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The Mechanism of Methylmercury Permeation through the Blood-Brain Barrier using *Caenorhabditis Elegans*

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Abstract: Methylmercury is a neurotoxin present in fish tissues that permeates the blood-brain barrier after consumption. Previous research has shown that methylmercury is harmful to neurons, causing pH alterations, oxidative stress, excitotoxicity, and parenchymal damage. Methylmercury is a known factor of neurological disorders including Alzheimer's and Parkinson's. The method by which methylmercury passes through the blood-brain barrier is largely unknown. According to preliminary studies, one way methylmercury crosses the blood-brain barrier is by creating a complex with L-Cysteine, which facilitates its passage by the LATs system through mimicking another amino acid existing in the body. The human blood-brain barrier was studied using C. *elegans* as a model organism. It was hypothesized that if methylmercury passes through the blood-brain barrier of C. *elegans* faster with L-Cysteine present than without L-Cysteine present, the methylmercury's adverse effects (death and locomotive difficulty) will occur sooner. Each of the four experimental groups contained one C. elegans: the control, the L-Cysteine group, the methylmercury group, and the methylmercury and L-Cysteine combination group. The effects of L-Cysteine and methylmercury on C. *elegans* were studied using three metrics: viability, locomotive disability, and time for locomotive effects to occur. The group that received both methylmercury and L-Cysteine had reduced viability rates and a decreased time for locomotive difficulty to develop, supporting the hypothesis. These findings suggest that L-Cysteine aids methylmercury permeation through the blood-brain barrier. Because the experiment indicates how methylmercury penetrates the blood-brain barrier, these results aid in finding a therapeutic solution to reverse methylmercury neurotoxicity in the brain. Additionally, this study further opens channels into potential therapeutic and preventative measures for dementia, improving morbidity and mortality in neurodegenerative diseases.

Keywords: Methylmercury; Alzheimer’s; Parkinson’s; Blood-Brain Barrier; L-Cysteine; Neurotoxicity

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1. Introduction

1.1 Methylmercury

Methylmercury (MeHg or CH_3Hg) is a type of mercury that forms when anaerobic bacteria react with inorganic mercury in water, soil, or plants. The anaerobic bacteria makes the inorganic mercury go through the process of methylation where it gains a methyl group (3 hydrogen atoms and 1 carbon atom in the formula CH_3 or the abbreviated Me). Methylmercury is biomagnified, meaning that the concentration of this toxin in tissues of tolerant organisms is at successively

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higher levels in the food chain. The concentration of methylmercury in organisms increases as it travels from bacteria to plankton to herbivorous fish to piscivorous fish. The concentration of methylmercury can be 1 to 10 million times higher in the top level of aquatic predators than the level in the water (1). Fish and other aquatic organisms are the main source of human consumption of methylmercury. (2, 3)

The mechanism by which methylmercury enters the body is when it is ingested by human consumption of fish. It is then completely absorbed by the gastrointestinal tract. From there it forms a complex with L-Cysteine (CH_3Hg—Cys), an amino acid found in the body. This complex is able to pass through the blood-brain barrier because it mimics the amino acid methionine. It is not readily eliminated because of its strong affinity to proteins (4).

Additionally, methylmercury is a neurotoxin and has substantiated evidence tying it to neurodegenerative diseases such as Alzheimer's and Parkinson's (5, 6, 7). The most damaging aspect of methylmercury neurotoxicity is its irreversible inhibition of selenoenzymes, such as thioredoxin reductase, in the brain. This is a major effect because selenoenzymes restore vitamins C and E, and a number of antioxidant molecules that help counteract oxidative damage in the brain. Early evidence suggests that methylmercury's affinity to selenol groups allows for its entry into the brain. This is due to how methylmercury's interruptions of selenium metabolism indicate answers to some unsettled phenomena such as why methylmercury specifically targets the brain and the latency between methylmercury exposure and the onset of its neurotoxic effects. Additionally, selenium has an affinity for mercury compounds that is approximately 1 million times greater than that of thiol groups, with an acid dissociation constant (K_a) of 10^{45}. Because of selenium's great affinity towards methylmercury, it is expected that it be predominantly found bonded to selenoproteins. On the contrary, more than 95% of the mercury content in the body is associated with thiol groups instead. Thus, research indicates that molecules containing thiol groups, such as L-Cysteine, facilitate methylmercury's entry into the brain where it is allowed to disrupt standard selenium metabolism (8). Additionally, methylmercury's interaction with thiol and selenol groups is seen to alter the structure of proteins in the brain, leading to downstream effects such as mitochondrial dysfunction, decreased glutathione levels, disruption of calcium homeostasis, and an overall increase in reactive oxygen species production in the brain (9).

