Dietary Intakes Influence on Metallomic Distribution in Vital Organs and Their Implications

Solomon W. Leung[1], Brad Williams[2] and James C. Lai[3]
[1]*Civil and Environmental Engineering Department and Measurement and Control Research Center, Idaho State University, Pocatello, Idaho, 83209, USA*
[2]*Civil and Environmental Engineering Department, Idaho State University, Pocatello, Idaho, 83209, USA*
[3]*Biomedical and Pharmaceutical Sciences Department, Idaho State University, Pocatello, ID 82309 USA*

Keywords: Elements Distribution, Mn, Nutrition Intake, Vital Organs

Abstract: The intake and concentration of metals and electrolytes in our diet are believed to be affecting our general health, in particular, the proper functions of vital organs. For example, in addition to other genetic and environmental factors, consuming water with high alkalinity for a prolonged time is suspected of leading to diseases such as kidney stones. There is evidence that elemental accumulation due to excessive metal intakes would lead to organ failure. This study is an extensive investigation of metallomic distribution in Wistar Rats after they have consumed 30 different elements (including heavy metals and electrolytes) via dietary intakes throughout their lifespan (from 5 to 750 days). In this study, the distributions of these elements in various vital organs such as heart, kidney, lung, spleen, liver, pituitary, and uterus over time were analyzed. In addition, how heavy metal supplement, such as Mn, influenced the elemental accumulations inside the organs was also conducted. This study has high impact to our understanding of how the environment would affect our well beings. This study would provide insights on how our diet would affect the accumulations of unwanted elements, such as heavy metals, in our vital organs. The results may also help researchers and health practitioner to identify possible links between daily diet and associated diseases inside the vital organs.

1 INTRODUCTION

Since the era of industrial evolution, living conditions for human have improved drastically; with the consequence of better living conditions and less physical activities, we are facing other aspects of health issues such as obesity and hyper immunity responses (allergy). In modern living, considerable attention has been paid to dietary intake or supplement due to health concerns. On the other hand, involuntarily consumption of unwanted chemicals and preservatives via processed foods and polluted water is also possible. One such example would be consumption of drinking water source that is laden with soluble ions and heavy metals. This occurs quite frequently for those that are living in rural areas with no proper treatment system for their drinking water in developing countries.

Attempts in understanding the homeostasis of different elements in brain and other major organs fell short significantly due to the vast complexity of the mechanisms involved (Pardridge, 2003). What cause this complexity are the multiple factors that can affect the dynamics of biological functions. For examples, an element of different compounds (chloride versus phosphate) would have various uptake rates (Anderson et al., 2008) and the uptake rate of elements in solution by the digestive system was proven to be faster than in food stuffs. Elemental accumulations are not solely related to exposure but likely have more to do with impairment of the relevant homeostasis mechanism (Bolognin et al., 2009); conversely, a known Cu deficient sample of mice were able to be revised by supplementation of Cu in drinking water (Bayer et al., 2003). In addition, larger sample size is needed to observe statistical significance in the small changes over lifetime exposure (Maynard et al., 2009). Such constraint creates a vast financial and operational obstacle to conduct research, and the hurdle is more difficult if human subject is involved.

Currently, the understanding of homeostasis mechanisms for accumulation and control of individual element in our body is very limited,

W. Leung, S., Williams, B. and C. Lai, J.
Dietary Intakes Influence on Metallomic Distribution in Vital Organs and Their Implications.
DOI: 10.5220/0008654100300036
In *Proceedings of the International Conference on Future Environment Pollution and Prevention (ICFEPP 2019)*, pages 30-36
ISBN: 978-989-758-394-0

hence, the influence of similar elements to each other is practically non-existent. However, the result of Zn replacing Cu in a competitive homeostasis mechanism in rat's brain was recently reported by Maynard et al. (2009). Therefore, it can be concluded that our understanding of elemental homeostasis mechanisms in our body systems is still in the beginning stage, and the opportunities for more research and development are immensely available.

