could be more therapeutically rewarding as compared to gabapentin in the management of cisplatin-induced neuropathic pain.[7] Also, it has been reported to diminish the incidence of common adverse effects of gabapentin, such as asthenia, ataxia, and motor disorders, with low incidences of motor discoordination or CNS depression.[7, 13] Although gabapentsal is said to have fewer side effects compared to gabapentin, its histological profile remains unknown; thus, this study aimed to evaluate and compare the histological effects of gabapentsal and gabapentin on liver and renal tissues.

Despite the widespread clinical use of gabapentin, concerns regarding its long-term hepatic and renal safety remain insufficiently addressed at the histological level. Chemical modification of gabapentin through Schiff base formation has been shown to enhance therapeutic efficacy while potentially reducing systemic toxicity. Gabapentsal, a salicylaldehyde derivative of gabapentin, has demonstrated superior antinociceptive effects with fewer central nervous system adverse effects. However, a comprehensive comparative histological evaluation of its effects on vital organs such as the liver and kidneys is lacking. Therefore, the present study was designed to systematically compare the histopathological effects of gabapentin and gabapentsal on hepatic and renal tissues using both qualitative and quantitative parameters.

METHODOLOGY

All animals were housed in polypropylene cages (six mice per cage) under standard laboratory conditions with controlled temperature (22 ± 2°C), relative humidity (55 ± 10%), and a 12-hour light/dark cycle. Animals had free access to a standard pellet diet and water ad libitum. All procedures were performed in accordance with institutional ethical guidelines for animal care.

This experimental study was conducted at the Institute of Pathology and Diagnostic Medicine, KMU, in collaboration with the Centre for Interdisciplinary Research in Basic Sciences, International Islamic University, Islamabad, and the Department of Pharmacy, COMSATS University, Abbottabad, Pakistan. Gabapentin was purchased from Hilton Pharma Limited, Karachi, and Gabapentsal was acquired from the Department of Pharmacy, COMSATS University, after which its pharmacokinetic profiling was performed at the Centre for Interdisciplinary Research in Basic Sciences, International Islamic University. A total of thirty BALB/c mice were procured from the veterinary research institute, Peshawar. They were divided into five groups, each consisting of six animals, using a simple randomization technique. The control group received 0.2 mL of normal saline, while the treatment groups were administered either gabapentin or gabapentsal, with the dosing of 2.5 mg/ kg or 5 mg/ kg body weight.14 Stock solutions of Gabapentin and Gabapentsal were prepared by dissolving 3 mg of each compound in 3 ml of a 3% Tween 80 solution (a non-ionic surfactant widely used in pre-clinical pharmacological research to facilitate dissolution and uniform dosing of poorly soluble compounds in oral gavage studies). The required doses (2.5 mg/kg and 5 mg/kg) were subsequently calculated based on the individual weight of each mouse (ranging from 25 g to 35 g) and administered via oral gavage using appropriately sized gavage tubes. The treatments were administered once daily for a period of eight weeks. The control group received the same volume of normal saline using the same method.

Mice were anesthetized by the use of chloral hydrate at the end of the treatment period. This was followed by the excision of their liver and kidneys, which were fixed in 10% neutrally buffered formalin for 24 hours. Subsequent to fixation, tissues were reduced into small sections of approximately 1-3 mm thickness before embedding into paraffin. Resulting sections were placed on glass slides and stained with hematoxylin and eosin. The slides were covered with coverslips and examined under an optical bright-field microscope. Histological features were digitally captured using a DSLR camera at magnifications of 20X and 40X.

Ethical approval was obtained from the institutional Ethical Committee, Institute of Pathology & Diagnostic Medicine on 25th Sept 2023, with approval number KMU/IPDM/IEC/2023/17.

Histological Scoring and Blinding:

Histological assessment was performed using a semi-quantitative scoring system evaluating inflammatory cell infiltration, vascular dilatation, cellular degeneration, and architectural distortion. Each parameter was graded on a scale from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Two independent observers, blinded to the treatment groups, performed the scoring, and mean scores were used for statistical analysis.