Methylmercury can also dysregulate essential neurotransmitters such as serotonin, acetylcholine, dopamine, norepinephrine, and glutamate. It can cause some of the most notable features of Alzheimer's disease such as plaques, beta-amyloid protein, neurofibrillary tangles, phosphorylated tau protein, and memory loss. Abnormal levels of different minerals in the body, such as aluminum, calcium, copper, iron, magnesium, selenium, zinc, and vitamins B1, B12, E, and C, occur in methylmercury toxicity as well as in Alzheimer's disease. Some studies have even been conducted showing elevated levels of mercury in the brain, blood, and tissues of Alzheimer's patients (10, 11). All of these features of methylmercury toxicity have also been associated with extremely damaging neurodegenerative diseases such as Alzheimer's disease, exemplifying the need to research this substance more thoroughly for its neurotoxic effects on the brain.

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Methylmercury has an affinity for sulfur-containing anions, specifically thiols. Because of its affinity to thiol groups, it will readily form complexes with compounds with thiols, including L-Cysteine (12, 13). Methylmercury is shown to be able to permeate the blood-brain barrier which is odd because of its highly selective permeability. The blood-brain barrier's high selectivity for essential amino acids such as methionine and isoleucine begs the question about how methylmercury is able to enter the brain in the first place. (14). The mechanisms by which methylmercury is able to enter the brain and cause damage are largely unknown but research suggests that it creates a complex with the amino acid L-Cysteine and utilizes molecular mimicry for the Large Amino Acid Transporter system (LATs) to allow it into the brain (15, 16, 17, 18).

$$[MeHg]^{+} + RSH \rightarrow MeHg—SR + H^{+}$$

This formula shows how methylmercury makes a complex with an amino acid (L-Cysteine) and in doing so spits out a hydrogen cation. A hydrogen cation is dangerous because since it is a single proton, it can steal electrons from other molecules and ionize them, setting them out of balance. This process creates reactive oxygen species in the brain and starts a rapid chain reaction that is highly damaging to nervous tissue in the brain. In addition, once inside the brain, methylmercury can then wreak havoc on neurons and their surrounding glial cells by targetting and killing neurons and the cell structure (19, 20, 21).

1.2 Caenorhabditis elegans

C. *elegans* is a model organism of the human nervous system and is commonly used for neurobiology research. C. *elegans* have approximately 60 to 80% of human genes, including genes involved in metal homeostasis and transportation (22, 23). Their nervous system is fully mapped and they have 302 neurons in their whole body. Any slight change in their nervous system, such as if a neuron has died, is visibly noticeable in their body's locomotive function.

C. *elegans* neurons have the same components as human neurons specifically in their overall structure. The only difference between their neurons and human neurons is the fact that C. *elegans* neurons do not have a myelin sheath. But the reason for this is because the purpose of a myelin sheath is as insulation for the electrical impulse to travel from neuron to neuron, however, with a worm the size of 1 millimeter, the distance neurons travel in C. *elegans* is too short of a distance to require a myelin sheath.

The way C. *elegans* neurons communicate with each other using electrical and chemical synapses is highly similar to humans as well. Electrical synapses are synapses that pass information between two neurons via gap junctions. They conduct nerve impulses faster than chemical synapses. Chemical synapses are the release of a chemical neurotransmitter from a presynaptic cell to chemically stimulate the postsynaptic cell. This is the most common type of synapse and occurs between neurons and muscle cells. This similar synaptic system is utilized in both humans and C. *elegans*, adding to why it is an optimal model organism.