There are chemicals (vitamins, for example) and elements and trace elements that we need to maintain proper bodily functions; in this study, we focused on the essence of major and selected trace elements and how these elements accumulated in our major organs. The major organs are: heart, kidney, lung, spleen, liver, pituitary, and uterus. Information matrices of these 30 different elements (including heavy metals and some electrolytes) that were fed to rats as part of a regular diet were obtained from the seven major organs and analyzed. Furthermore, we fed the rats with various concentrations of Mn (as a surrogate of heavy metal) and observed how these 30 elemental accumulations in the vital organs were affected by the different consumptions of Mn in the diet as an adult (120 days).

2 EXPERIMENTS AND PROCEDURES

The 30 elements included in this study were: Al, As, Ba, Br, Ca, Cd, Cl, Co, Cr, Cu, F, Fe, Hg, I, K, La, Mg, Mn, Mo, Na, Rb, S, Sb, Sc, Se, Si, Sm, Sr, V, and Zn. Analytical measurements of the elements from the organs of adult (120 days) Wistar rats and diet pellets that were used to feed the rats were reported in a previous paper (Wright et al.). Table 1 lists the elements of the rat food pellet detectable by Instrumental Neutron Activation Analysis (INAA), elements that were from the 30 interested elements but not listed in Table 1 were not detectable by INAA due to low concentration. All values listed are means ± standard deviations of the 20 detectable elements. ND indicates not detectable, and values in brackets are the maximum elemental concentrations present in the pellet diet.

The main analysis for this paper is to compare elemental accumulations in the said organs above in relations to control adult rats and Mn-treated adult rats. The Mn dosages of control and three different adult groups are listed as follows:

1. Control samples taken from 120- days-old adult female Wistar Rat.
2. Group A adult with life-long manganese treatment with 1 mg/ml $MnCl_2 \cdot 4H_2O$ in drinking water.
3. Group B adult with life-long manganese treatment with 10 mg/ml $MnCl_2 \cdot 4H_2O$ in drinking water.
4. Group C adult with life-long manganese treatment with 20 mg/ml $MnCl_2 \cdot 4H_2O$ in drinking water.

Table 1: Elemental concentration of rat food pellet

Element		Concentration	
Ca	mg /g	6.393	1.68
Cl	mg /g	2.305	0.485
Fe	mg /g	0.25	0.051
K	mg /g	5.362	0.951
Mg	mg /g	1.168	0.322
Na	mg /g	1.475	0.32
Al	µg /g	98.06	8.05
Br	µg /g	10.57	2.26
Co	µg /g	0.2	0.04
Cr	µg /g	1.5	0.44
Cu	µg /g	7.21	2.12
Fe	µg /g	ND(5.0)	
Hg	µg /g	ND(.25)	
I	µg /g	ND(.5)	
Mn	µg /g	49.34	8.65
Mo	µg /g	2.8	0.45
Se	µg /g	ND(.25)	
Rb	µg /g	12.73	2.61
V	µg /g	ND(.5)	
Zn	µg /g	47.73	4.11

3 RESULTS

3.1 Heart

Mercury (Hg) is most drastically impacted by Mn treatment. Hg content has increased about 18 times from the control concentration. Along with the increase in Hg, there is higher Hg concentration with higher dosages of Mn treatment. Hg concentration

in the heart is showing an impact with prolonged Mn intake. Molybdenum (Mo) also had a large increase in concentration from control levels. An interesting effect is with Calcium (Ca). From the A dosage level Ca increased almost 100% but then on the B dosage level Ca slightly decreased. Then Ca increased again on the C dosage level.

The impact of Mn on Hg is an important point to highlight. Mn has been known to be present in drinking water and also used to treat drinking water that would lead to Mn ingestion. There are known harmful elements that will greatly increase in accumulation in the body by Mn ingestion. Increased Hg in the heart is a concern also because Hg is a well-known neurotoxin. Its impact on the heart directly may not be clear but there are other known adverse effects on the brain, nervous system, and kidneys.

In general, above normal elemental accumulation in the heart can lead to functional loss or heart failure. The risk of heart failure by increased accumulation of heavy metal in itself is worth additional study and investigation. From this analysis, increases in heavy metal's presence that are induced by Hg may contribute to heart failure.