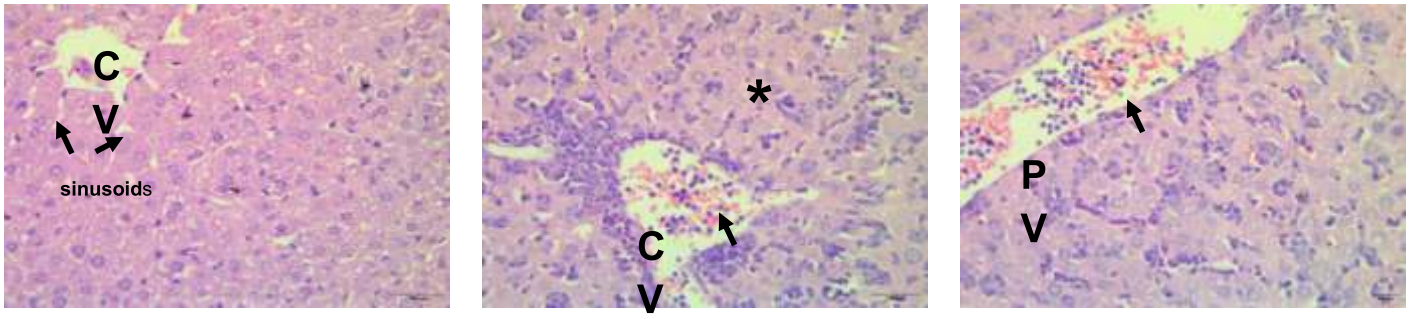
Statistical Analysis

Data were tested for normality using the Shapiro–Wilk test before inferential analysis. As data followed a normal distribution, one-way ANOVA was applied followed by Tukey's post-hoc test for multiple group comparisons. Statistical significance was set at $p < 0.05$.

RESULTS

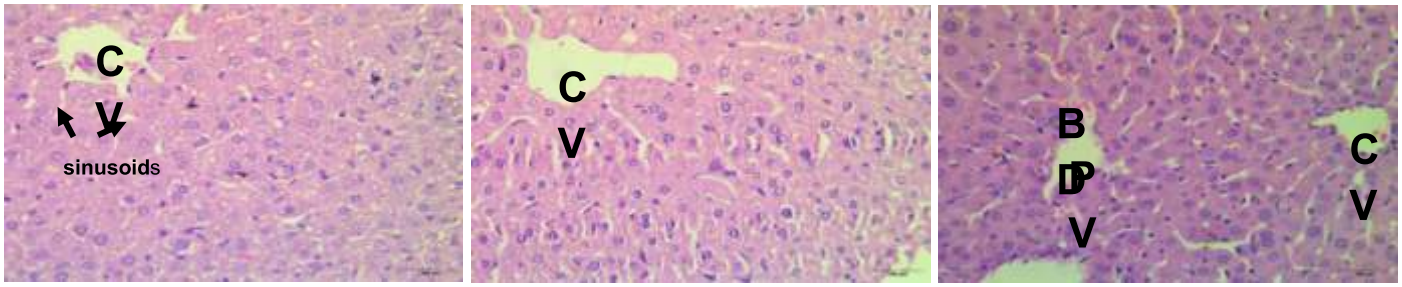
Histological Changes in Liver Tissue

The gabapentin-treated groups (Groups II and III), demonstrated marked histopathological changes in liver tissues, characterized by lobular cellular infiltration, dilatation of the central vein, marked inflammation of portal and periportal areas, hemorrhage, and loss of hepatic architecture (Figure 1B & C). In contrast, the liver tissues of the Gabapentsal-treated groups (Groups IV and V) maintained hepatic architecture intact, with no observable changes in the sinusoids or central vein. Mild lobular and portal/periportal inflammation was, however, noted (Figure 2B & C).



A- Control liver 40x B- Gabapentin 2.5 mg 40x C- Gabapentin 5mg 40x

Figure 1. Effect of Gabapentin on liver tissue. A: Group I (Control), B: Group II (Gabapentin 2.5 mg/kg), C: Group III (Gabapentin 5 mg/kg). Liver tissues from the gabapentin-treated groups showed cellular infiltration, central vein congestion, mild portal inflammation (arrow), and distortion of hepatic architecture (asterisk). Magnification 40X (H&E).



