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PART 1:

Journal Name:	British Journal of Medicine and Medical Research
Manuscript Number:	**MS: 2012/BJMMR/2065**
Title of the Manuscript:	**A HISTOLOGICAL STUDY OF THE HEPATIC AND RENAL EFFECTS OF SUBCHRONIC, LOW DOSE ORAL MONOSODIUM GLUTAMATE IN SWISS ALBINO MICE.**

General guideline: Reviewers are requested to follow these guidelines during review: *(Note: Title of different sections as proposed below may differ in case of review paper / case reports)*

- Introduction *(Is the problem/objective of this study original, important and well defined?)*
- Materials & methods *(Kindly comment on the suitability of the methods. Sufficient details of the methods should be provided to allow peers to evaluate and/or replicate the work)*
- Results & discussion (Kindly comment on: 1. Are the data well controlled and robust? 2. Authors should provide relevant references during discussion. 3. Discussion and conclusions should be based on actual facts and figures. Biased claims should be pointed out. 4. Are statistical analyses must for this paper? If yes, have sufficient and appropriate statistical analyses been carried out?)
- Conclusion (Is the conclusion supported by the data, discussed inside the manuscript? Conclusions should not be biased and should be based on the data, presented inside the manuscript only)
- Are all the references cited relevant, adequate? Are there any other suitable current references authors need to cite?
- This form has total 9 parts. Kindly note that you should use all the parts of this review form.

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PART 2: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part and write here 'Corrected'/ if not agreed, give suitable justifications)*
COMPULSORY REVISION comments	**ABSTRACT:** This needed substantial revision. Remember, this particular Journal allows you up to 300 words, and your submitted Abstract was just over 200. The Abstract is often the most important part of your manuscript, especially if Readers cannot access the rest of the article, so make your Abstract carry as much relevant information as you can squeeze into the allotted word limit. Importantly, please cite previous data relevant to your current study, and this would be the work of Nakanishi *et al* (2008). In the Results section, it is better to begin with the most important statistically significant data that you have, and save non-significant trends for last. I have provided a suggestion for the revised Abstract which is just under 300 words long.	

	Suggested Revised ABSTRACT Previous studies have shown that exposure to large doses of monosodium glutamate (MSG) during the neonatal period may result in steatohepatitis and indications of pre-neoplastic changes in the liver. However, the effect of low dose, chronic oral MSG intake on the histology of the liver and kidneys have not been addressed to date. Our aim was to determine whether MSG consumption at these doses is associated with histological evidence of hepatic or renal injuries. Forty adult Swiss albino mice weighing between 20-25 mg were assigned into 4 groups A, B, C and D. Group A served as control and received normal saline while groups B, C and D received MSG daily at 0.5, 1.0 and 1.5 mg MSG /kg body weight (BW) dissolved in normal saline respectively for 28 days. On day 29 of the study animals were sacrificed, and the liver and kidneys were removed, weighed and processed for histological examination. Statistical analysis was by one way ANOVA followed by a posthoc test,	

	and results were expressed as mean ±S.E.M. Results: MSG consumption resulted in a significant increase in the relative liver weight at 1.0 and 1.5 mg MSG /Kg BW, and a relative increase in kidney weight occurring at 1.5 mg/Kg BW ($P<0.05$). This was accompanied by a dose-dependent increase in body weight compared to control which failed to reach statistical significance. Liver and kidney histology indicated a loss of normal liver architecture with varying degrees of disorganization and apoptotic cell death compared to controls. The kidneys of MSG-exposed mice exhibited contraction of the renal glomerulus and thickening of the walls of the renal tubules. The study provides evidence that oral consumption of MSG at doses within the Acceptable Daily Intake (ADI) may promote hepatic and renal injuries. *(291 words).* **INTRODUCTION** :The Introduction is long, and in parts, irrelevant. It therefore requires revision. Write only what is necessary for the Reader to	

	understand the relevant context of your current study. After all, you are not writing a Review of the History of MSG research from the early 1970s onwards, you are writing about your experiments on chronic oral intake of MSG on rodent kidney and liver. It is OK to begin with a brief description of what MSG is, and relevant data on estimates of MSG intake. This should be followed by a description of what is already known about the effects of acute doses of large amounts of MSG neonatally on the liver and kidneys. It is essential to include the elegant work of Nakanishi *et al* (J Autoimmunity, 2008). Also of essential relevance is the recent work on chronic low-dose MSG intake on the pancreas, since the authors used roughly similar doses to your present study and found histological evidence of pancreatic damage (Leshchenko et al 2012). Your Introduction would be greatly enhanced by a brief explanation of some of the mechanism responsible for the effects previously observed. This would be far more relevant than describing in detail the	

