SDI Review Form 1.6

Journal Name:	**International Journal of Biochemistry Research & Review**
Manuscript Number:	**2014_IJBcRR_13913**
Title of the Manuscript:	**A REVIEW ON EFFECTS OF HEAVY METAL TOXICITY ON HEALTH OF AUTISTIC POPULATION**
Type of the Article	**Review Article**

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.
To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline)

SDI Review Form 1.6

PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments	**I think the first thing that has to be considered when evaluating whether a particular metal may play a causative role in the recent surge in autism is to see whether environmental exposures to that metal are increasing in step with the increase in autism. This consideration pretty much rules out lead, even though lead is neurotoxic, because of the widespread adoption of unleaded gasoline. When you look at the authors' Figure 2, what jumps out is the very high levels of aluminum (5-fold higher than the next highest element, which was lead), yet the authors have dismissed aluminum out of hand. A recent paper investigating various chemical exposures and their relationship to autism narrowed the choices down to three in particular that were on the rise in the environment in recent decades: aluminum, glyphosate (the active ingredient in the pervasive herbicide, Roundup) and flame retardants.** **See: Cynthia Nevison. A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors. Environmental Health 2014, 13:73** **Of these, aluminum is the only one that is a metal, but it seems apparent to me that aluminum is a top candidate for toxicity associated with autism, in part because of its clear recent increase in pervasiveness.**	Thanks for constructive feedback. As per your guidance, we will make necessary amendment in revised paper.

	This is particularly striking because the experiment at the turn of the century where the mercury content in vaccines was reduced failed to show a subsequent decrease in autism. In fact, the rates continued to rise following this intervention. The reason may well be because the aluminum burden in vaccines was simultaneously increased. There are many papers in the research literature now describing the neurotoxicity of aluminum and the potential role it plays in autism. Particularly striking is the link between aluminum contamination in parenteral nutrition in premies associated with a striking increase in autism in this population. **See:** **C.A. Shaw and L. Tomljenovic. Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity. Immunol Res 2013 Jul;56(2-3):304-16.** **Tomljenovic L1, Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? J Inorg Biochem. 2011 Nov;105(11):1489-99.** **S Seneff, R Davidson, and JJ Liu. Empirical Data Confirm Autism Symptoms Related to Aluminum and Acetaminophen Exposure Entropy 2012, 14, 2227-2253.** **The topic of mineral deficiencies is important, as several links have been found in association with autism, as you rightly point out. These include zinc, iron, cobalt (cobalamin), and possibly manganese. Manganese is particularly interesting because it is involved in glutamate detoxification and in**	

	protection from oxidative damage in the mitochondria, and these are key pathologies in autism. So it would be good to mention manganese deficiency as a possible contributor. You might also mention selenium and sulfur as being deficient in autism, and being important for detoxification. **I'd suggest a major reorganization of the paper. I'd begin with a discussion of which metals might plausibly be involved in the autism epidemic by considering the environmental exposure trends, therefore pointing to aluminum as a clear candidate and referencing the Nevison paper. You can also explain the experiment with mercury being phased out in vaccines while aluminum was phased in, explaining why removing mercury didn't help, and therefore keeping mercury as a candidate for inducing autism. You can also reference this paper which shows that HEP-B given at birth is a risk factor for autism. HEP-B contains aluminum, so this is supportive of the aluminum connection.** **See:** **Gallagher CM1, Goodman MS. Hepatitis B vaccination of male neonates and autism diagnosis, NHIS 1997-2002. J Toxicol Environ Health A. 2010;73(24):1665-77.** **You can also put all your materials on mercury in this section. Even though mercury has been phased out of vaccines, it is still commonly used in dental amalgams, and it is very clearly neurotoxic.** **The next section could be on hair analyses. You have talked about these in various places, sometimes**	

	mentioning excess content of a particular metal and sometimes mentioning a DECREASE in association with autism. This becomes very confusing to the reader. I think you need to get into the issue of the complications in hair analyses due to the child's potentially impaired ability to detox metals by exporting them in hair. Hair analyses will show excesses when there is both an increased burden and a functioning system for export into hair. But if the child is defective in export (which could easily be due to a vitamin D deficiency and elevated parathyroid hormone) then an excess burden may not show up in hair, and a DECREASE in hair content may be an indication of retention of the metal in the brain. **You could follow with a section on mineral deficiencies, pointing to the literature that supports zinc and iron deficiency, and newly arguing that manganese deficiency may be an issue given the manganese superoxide dismutase link in the mitochondria and the glutamine synthase link connecting to excess glutamate, a known risk factor in autism. You can discuss here the issue that an imbalance between important biologically relevant minerals and toxic metal competitors may be a factor here (for example, aluminum displacing iron in heme).** **You should omit the paragraph discussing MMR and Dr. Andrew Wakefield. This is irrelevant to your work because MMR contains neither mercury nor aluminum. You can preserve the part in this paragraph about professional ethics but migrate it into the earlier section that is mainly on aluminum and mercury.**	

	Your title currently contains the word "heavy", and aluminum is not a heavy metal. This might give you an excuse to leave it out, but that is like leaving out the elephant in the room. I'd suggest a change in the title of the paper to: A review of the potential roles of metal toxicity and mineral deficiency in autism.	
Minor REVISION comments	You consistently spell thimerosal wrong (as thiomersal). Autistic Spectrum Disorder --> Autism Spectrum Disorder. This paper will need editing from a native speaker of English once it is revised in content and organization.	
Optional/General comments	This paper proposes that toxic metals, particularly heavy metals, along with mineral deficiencies, may be causal in autism, and it provides a review of the literature to support the claim. While I agree with the general claim, the paper needs significant modifications both in organization and in content before I will consider it suitable for publication.	

SDI Review Form 1.6