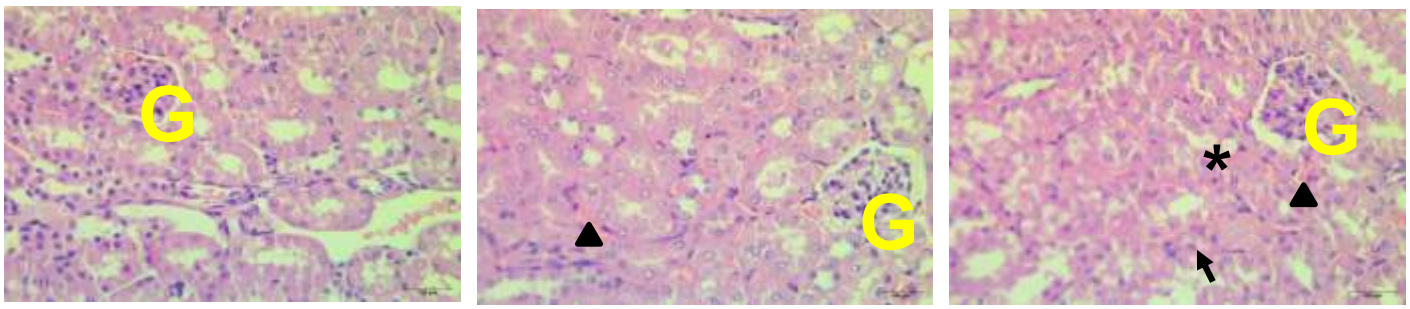
A- Control liver 40x B- Gabapentsal 2.5 mg 40x C- Gabapentsal 5mg 40x

Figure 2. Effect of Gabapentsal on liver tissue. A: Group I (Control), B: Group IV (Gabapentsal 2.5 mg/kg), C: Group V (Gabapentsal 5 mg/kg). Liver tissues from the Gabapentsal 2.5 mg/kg group showed mild portal/periportal inflammation (B), while tissues from the Gabapentsal 5 mg/kg group exhibited mild lobular and portal inflammation (C). Central vein (CV), portal vein (PV), and bile duct (BD) are indicated. Magnification 40X (H&E).

Hepatocyte count, central vein diameter, and granulocyte count were analyzed using Image-J software. As shown in Table 1, hepatocyte counts were markedly reduced in the gabapentin-treated groups compared with the control ($p < 0.001$), whereas the gabapentsal-treated groups exhibited moderate changes, reflecting a weaker statistical difference from the control ($p < 0.05$). The mean central vein diameter increased in the gabapentin-treated groups. In contrast, the gabapentsal-treated groups showed reductions, with a smaller decrease in Group IV ($p < 0.05$) and a more pronounced decrease in Group V ($p < 0.001$). The mean granulocyte count increased markedly in the gabapentin-treated groups, whereas a moderate increase was observed in the gabapentsal-treated groups; all treatment groups differed significantly from the control ($p < 0.001$).