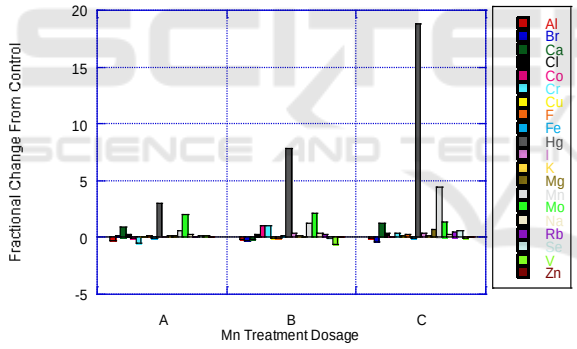

Figure 1: Results of heart with Mn treatment for Group A, B, and C as compared with control.

3.2 Kidney

For Mn treatment, the kidney showed increases in Mn but also showed decreases in V. Mo increased for treatment dosage A but then decreased to treatment dosage C. Cobalt (Co) showed an increase on treatment dosage B but very little change for A and C. Chlorine (Cl) increased with increased Mn. Cl reached nearly a 100% increase for treatment dosage C. Mn impacts electrolyte's balance.

The observations worthy of discussion are that Mo showed an increase of over 100% by introducing Mn at the dosage level A. But then as dosage levels increase the amount of change for Mo decreases. This suggests a competition mechanism between Mn and Mo for retention or accumulation in the kidney.

Very few elements showed decrease in accumulation due to Mn treatment. This would suggest that Mn increases accumulation of the majority of the elements in the kidney. Also similar to Mo, the lower dosage of group A had the least amount of decrease in accumulation from control for all the elements. Then with increased Mn intake, the elemental accumulation either increases or decreased more than those obtained with the lower Mn dosage. This suggests that Mn has a concentration-related impact on accumulation.

The kidney controls electrolyte balance to collect or accumulate excessive levels of different elements that may be present in the body. By introducing Mn treatment, this also increases the overall elemental accumulation compared to other organs. Next step analysis would be a mass balance and how well the kidney flushes elevated concentrations from the body.

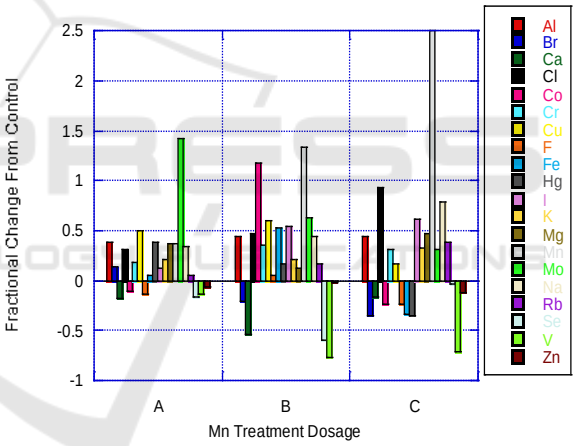

Figure 2: Results of kidney with Mn treatment for Group A, B, and C as compared with control.

3.3 Lung

For the lung, Hg also shows significant increase from control. Treatment dosage B showed the highest Hg levels but dosage C induced almost a 300% increase. Many elements showed at or above 50% increase for the highest Mn dosage with all of them becoming increasingly concentrated with increased Mn dosage. Mn treatment shows evidence that there is a wide range of elements that have concentration impacts related to Mn.

Mn ingested by diet has a very large impact on elemental accumulation of the lungs. This relationship is extremely important because one of

the most common methods of exposure and intake is by the lungs and breathing air. From this data set, a link to practical use is that an increased Mn intake may allow the subject to be at higher risk for toxic elemental accumulation in the lungs that could lead to illness and other health concerns.

This data shows effect via ingestion then through the blood to the lungs which is different than most studies that look at inhalation and the accumulation by inhalation. What is shown by this analysis is that orally ingested Mn can increase the accumulation of elements ingested orally. For further investigation, the relationship between orally ingested Mn and the accumulation of elemental exposure by inhalation would be important. Miners and similar type of industrial workers are often exposed to highly elevated inhalation of different elements. This link between orally ingested Mn and elemental exposure by inhalation could greatly impact mining personnel protective equipment and medical treatment of miners. Current exposure limits are debatable and may need to be adjusted with consideration of possible Mn ingestion.