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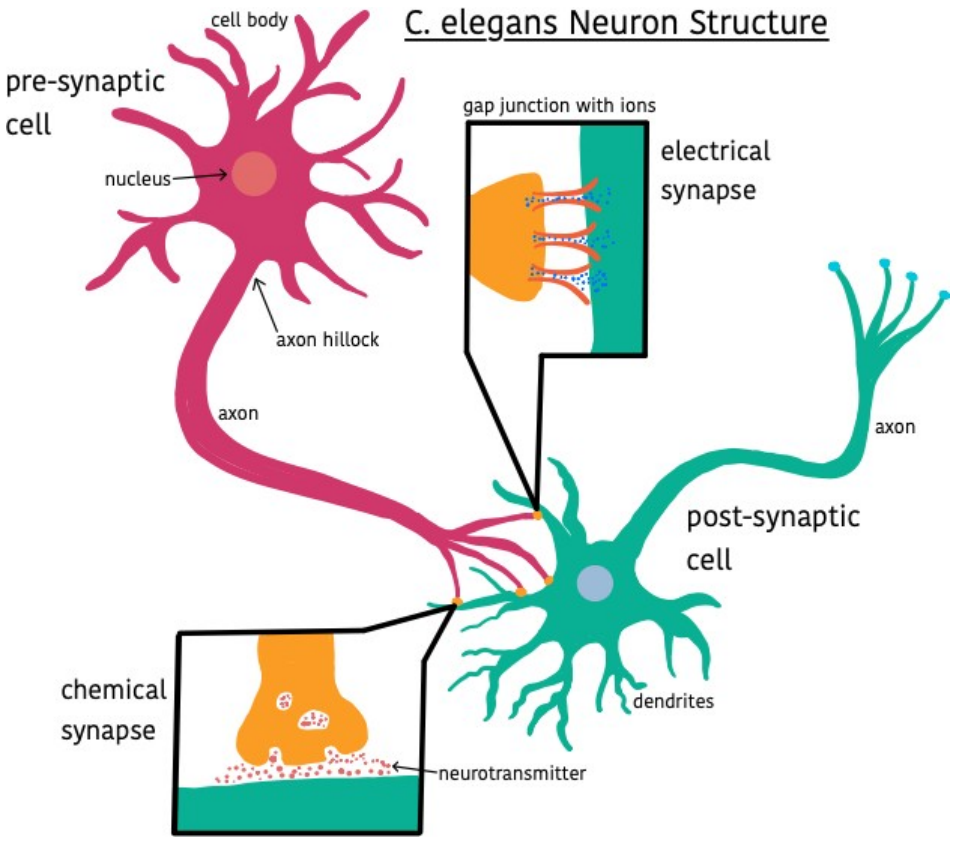

Figure 1. C. *elegans* neuronal structure is highly conserved to human neurons.

C. *elegans* neurons are pictured and the similarities between human and C. *elegans* neurons are demonstrated in the different parts of neurons, with the cell body, axon, and dendrite all appearing to be highly conserved to the human neuron. In addition, the types of synapses between neurons are conserved, as pictured in **Figure 1**. This is seen in how both human and C. *elegans* neurons have chemical and electrical synapses, with their own component features of neurotransmitters and existing gap junctions with ions.

Additionally, C. *elegans* nervous systems have the same basic organization of neuron subtypes into sensory, interneuron, and motor neurons. Sensory neurons in C. *elegans* make up 28 neurons that are specialized for detecting external stimuli such as temperature and chemical changes in their environment. The sensory and interneurons make up a cluster of nerve cells called the head ganglia which is loosely referred to as the “brain” of the C. *elegans*. Interneurons receive incoming synapses and send ongoing synapses to other neurons. They are the largest group of neurons in C. *elegans* and in humans. They are information processors and their main objective is to relay inputs from one or more classes of neurons and outputs to other neurons. They

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function as circuit couplers, sending information from two or more circuits that converge to establish circuit hierarchies. Motor neurons make synaptic connections to effector cells, such as muscle cells, to execute an objective.

The C. *elegans* nervous system has the same structural organization as humans even though the complexity of the human connectome, the structural connectivity of a nervous system, is far greater. In the C. *elegans* nervous system, sensory neurons send dendrites from the head ganglia to the nose and transmit sensory info to interneurons. The interneurons in the head ganglia are responsible for analyzing and interpreting information. The interneuron network then determines the action they should take based on the sensory input. Then the interneurons stimulate the motor neurons to execute the desired outcome. Motor neurons then interface with effector cells, cells such as muscle cells, to control their activity. This allows the organism to move in response to the directions from the interneurons. This basic system is the same as the human nervous system. In the human nervous system, sensory neurons transmit information to interneurons in the central nervous system. Interneurons then stimulate the motor neurons for action. The outcome is produced by either muscle cells or other specialized cells in the body through nerve cell communication. The way neurons communicate in the body highlights a similarity between the human and C. *elegans* nervous system (24, 25).