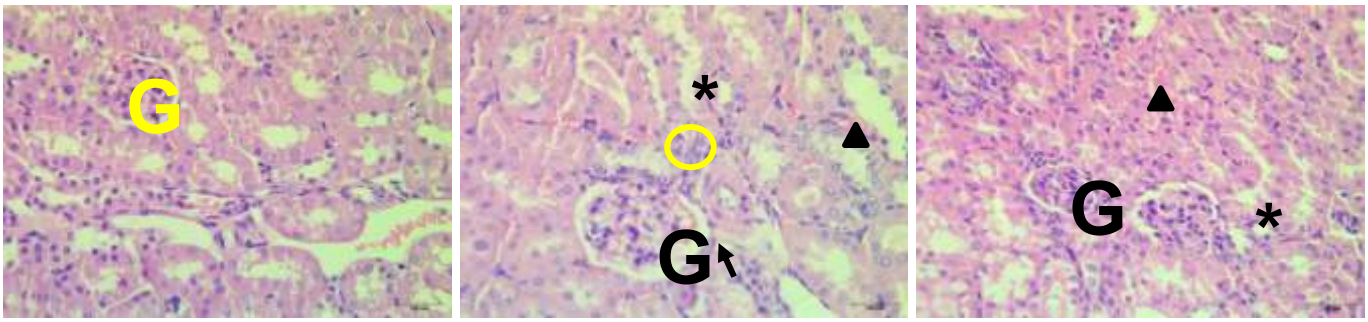
Histological Changes in Kidney Tissue

The kidney tissue of the control group (Group I) exhibited normal histological characteristics. In contrast, the kidney tissues from the gabapentin-treated groups (Groups II and III) demonstrated significant pathological changes, including severe dilatation of the cortical tissue, enlarged glomeruli, dilated blood vessels, and infiltration of inflammatory cells, as illustrated in Figure 3B & C. Conversely, kidney tissues from the gabapentsal-treated groups (Groups IV and V) displayed only mild architectural alterations, including slightly dilated glomeruli and blood vessels, along with mild inflammatory cell infiltration (Figure 4B & C).



A- Control kidney 40x B- Gabapentin 2.5 mg 40x C- Gabapentin 5mg 40x

Figure 3. Effect of Gabapentin on kidney tissue. A: Control, B: Gabapentin 2.5 mg/kg, C: Gabapentin 5 mg/kg. Kidney tissues from the gabapentin-treated groups exhibited cortical dilatation (asterisk), dilated glomeruli (G) with endothelial cell swelling (arrow), and early necrotic changes in the tubules (arrowhead) (B–C). Magnification 40X (H&E).



A- Control kidney 40x B- Gabapentsal 2.5 mg 40x C- Gabapentsal 5mg 40x

Figure 4. Effect of Gabapentsal on kidney tissue. A: Control, B: Gabapentsal 2.5 mg/kg, C: Gabapentsal 5 mg/kg. Kidney tissues from gabapentsal-treated mice exhibited mild architectural alterations, with hemorrhage (arrowhead) among degenerated tubules and inflammatory cell infiltration (circle) (B–C). Magnification 40X (H&E).

Quantitative morphometric analysis was performed using ImageJ software. All values are expressed as mean ± standard deviation (SD). Gabapentin-treated groups exhibited a significant reduction in hepatocyte count and a marked increase in central vein diameter and granulocyte infiltration compared to controls ($p < 0.001$). Gabapentsal-treated groups demonstrated significantly lower histological scores and milder changes ($p < 0.05$ vs control) (Table 1).

Table 1. Comparison of liver and kidney parameters across different groups

Parameter	Group I (Control)	Group II (Gabapentin 2.5 mg/kg)	Group III (Gabapentin 5 mg/kg)	Group IV (Gabapentsal 2.5 mg/kg)	Group V (Gabapentsal 5 mg/kg)	p-value (vs Control)
Liver parameters						
Hepatocyte count (cells/field)	138.0 ± 6.4	91.6 ± 7.2	68.6 ± 5.9	182.0 ± 8.1	152.0 ± 7.5	Group II & III: $p < 0.001$; Group IV & V: $p < 0.05$
Central vein diameter (µm)	608.6 ± 32.4	976.5 ± 41.6	862.1 ± 38.7	570.0 ± 29.1	369.4 ± 24.8	Group II & III: $p < 0.001$; Group IV: $p < 0.05$; Group V: $p < 0.001$
Granulocyte count (cells/field)	40.0 ± 4.3	257.6 ± 15.2	277.6 ± 17.1	82.6 ± 6.8	79.0 ± 6.3	All treatment groups: $p < 0.001$
Kidney parameters						
Glomerular diameter (µm)	783.4 ± 35.6	832.7 ± 41.3	879.9 ± 44.8	674.5 ± 32.1	1014.5 ± 51.2	Group II, III & V: $p < 0.001$; Group IV: $p < 0.05$
Blood vessel dilatation (µm)	347.1 ± 21.5	723.6 ± 38.9	782.1 ± 42.7	573.4 ± 31.6	585.4 ± 34.2	All treatment groups: $p < 0.001$
Granulocyte count (cells/field)	25.0 ± 3.2	78.3 ± 6.1	90.0 ± 7.4	70.0 ± 5.6	83.3 ± 6.8	All treatment groups: $p < 0.001$

Values represent mean measurements. Statistical analysis performed using one-way ANOVA followed by post-hoc Tukey; significance set at $p < 0.05$.