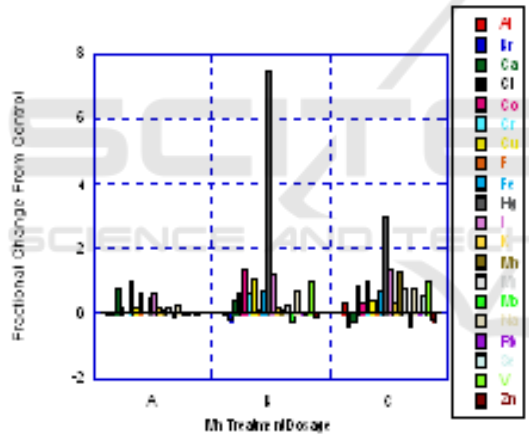

Figure 3: Results of lung with Mn treatment for Group A, B, and C as compared with control.

3.4 Spleen

Mn shows increased concentration compared to control for increased Mn dosages indicating a possible correlation. V has drastic variations going from nearly 75% less than control to nearly 3 times the control value. Co shows an increased concentration for only one dosage but almost no change for the other dosage treatments. Iron (Fe) shows elevated concentration for dosage A and then decreases to negative values for the largest Mn dosage.

The fractional change from control is very sporadic with the spleen. At one dosage level a particular element will show an increase and then at a different dosage show a decrease. Cr is one element that at the small Mn dosage shows a large increase but with increased Mn the fractional change of Cr goes negative. At a low dosage more Cr is accumulated and at a high dosage less Cr is accumulated. This suggests that starting with low Mn treatment creates a mechanism allowing more Cr to accumulate. Then as Mn increases it competes with and displaces Cr to levels even below the control.

In the case of Cu, treatment with Mn reduces accumulation. The reduced accumulation is relatively the same at all three Mn concentrations. This suggests that Cu has an interaction with Mn but is not correlated to Mn dosage concentration.

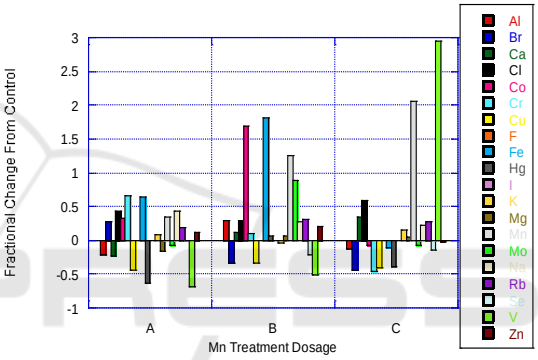

Figure 4: Results of spleen with Mn treatment for Group A, B, and C as compared with control.

3.5 Liver

The liver is not showing any individual elements that have drastic increases as compared to organs discussed in previous sections. Of all the elements there are only five that show greater than a 50% change and only one element that shows over a 100% change. Cr shows an increasing trend that relates to increased Mn dosage. Decreases in Rubidium (Rb) and Iodine (I) were not observed in previous organs as with the liver.

In comparison to the spleen, Cr in the liver increases with increased Mn as opposed to the spleen where Cr was observed to decrease with increased Mn. This observation may suggest a relationship between increasing accumulation in the liver and decreasing accumulation in the spleen. An observation that has not been seen on previous organs is with I. Iodine starts out with negative accumulation at the lower Mn dosage. As Mn dosage increases, Iodine fractional change becomes

less. This suggests a mechanism that has the most impact at lower dosage and then has less impact as Mn dosages increase.

Another observation is that as Mn dosage increases, more elements trend to a negative accumulation. For unwanted or toxic elements, an increased Mn dosage treatment reduces the accumulation in the liver. As discussed with results obtained with the kidney, the liver serves a similar function in detoxification. This data supports that increased Mn treatment provides for less accumulation in the liver. There could be at least two possible mechanisms. First is that increased Mn treatment increases accumulation in other organs so that the element is not available to accumulate in the liver. A second possibility is that Mn treatment improves the liver's ability to filter out or flush away unwanted elements.

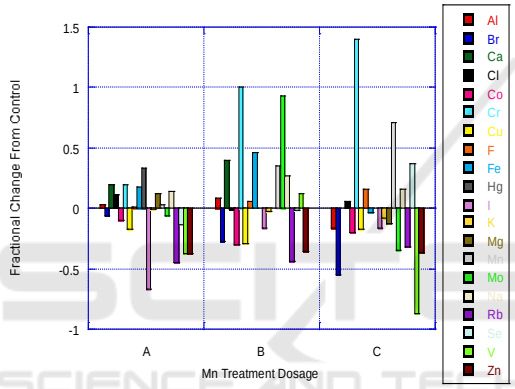

Figure 5: Results of liver with Mn treatment for Group A, B, and C as compared with control.

3.6 Pituitary

The pituitary shows an interesting trend that for each treatment, the amount of change from control is relatively the same. The same elements that show increases show nearly the same increase for each dosage treatment. Then for the elements that show a decrease, maintain similar decreases cross the dosage treatments.

In the pituitary, Mn treatment has a baseline impact that is unrelated to Mn dosage level. The presence of Mn has an impact but the concentration of Mn dosage has little impact. . As overall more elements have a negative impact for dosage treatments in groups B and C compared to A. The pituitary is not significantly impacted by Mn treatment compared to other organs likely due to the effect of the blood brain barrier.

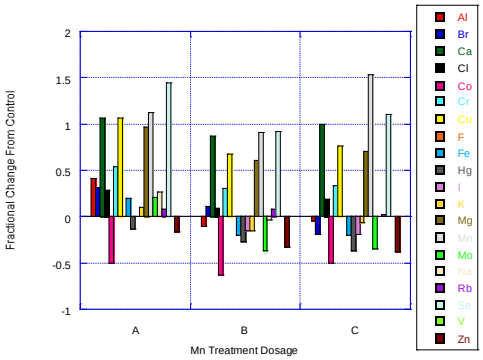

Figure 6: Results of pituitary with Mn treatment for Group A, B, and C as compared with control.

3.6 Uterus

The uterus shows more concentration decreases than increases. Co, Cr and Cu show the most significant increases. V, Fe and F show the most significant decreases. For most elements, Mn decreases accumulation. The large increases in heavy metals (e.g. Co, Cr, and Cu) should be a signal for more detailed investigation. The uterus is the key organ in reproduction and significant accumulations can have a detrimental impact on birth defects and maternally associated diseases. As an overall observation, increased Mn may be used to reduce elemental accumulation in the uterus as well.

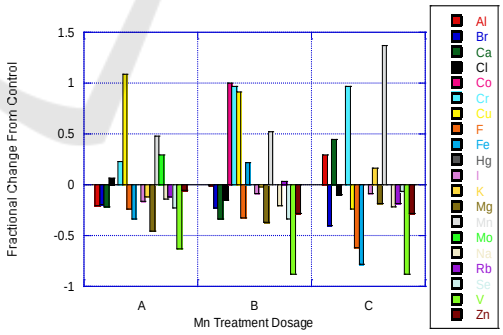

Figure 7: Results of Uterus with Mn treatment for Group A, B, and C as compared with control.

4 DISCUSSIONS

Each organ has different characteristics as indicated by some showing overall accumulating concentrations and some showing overall

diminishing concentrations, and others showing mixed trends with increasing elemental concentrations and decreasing elemental concentrations. In a few instances, there were some elements that showed a possible correlation with Mn dosage. Both increasing concentrations with increased Mn dosage and decreasing with increasing Mn dosage were present suggesting positive and negative correlations.

Three main observations can be concluded from this analysis:

4.1 Elements Showing Increases

In most cases, treatment with Mn showed increased elemental accumulation. Elements showing accumulation in at least four organs are: Ca, Mg, Co, Cr, Cu, Mo, and Se. In this group of elements, there are some elements with known impacts on human health and degenerative diseases (e.g., Cu related to Alzheimer's and Parkinson's diseases). The findings emphasize the importance of more extensive studies where Mn may have been used in applications that may have increased human ingestion such as treatment of drinking water.

Elements showing accumulation in two or fewer organs are: F, K, Na, Br, Hg, I, Rb, V, and Zn. Even though accumulation was shown for this group of elements, only certain organs displayed accumulation. This is important to help identify elements that may have more complicated homeostatic mechanisms and are more selective to individual organs. In this group, there also are elements with known health impacts.

4.2 Elements Showing Increases

The liver and uterus show more overall decreased elemental concentrations. The spleen and pituitary also had several elements that decreased in elemental concentration with Mn treatment. Elements that show decreasing concentrations in three or more organs are: Br, Hg, Se, V, and Zn. Elements that show decreased concentration in one organ are: Cl, Fe, K, Mg, Na, Al, Cr, Fe, I, and Rb. Overall, more elements showed increased concentrations or accumulation due to Mn treatment than elements that showed decreased concentrations.

4.3 Overall Accumulating, Diminishing, and Mixed

The organs that showed decreasing elemental concentrations were the liver and uterus. The uterus, showing a decrease in overall concentration, may provide a link to the impact of Mn exposure and possible birth defects. The liver, showing decreased concentrations, may have two possible impacts. First is the possibility that the elements are being excreted from the body. This may be a positive impact in regard to applications that would need to reduce the concentration of a particular toxin in the body. The second possible result in the liver showing reduced elemental concentrations is that the function of the liver is being reduced and therefore is not pulling contaminants from the body.

5 CONCLUSIONS

From the literature search listed in this study, it is evident there are many focused and detailed studies showing the health impacts due to increased elemental concentrations of particular elements. One study identified Cu, Zn, Fe, and Mn are essential for normal brain function, but also show that above normal concentrations may lead to no detectable (ND) symptoms. In this study, we found the concentration of Cu is increasing in many organs due to Mn treatments. In an evaluation of all brain data, Cu decreases by 100% from adult control (AC) to old control (OC) rats (Wright et al.).

The treatment of Mn could be beneficial in some cases and detrimental in other cases. An increase in Cu concentration (≈ 10%) in the brain may be beneficial but an increase in Hg in the heart (≈ 1500%) may be detrimental to humans. This data set will provide a key piece in understanding human health effects due to elevated elemental (i.e., heavy metal) ingestion over the full life span.

The fact that there is hardly any information available regarding elemental accumulation in organs such as spleen, pituitary, and uterus makes this massive collective study ever more valuable.

ACKNOWLEDGEMENTS

We want to acknowledge that Dr. Thomas K.C. Leung, Institute of Molecular and Cell Biology, Proteos, Singapore for his contributions in collecting and organizing the data, and Professor Margret Minsky, University of London for organizing and conducting the elemental analyses.

REFERENCES

Anderson, J.G., Fordahl, S.C., Cooney, P.T., Weaver, T.L., Colyer, C.L., Erikson, K.M., 2008, Manganese exposure alters extracellular GABA, GABA receptor

and transporter protein and mRNA levels in the developing rat brain, *Neurotoxicology*, Vol. 29, pp. 1044-1053.

Bayer ,T.A., Schafer, S., Simons ,A., Kemmling, A., Kamer, T., Tepest, R., Eckert ,A., Schussel, K., Eikenberg, O., Sturchler-Pierrat ,C., Abramowski, D., Staufenbiel ,M., Multhaup, G., 2003, Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid Abeta production in APP23 transgenic mice, *Proc Natl Acad Sci USA*, Vol. 100, pp. 14187–14192.

Bolognin, S, Messori, L, Zatta, P., 2009, Metal Ion Physiopathology in Neurodegenerative Disorders, *Neuromoloecular Medicing*, Vol. 11, pp. 223-238.

Maynard, C.J., Cappai, R., Volitakis, I., Laughton, K.M., Masters, C.L., Bush, A.I., Li, Q.X., 2009, Chronic Exposure to High Levels of Zinc or Copper Has Little Effect on Brain Metal Homeostasis or A beta Accumulation in Transgenic APP-C100 Mice, *Cellular & Molecular Neurobiology*, Vol. 29, pp. 757-767.

Pardridge, W., 2003, Blood-brain barrier drug targeting: The future of brain drug development, *Molecular Interventions*, Vol. 3, pp. 90–105. Pardridge, W., 2003, Blood-brain barrier drug targeting: The future of brain drug development, *Molecular Interventions*, Vol. 3, pp. 90–105.

Wright, G., Lai, J., Chan, A., Minski, M., Leung, S., 2010, Metallomic Distribution in Various Regions of the Brain as Influenced by Dietary Intakes and Implications, *Procedia Environmental Sciences*, Vol 2, pp. 149-161. (www.elsevier.com/locate/procedia)/(www.sciencedirect.com)