	neurological effects on the retina and impaired memory which are not particularly relevant to the present study. I have provided a suggestion for the revised Introduction which is just under 500 words long. Please note several sentences from your Original submission have been removed, and two more references have been suggested. INTRODUCTION: Monosodium glutamate (MSG) is a naturally occurring sodium salt of glutamic acid which was initially synthesized from wheat gluten but now produced in commercial quantities by bacterial fermentation (Leung and Foster, 2003). MSG is found in some quantity in many natural food substances and as either an additive and flavor enhancer in many commercially packed food products. MSG is used in both home and restaurant cooking and it is a common component of Asian diets (Walker and Lupien, 2000). The unique flavor and taste of this compound has been categorized and established as a separate taste sensation "*umami*" taste (Ikeda, 1909). It is	

	marketed in Nigeria as *Ajinomoto*, other trade names include: Vetsin, Accent and Tasting powder. MSG is composed of white colorless odorless crystals that exist in two forms called enantiomers although only the L forms are used as flavouring agents (Leung and Foster, 2003).The liver plays an important role in the metabolism of glutamate, some glutamate is converted here into lactate while the kidney takes part in its elimination although some MSG is metabolized by conversion into alanine in the intestinal mucosa (Garattiini, 2000). Daily dietary composition of glutamate varies from one race to another, however daily oral consumption ranges from 0.5 mg/kg amongst Americans and over 3g/kg in Taiwanese diets (Zhou *et al.*, 2003; He *et al.*, 2008; Shi *et al.*, 2010), the quantity of MSG consumed by Nigerians we believe would fall somewhere between 1-2.5 g/day. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluation in 1987 declared L-glutamate safe by arriving at an	

	"Acceptable Daily Intake (ADI) not specified" this was also reaffirmed in 2004 (JECFA, 1987; JECFA, 2004). Previous studies by Nakanishi et al (2008) have shown that exposure to large doses of monosodium glutamate (MSG) during the neonatal period may result in steatohepatitis and indications of pre-neoplastic changes in the liver. This study used relatively large doses of MSG administered during the neonatal period, when the blood-brain-barrier is immature and vulnerable to excitotoxic damage by glutamate (add reference by Olney, 1971). More recently, chronic exposure to low-dose MSG has been shown to result in damage to the pancreatic structures including necrotic, necrobiotic and degenerative changes to pancreatic exocrine and endocrine cells (Leshchenko *et al* 2012). During an earlier study on the neurobehavioural effects of MSG(Onaolapo and Onaolapo, 2011), some histological changes were noticed in the liver and kidneys of some of the animals randomly selected	

	necessitating a full evaluation of its effect on liver and kidney microanatomy at doses well below those known to be toxic. MATERIALS AND METHODS: This is good. The suitability of the methods are correct. Please state whether the dosage of MSG refers to mg/Kg body weight, or mg/Kg saline solution (w/w). RESULTS: The Results section provide data that is well controlled and robust, and the analysis is sound. However a suggestion is to put the statistically significant data on relative liver and kidney weight before the non-significant body weight data. Sadly, this Reviewer was unable to see the histological figures (plates 1-4), and these will have to be included in the revised manuscript. DISCUSSION AND CONCLUSION: The Discussion is appropriate, relevant and non-biased and the Conclusion is supported by the results provided, however the Conclusion would	

	benefit from some revision. A suitable suggestion would be the following: CONCLUSION: This study suggests that continuous consumption of MSG in the dosage range tested herein may result in varying degrees of liver and kidney injury, depending on the concentration administered. It is important to note that the amount of MSG used in many previously published studies were very high, in contrast to the present study which showed evidence of organ injury at relatively lower doses administered chronically over a period of time. Our data suggests that further research is warranted to examine the safety profile of this widely used food additive.	

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Minor REVISION comments	RESULTS: The Results section provide data that is well controlled and robust, and the analysis is sound. However a suggestion is to put the statistically significant data on relative liver and kidney weight before the non-significant body weight data.	
Optional/General comments		

Note: Anonymous Reviewer