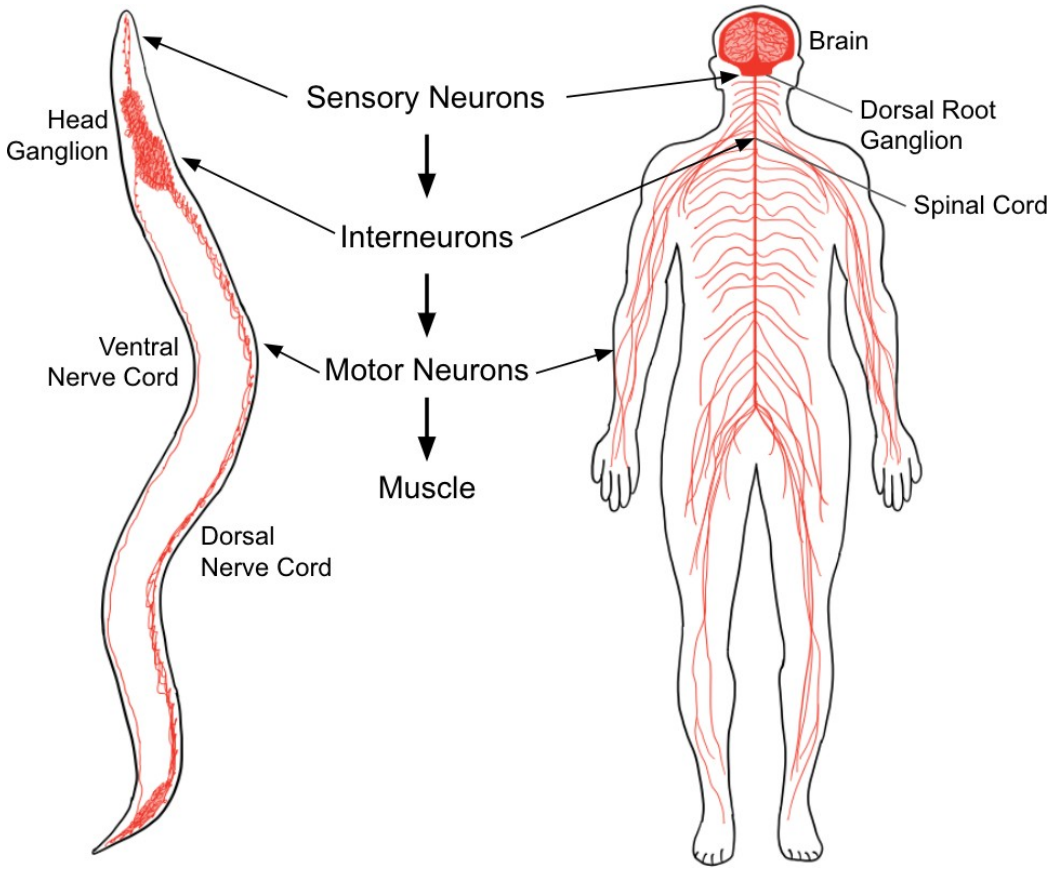

Figure 2. Basic structural organization of the C. *elegans* nervous system is highly conserved between humans and C. *elegans.*

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This image highlights the similarity in information processing between the C. *elegans* and human nervous systems.

The blood-brain barrier in C. *elegans* is conserved to the human blood-brain barrier as well in how they both act as a barrier to protect the "brain" of the organism from foreign substances (26, 27). This is because how C. *elegans* contain a structure within the head ganglia called the nerve ring. This nerve ring in C. *elegans* acts as the "brain" of the C. *elegans* in that it is the most synapse-rich part of its body and consists of a tight axon bundle containing processes from over half of the C. *elegans* neurons (28). Studies show that C. *elegans* contain specialized glial cells or sheath cells that isolates the nerve ring in the same way that the blood-brain barrier does in humans, thus making C. *elegans* an ideal organism to model the Central Nervous System and the blood-brain barrier (29).

2. Methods

Upon seeing the similarities between the human and C. *elegans* nervous systems, C. *elegans* was utilized as a model organism to test methylmercury's permeability into the brain and its neurodegenerative properties. Four experimental groups containing one C. *elegans* each were performed: a control containing only the nematode growth agar, a group containing L-Cysteine dissolved in nematode growth agar, a group containing methylmercury dissolved in nematode growth agar, and a combination group containing both L-Cysteine and methylmercury dissolved in nematode growth agar. Three metrics were used to analyze data: viability, locomotive ability, and the length of time for locomotive effects to take place. Viability measured how long each C. *elegans* lived and was recorded in hours. As well, viability was checked by prodding each C. *elegans* with a nicromium wire to see its reaction to touch stimulus. Locomotive ability examined the ability for C. *elegans* to continue its usual function and was recorded with qualitative description. The length of time for locomotive effects to take place was recorded in seconds of time and measured because the length of time for locomotive effects to take place is equal to the time it took for methylmercury to permeate across the C. *elegans* blood-brain barrier and damage neurons.