DISCUSSION

The liver and kidneys are quite sensitive to the toxic action of xenobiotics, as they are richly supplied with blood and are involved in the basic biotransformation and excretory processes in the body. Among the various categories of drugs, these are two organs commonly implicated in drug-induced toxicity. Thus, the study of the safety of drugs on these organs is paramount.[15,16]

In the current study, due to prolonged administration of gabapentin, liver tissues exhibited changes like hepatic architecture disruption, inflammation of portal and periportal veins, and dilatation of the central vein. These changes are consistent with the findings of Abdulhussein et al., narrating that prolonged gabapentin exposure may lead to hepatocellular degeneration and inflammatory infiltration. Likewise, effects of vascular and inflammatory alterations have been reported for drug-induced hepatotoxicity.[8] In the current study, gabapentsal-treated mice exhibited preserved hepatic architecture with mild inflammation, relating with evidence where schiff-base derivatives showed reduced systemic toxicity compared to gabapentin.[17]

The dilatation and congestion of sinusoids, central venules, portal veins, and hepatic arteries are the outcomes of inflammation. It is initiated by transient vasoconstriction followed by vasodilatation, mainly through the action of histamine from mast cells and basophils. This increases regional blood flow and overflows downstream capillaries, which become more permeable and allow protein-rich fluid and WBCs into extravascular tissues. RBC concentration consequently increases, reducing blood flow and making circulation slower. This corresponds microscopically to numerous dilated small vessels packed with erythrocytes.[18]

In this study, kidney specimens from gabapentin-treated groups showed severe cortical dilatation, dilated glomeruli, expanded blood vessels, and inflammatory cell infiltration. These findings are in agreement with other studies showing that chronic gabapentin treatment causes significant histological changes in the kidneys.[9]

Moreover, pregabalin, an anticonvulsant drug structurally related to gabapentin, in high doses can also induce renal histological changes characterized by dilated glomeruli, tubular damage and vacuolation.[11] Numerous studies have documented significant histological alterations in the glomeruli and tubules of renal tissue following exposure to various toxic substances.[19-21] The tissue destruction noted in our findings are mainly brought about by inflammatory cells. It is accompanied by repair processes such as blood vessel dilatation, congestion, new vessel proliferation, and fibrosis, which constitute chronic inflammation. This form of inflammation occurs when the acute response cannot be resolved by the persistent injurious agents. It is characterized by the infiltration of mononuclear cells, primarily macrophages, lymphocytes, and plasma cells.[8]

Conversely, gabapentsal produced mild renal morphological changes, as also reported in other studies, which suggest that chemical modification of gabapentin reduces its potential for nephrotoxicity. Moreover, Schiff base derivatives contain an azomethine group (R–C=N) and are known to exhibit various biological activities with low toxicity.[17,22]

This study has certain limitations. Biochemical markers of hepatic and renal function were not assessed, which could have provided additional functional correlation to the histological findings. The study was limited to a single animal species and a fixed treatment duration; therefore, dose-response relationships and long-term toxicity profiles require further investigation. Future studies incorporating molecular and oxidative stress markers are warranted to elucidate better the mechanistic basis of the observed histological changes.

CONCLUSION

This study demonstrates that prolonged gabapentin administration produces pronounced histopathological damage in hepatic and renal tissues, including inflammatory infiltration, vascular dilatation, and disruption of normal architecture. In contrast, gabapentsal induced only mild structural alterations with largely preserved liver and kidney morphology, even at higher doses. These findings indicate that gabapentsal has a comparatively safer hepatic and renal toxicity profile than gabapentin following chronic exposure.

RECOMMENDATIONS:

Further studies should incorporate biochemical markers of liver and kidney function to corroborate the histological findings. Mechanistic investigations are recommended to elucidate the pathways responsible for the reduced toxicity of gabapentsal. Long-term and dose-escalation studies, as well as comparative efficacy evaluations, are warranted to better define its safety margin. Additionally, translational and clinical studies should be considered to assess the therapeutic applicability of gabapentsal as a safer alternative for long-term management of neuropathic disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this publication

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C.Manuscript writing
D.Critical Review and approval
All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved