

# Effects of Selenium, Vitamin E, and Phytate on Methylmercury Toxicity in Male Sprague-Dawley Rats

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## ABSTRACT

Mercury remains an environmental contaminant of concern, particularly in the North, where it continues to accumulate in the traditional food sources of the Inuit. As such, there is a need to characterize the risk of mercury exposure among Inuit communities. Numerous studies have shown that dietary nutrients and supplements might protect against methylmercury toxicity. The main sources of mercury in the northern diet, such as fish and marine mammals, are also rich sources of nutrients, including selenium and vitamin E. Whether any of these nutrients offer protection against methylmercury toxicity has very direct relevance to several Inuit populations that have very high dietary intakes of methylmercury.

Methylmercury exposure can cause variations in neurochemical function in the brain in markers such as monoamine oxidase (MAO), acetylcholinesterase (AChE), acetylcholine (ACh), and muscarinic acetylcholine receptors (mAChR). Measurement of these changes can provide quantitative data relating to early signs of neurotoxicity. While it is not possible to measure these changes directly in the human brain, variations have also been shown to occur in peripheral tissues such as platelets and lymphocytes, giving rise to the possible use of these tissues as surrogate markers.

The objectives of this study are to examine the effects of selenium, vitamin E, and dietary fibre on methylmercury kinetics and toxicity in rats and to measure the changes in MAO, AChE, and ACh activity, and in mAChR binding levels in blood and brain tissues as a means of establishing early, sensitive biomarkers of methylmercury toxicity. This study will seek to further describe the effects of diet on modulation of methylmercury toxicity and to provide additional tools in the form of neurochemical biomarkers for the early detection of neurotoxic damage from environmental contaminants.

Preliminary results from the mercury analysis portion of the project will be presented in this poster.

## INTRODUCTION

### Methylmercury Toxicity (MeHg)

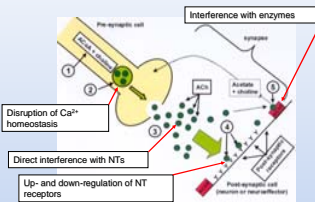
- Ubiquitous, highly neurotoxic environmental contaminant
- Most significant form of Hg in terms of toxicity from environmental exposure
- Exposure occurs through consumption of contaminated foods, such as fish, marine mammals, and caribou

### Mechanisms of Action

- Oxidative Stress:
  - Direct targeting of glutathione and glutathione peroxidase leads to inhibition of detoxifying reactions
  - Reduced detoxification leads to increased concentrations of free radical intermediates, xenobiotics, and reactive oxygen species (ROS), all of which can lead to lipid peroxidation, apoptosis, and necrosis

### Neurotransmitter Damage:

- Indirect damage through disruption of Ca<sup>2+</sup> homeostasis in vesicles, which disrupts binding to pre-synaptic terminal
- Directly, by damaging neurotransmitters
- By up- or down-regulation of receptors
- By interference with enzymes such as AChE and MAO, which are responsible for the degradation of neurotransmitters



### Dietary Interactions: Vitamin E & Selenium

- Natural antioxidant compounds.
- Possible modes of action by Vitamin E against MeHg include prevention of membrane degradation, prevention of glutathione peroxidase degradation, and inhibition of ROS production.
- Possible modes of action by Selenium against MeHg include increased glutathione peroxidase activity, formation of an equimolar complex with MeHg and binding to selenoprotein P, and redistribution of MeHg to less sensitive tissues.
- Dietary sources of both Vitamin E and Selenium include marine mammals, caribou, & fish.

### Dietary Fibre

- Primary role in prevention of MeHg toxicity is inhibition of Me-Hg re-absorption following enterohepatic circulation.
- Acts in conjunction with the intestinal flora to increase the excretion of MeHg.
- Increases the demethylation rate of MeHg; this leads to increased concentrations of inorganic Hg, which is more readily excreted form of Hg.

## OBJECTIVE

To determine the effects of selenium, vitamin E, and phytate on the pharmacokinetics and toxicity of methylmercury in male Sprague-Dawley rats.

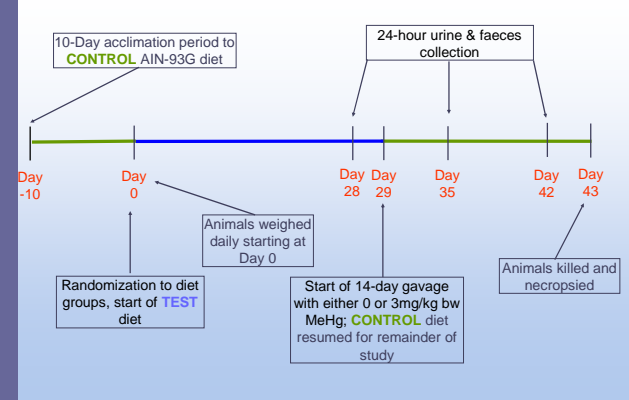
## MATERIALS AND METHODS

### Feeding Trial

288 male Sprague-Dawley rats were randomised to 22 diet groups; 12 per group + 12 quality control + 12 replacement

Control (0mg/kg MeHg)		Treatment (3mg/kg MeHg)	
Control	C	Control	C
Low Se (1ppm)	A	Low Se (1ppm)	A
High Se (3ppm)	B	High Se (3ppm)	B
Low Vit. E (250IU/kg diet)	D	Low Vit. E (250IU/kg diet)	D
High Vit. E (750IU/kg diet)	E	High Vit. E (750IU/kg diet)	E
High Se/High Vit. E	F	High Se/High Vit. E	F
Low Se/Low Vit. E	G	Low Se/Low Vit. E	G
High Se/Low Vit. E	H	High Se/Low Vit. E	H
Low Se/High Vit. E	J	Low Se/High Vit. E	J
Low Phytate (10g/kg diet)	K	Low Phytate (10g/kg diet)	K
High Phytate (70g/kg diet)	L	High Phytate (70g/kg diet)	L

### Study Time-Line



### Sample Analysis

#### Tissues

- Brain, liver, kidney, whole blood, faeces (days 0, 7 & 14), and urine (days 0, 7 & 14) samples were obtained from each animal.
- Cerebellum, cerebral cortex and frontal lobe sections were dissected from each brain sample and stored separately.

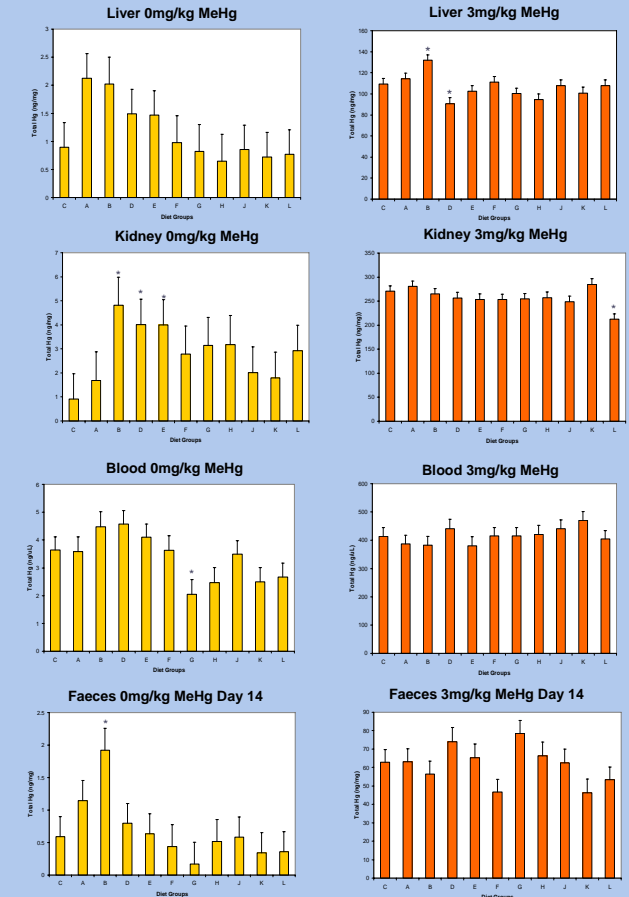
#### Tissue Storage

- Brain samples were stored at -80°C prior to analysis.
- All other samples were stored at -20°C prior to analysis.

#### Mercury Analysis

- All tissue and fluid samples (with the exception of cerebellum and cerebral cortex) were analysed for total mercury content by atomic absorption spectroscopy coupled with gold amalgamation.
- Blood samples were diluted with Nanopure water prior to analysis.
- Liver and kidney samples were homogenized and diluted with Tris HCl buffer.
- Faeces, urine and frontal lobe samples were analysed in their unaltered state.

## RESULTS



\* Significantly different from control group, p<0.05

## CONCLUSIONS

- Rats receiving high levels of Selenium in the diet showed an increased accumulation of Hg in the liver.
- Rats receiving low levels of Vitamin E in the diet showed a decreased accumulation of Hg in the liver, whereas rats receiving high levels of Vitamin E in the diet showed no difference in Hg accumulation.
- Rats receiving high levels of phytate in the diet showed a decreased excretion of Hg in the faeces.
- Further results from the study, including brain mercury levels and results of neurotransmitter assays, are forthcoming.

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