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3. Results

Experimental groups: Trial 1	Viability (in hours)
Control	72
L-Cysteine	72
Methylmercury	48
Methylmercury and L-Cysteine	24

Experimental groups: Trial 2	Viability (in hours)
Control	72
L-Cysteine	72
Methylmercury	36
Methylmercury and L-Cysteine	12

Experimental groups: Trial 3	Viability (in hours)
Control	72
L-Cysteine	72
Methylmercury	36
Methylmercury and L-Cysteine	12

Table 1. Trials 1, 2, and 3 of the Viability of C. elegans Administered with L-Cysteine, Methylmercury, and a Combination of the Two Measured over 72 Hours

The three trials testing the viability of each experimental group of C. *elegans* exposed to L-Cysteine, Methylmercury, and a combination of both demonstrated the most decreased viability rates in the combination groups in contrast to the control, L-Cysteine, and methylmercury groups.

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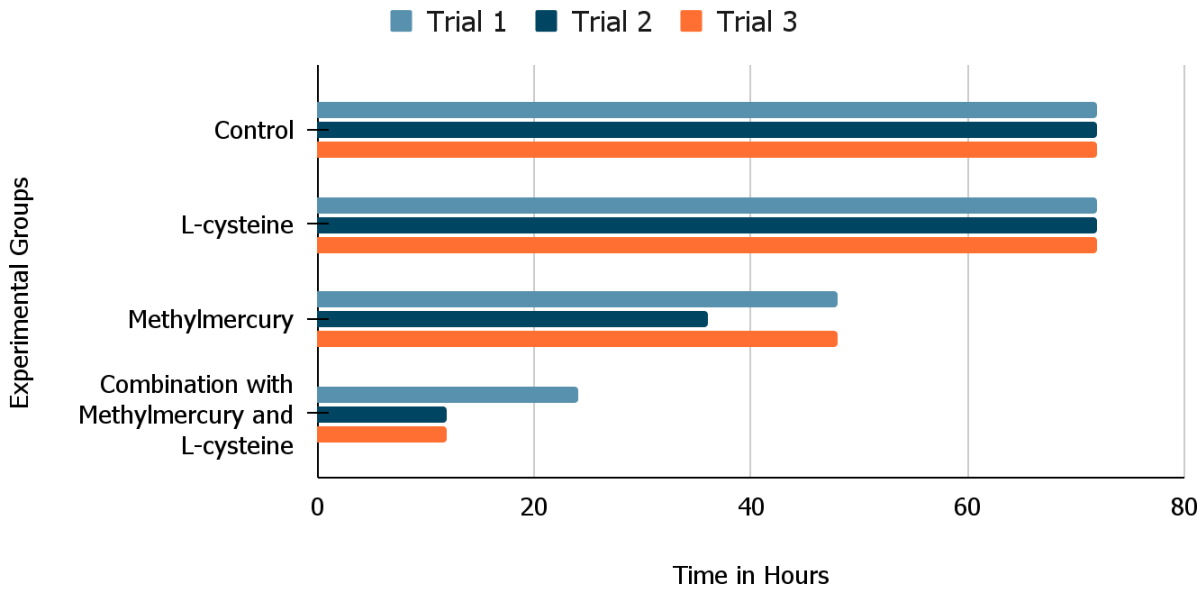

Figure 3. This is a representation of the viability of each C. *elegans* administered with L-Cysteine, methylmercury, and a combination of both measured over 72 hours in a horizontal bar graph.

As seen in **Figure 3**, the viability of each C. *elegans* was significantly reduced in the combination group of methylmercury and L-Cysteine in comparison to the methylmercury group as well as the control and L-Cysteine groups.

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Experimental groups: Trial 1	Locomotive Ability
Control	Normal locomotive function
L-Cysteine	Normal locomotive function
Methylmercury	- Moved like normal at first but stopped moving completely after 136 seconds - Would only move when prodded with wire
Methylmercury and L-Cysteine	- Moved like normal at first but stopped moving completely after 57 seconds - Would only move when prodded with wire

Experimental groups: Trial 2	Locomotive Ability
Control	Normal locomotive function
L-Cysteine	Normal locomotive function
Methylmercury	- Moved like normal at first but stopped moving completely after 184 seconds - Would only move when prodded with wire
Methylmercury and L-Cysteine	- Moved like normal at first but stopped moving completely after 75 seconds - Would only move when prodded with wire

Experimental groups: Trial 3	Locomotive Ability
Control	Normal locomotive function
L-Cysteine	Normal locomotive function
Methylmercury	- Moved like normal at first but stopped moving completely after 110 seconds - Would only move when prodded with wire

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Methylmercury and L-Cysteine	- Moved like normal at first but stopped moving completely after 39 seconds - Would only move when prodded with wire

Table 2. Trials 1, 2, and 3 of the Locomotive Difficulty of C. elegans Administered with L-Cysteine, Methylmercury, and a Combination of the Two

The locomotive ability of the C. *elegans* in the control and L-Cysteine groups was significantly better than both groups containing methylmercury, as seen by how both C. *elegans* exposed to methylmercury had not been able to resume normal locomotive function after a certain number of seconds.

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	Experimental groups	Length of time for locomotive effects to occur (in seconds)
Trial 1	Methylmercury	136
	Methylmercury and L-Cysteine	57
Trial 2	Methylmercury	184
	Methylmercury and L-Cysteine	75
Trial 3	Methylmercury	110
	Methylmercury and L-Cysteine	39
Average	Methylmercury	143
	Methylmercury and L-Cysteine	57

Table 3. Trials 1, 2, and 3 of the Length of Time for Locomotive Effects to Occur in the Methylmercury Group and the Combination Group with Methylmercury and L-Cysteine

As seen in **Table 3**, the C. elegans impacted by the insult of both methylmercury and L-Cysteine present had a significantly decreased time for locomotive difficulty to take place.

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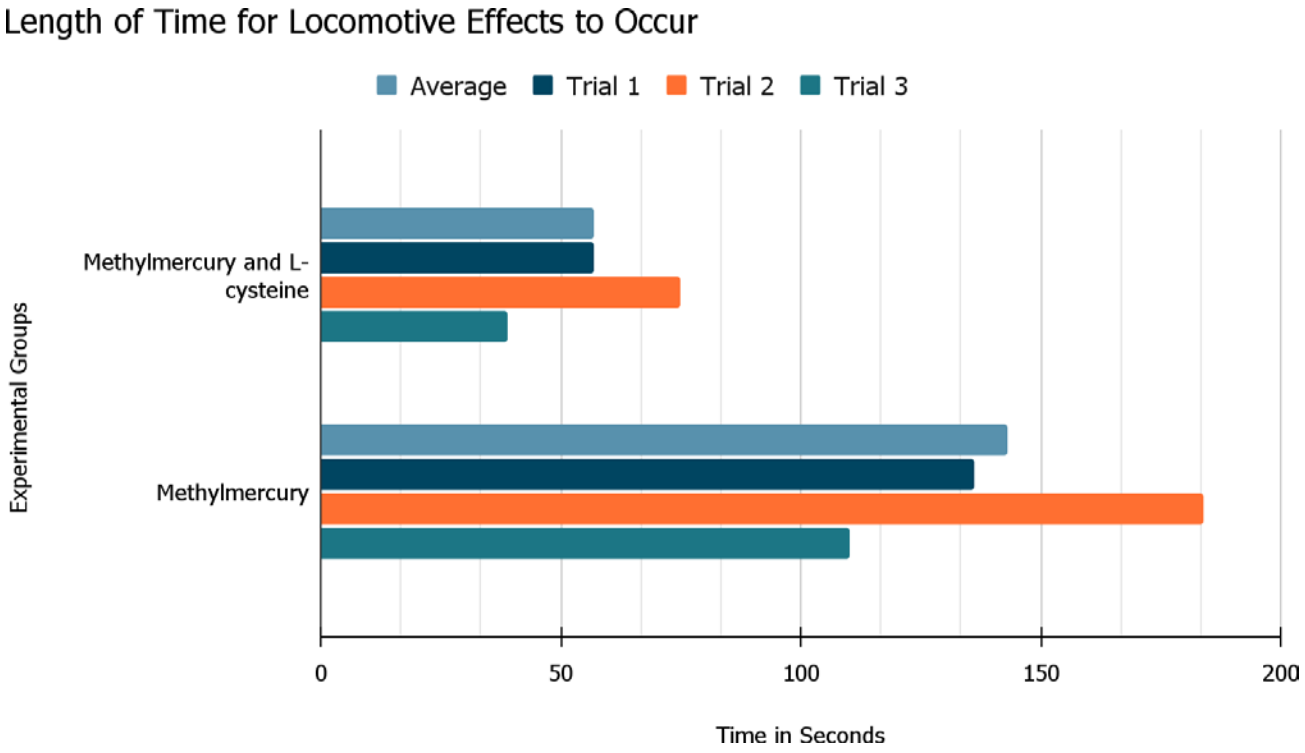

Figure 4. This is a representation of the length of time for locomotive effects of methylmercury to occur in the C. *elegans* in a horizontal bar graph.

The petri dish with methylmercury and L-Cysteine present displayed locomotive difficulty at a rate 2.5% faster than the petri dish with only methylmercury present. These results are only from the methylmercury group and the combination groups because it records the length of time for the methylmercury to permeate across the blood-brain barrier, which is only relevant to the experimental groups containing methylmercury.

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3.1 Statistical Analysis

Experimental Groups	Mean (M)	Standard Deviation (SD)	p-value
Methylmercury (μ1)	143 seconds	30.7	0.0229
Methylmercury and L-Cysteine (μ2)	57 seconds	14.7	

Figure 5. $p < \alpha$ ∴ $\mu 1 \neq \mu 2$ ∴ reject null hypothesis ∴ significant statistical difference

A two-sample t-test was performed to compare the length of time for locomotive effects to occur in the methylmercury group in comparison to the methylmercury and L-Cysteine group. Tests were conducted with an alpha value of 0.05 and a 95% confidence interval. The null hypothesis (H0) is that there is no statistically significant difference between the mean of the length of time for locomotive disability to occur in the methylmercury group (μ1) in comparison to the methylmercury and L-Cysteine group (μ2). Because the calculated p-value of 0.0229 is less than 0.05, this null hypothesis was rejected, demonstrating a significant statistical difference in the length of time for locomotive effects to occur between the methylmercury group (M = 143 seconds, SD = 30.7) and the methylmercury and L-Cysteine group (M = 57 seconds, SD = 14.7).

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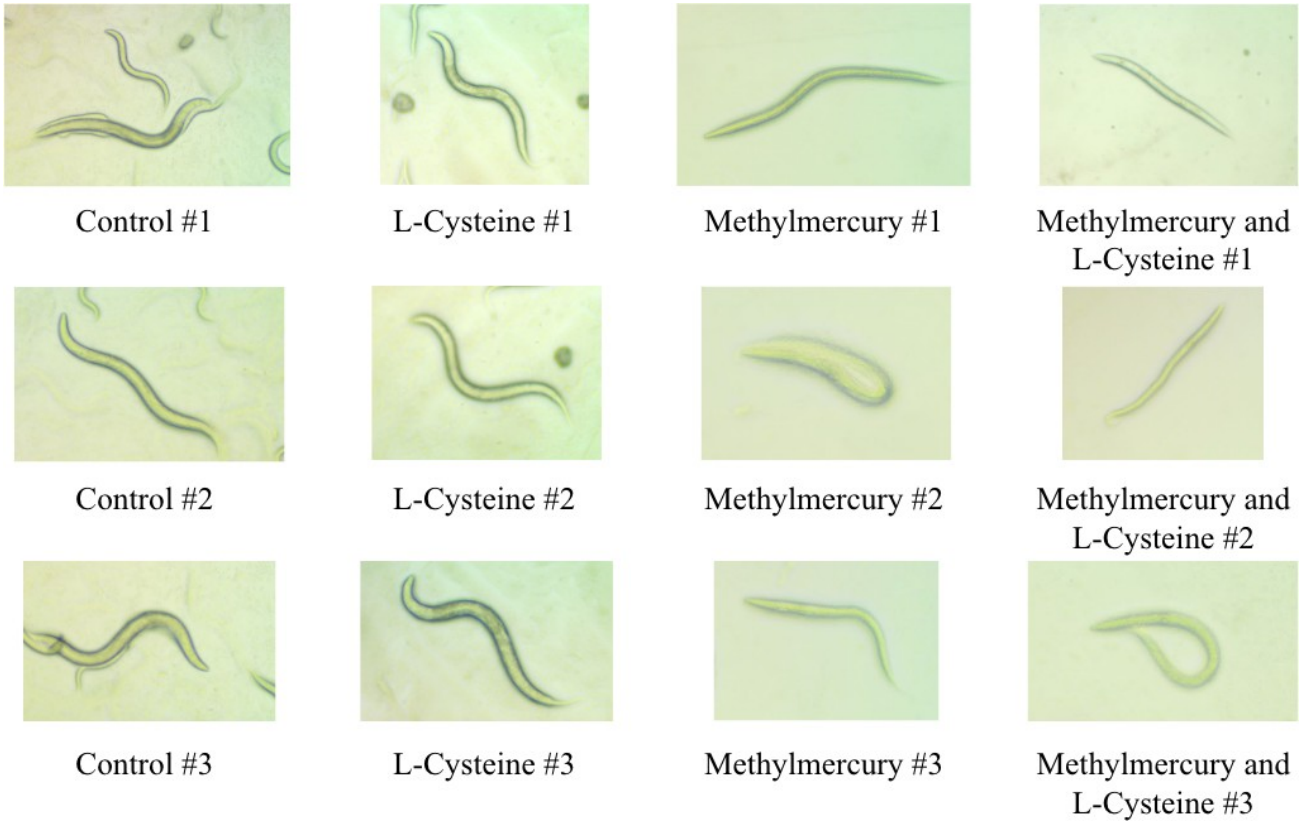

Figure 6. The experimenter took these images with a trinocular microscope at 40X magnification using a 10X ocular lens and a 4X objective lens.

These images show the locomotive disabilities of C. *elegans* as a result of the methylmercury. The experimental groups with methylmercury present show slimmer bodies that are unable to move.

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4. Discussion

4.1 Conclusion

Because the petri dish with methylmercury and L-Cysteine present displayed locomotive disabilities at a rate approximately 2.5% faster than the petri dish with only methylmercury present, and because the C. *elegans* with methylmercury and L-Cysteine present had average viability of 28 hours less than the petri dish with only methylmercury present, this means that methylmercury can permeate across the Blood-Brain Barrier (BBB) of C. *elegans* faster with L-Cysteine present than without. Because of this, it can be concluded that the mechanism by which methylmercury enters the brain is through making a complex with L-Cysteine. As well, the effects of the methylmercury on the C. *elegans* included locomotive disability and death, suggesting that the nervous system was detrimentally impacted to the point of neuronal death.

4.2 Applications

Because of the detrimental effects that methylmercury has on the nervous system, future research is imperative to fully understand the mechanism of how it is able to pass through the Blood-Brain Barrier and exact this damage upon neurons. This research can be applied to future experimentation because now that this experiment has defined the possible mechanism for how methylmercury is able to enter the brain, this information can be used to prevent this chemical reaction from occurring and prevent methylmercury from being able to enter the Central Nervous System. Because methylmercury pollution affects extremely large quantities of fish worldwide, finding how to prevent its detrimental effects on the brain is imperative to preventing rising dementia rates worldwide.

4.3 Limitations

A limitation that arose in this experiment was that methylmercury chloride (H_3CHgCl) had to be used instead of pure methylmercury (H_3CHg) because that is the only form of methylmercury available to purchase and because the addition of chlorine allows the substance to be more miscible in different solutions, in this case being the nematode growth agar. While it is unlikely, there is a possibility that the chlorine molecule could cause an interruption in the formation of the methylmercury—L-Cysteine complex. While this should not change the results of this experiment, it is optimal to use the same form of methylmercury that causes neurotoxicity in the brain in this experiment.

4.4 Future Research

Further research would be conducted by investigating chelators and antioxidants which have preliminary research for being effective against methylmercury neurotoxicity. Chelators are molecules that can bond very closely to metal ions, and then can be removed from the body. These substances have the potential to be used as a solution for the removal of methylmercury

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from the brain. Past studies have presented preliminary results towards being able to use chelators for the extraction of metal ions in the brain (30). To further this research, different types of chelators would be investigated to remove methylmercury ions from the brain, thus reversing methylmercury neurotoxicity and preventing a potential neurodegenerative disease such as Alzheimer's or Parkinson's from taking place.

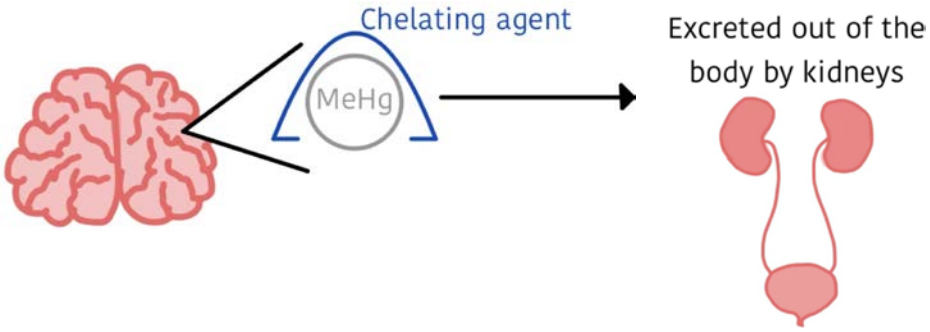

Figure 7. This diagram presents exactly how a chelator would function to remove methylmercury from the brain, through bonding closely to it and forming somewhat of a shell around it, thus allowing for its detrimental effects to be neutralized, where it would then be excreted from the body by the kidneys.

Additionally, natural and synthetic antioxidants would be investigated because of how promising research has shown in minimizing the neurotoxicity of methylmercury in the brain. This is another pathway to pursue to curtail the damaging effects of methylmercury on the brain's parenchyma. By applying this from Petri dish to its application in real-world health care, this research can potentially save lives.

Conflicts of Interest: The author declares no conflict of interest.

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