Similar Mechanisms of Action for Mercury and Acrylamide and Their Effects

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ABSTRACT

Food can be contaminated by various classes of chemicals. Mercury, a heavy metal used in a variety of medicinal and industrial products, can contaminate seafood, especially fish, through biomagnification. The way in which food is processed can also lead to other routes of chemical exposure. Acrylamide, an important chemical used in the manufacturing industry, can be found in starchy foods that are cooked at high temperatures. Dietary exposure to acrylamide and mercury are points of concern, as they are associated with cellular oxidative stress and neurotoxicity. Other routes of exposure for both chemicals are possible in occupational environments through inhalation and dermal contact. Younger populations tend to be exposed to higher levels of both compounds through their diet, and are more at risk of negative health effects than the general population. Both compounds: are readily absorbed by the body, are capable of crossing the blood-brain barrier, bio-accumulate in the brain and disrupt neural pathways, and disrupt normal function of DNA that can affect the normal life cycle of neural cells. It is possible that since these compounds have similar mechanisms, they can also have an additive or synergistic effect.

INTRODUCTION

Acrylamide (ACR), an organic odorless chemical, has been widely used in: the production of polyacrylamide, as a papermaking additive, for sewage treatment, and as a coagulating aid for drinking and waste water treatment. In addition, ACR forms in various carbohydrate-rich foods that are subject to high heat (>120°C). ACR formation is due to the Millard reaction between reducing sugars (such as glucose and saccharose) and the amino acid Asparagine (Asn) [2]. The fact that ACR is ubiquitous in the human diet recently raised worldwide attention regarding its health effect, since it is a known neurotoxic compound in humans and animals, as it increases oxidative stress in nervous system and has the potential to be a carcinogen in humans [11]. ACR is also prevalent in occupational environments which could cause an additive or synergistic effect. The carcinogenicity of ACR can be attributed to its metabolite glycidamide, which has an epoxide structure and is more toxic at lower concentrations [16].

Mercury (Hg) is a heavy metal that has been widely used in a variety of fields, including medicine (as a dental amalgam), an antiseptic, and in skin ointments. It is also used in manufacturing, such as in battery, thermometer, and barometer production. Mercury exists in three forms: elemental mercury (Hg^0), inorganic salts known as mercuric chloride, and organic compounds, primary as methyl mercury (MeHg). Mercury can cause toxicity at very low concentration and is capable of bioaccumulation in the environment and biomagnification in the food chain. In the environment, the inorganic species of mercury is converted in to its organic states [6]. Methyl mercury (MeHg), the most common organic form of mercury, is formed via methylation of inorganic species. MeHg accumulates in aquatic systems and contaminates seafood products, especially fish. MeHg in the body forms a water soluble compound that can easily attach to sulfur atoms of thiol ligands and cross the blood brain barrier, which affects the central nervous system. MeHg is known to cause neurotoxicity, genotoxicity, and endocrine disruption [20].

ROUTES OF EXPOSURE

	Acrylamide	Mercury
Average Dietary Intake Estimated by WHO (general population)	0.3-0.8 µg/kg/day [21]	23.6 µg/kg/day [31]
Average Dietary Intake Calculated from Food Samples (Under 21)	0.21-0.43 µg/kg/day [21]	N/A
Average Dietary Intake Calculated from Food Samples (Women 16-49)	N/A	26.7 µg/kg/day [31]
Average Dietary Intake Calculated from Food Samples (Children)	0.61 µg/kg/day [21]	55.4 µg/kg/day [31]
Main Source of Exposure	The leading cause of human exposure to acrylamide occurs in the workplace via **dermal contact and inhalation** [17]. Industrial production of adhesives, mining chemicals, textiles, pharmaceuticals, animal feed. Also used in laboratories when preparing polyacrylamide gels for electrophoresis Tobacco smoke [22]	**Elemental**: Occupational (inhalation) [28] **Inorganic**: Antiseptics [28] **Organic**: Dietary (Fish) [28]
Other Sources of Exposure	**Dietary**: [8, 11,24] Potato Chips - 1249 µg/kg French Fries - 351 µg/kg Crackers - 604 µg/kg Gingerbread - 890 µg/kg	**Elemental**: Production of batteries, barometers, paint [28] **Inorganic**: Bleaching creams, laxatives [28] **Organic**: Grains and seeds, fungicides and insecticides, processed woods and paper, vaccines [28]
Safe Exposure Level	**Dietary**: Tolerable Daily Intake (TDI) 937] Neurotoxicity - 40 µg/kg/day Cancer - 2.6 µg/kg/day **Occupational**: NIOSH* and ACHIH's **Recommended exposure limit: 0.03 mg/m³ [17]	No known safe level of exposure [4]
Absorption	Acrylamide is readily absorbed via inhalation [22] Absorption after ingestion is not fully understood. 35-81% of dose is excreted via urine; the remaining dose is not accounted for [3]	Ingested elemental mercury and Inorganic mercury are not readily absorbed through the GI tract. Inorganic mercury absorbs easily through skin. Inhaled elemental mercury vapor is absorbed and diffused quickly throughout the body. Organic mercury is readily absorbed through inhalation, ingestion and dermal contact [28]

*NIOSH = National Institute of Occupational Safety and Health
** ACGIH = American Conference of Governmental and Industrial Hygienists

EXPOSURE LIMITS

Exposures to acrylamide or mercury post significant effects on human health. The health effect caused by acrylamide depends on the amount of acrylamide present in food, the portion size consumed, and the frequency of consumption, as well as cooking and storage methods [48]. According to the International Agency for Research on Cancer, acrylamide is classified as a group 2A carcinogen for humans. Previous studies also show that the cancer risk has been estimated on the basis of the exposure dose of glycidamide. Administration of acrylamide to experimental animals resulted in damage to peripheral nerves as the most sensitive effect [24, 38]. Acute (short-term) and chronic (long-term) oral exposures to acrylamide have resulted in damage to the nervous system in humans and animals; in fact, major health effects of acrylamide are skin irritation such as redness and peeling of the skin and neuropathy regarding the central nervous system and the peripheral nervous system [16, 17]. These effects are characterized by abnormal fatigue, sleepiness, memory difficulties, and dizziness. With severe poisoning, confusion, disorientation, and hallucinations occur [17].
The World Health Organization considered mercury as the top ten chemicals or groups of chemicals of major public health concern. Exposure to mercury may have toxic effects on the nervous, digestive and immune systems, and on lungs, kidneys, skin and eyes [41]. The health effect of acute exposure to high level of mercury can lead to darkened discoloration of the oral mucous membrane and cause severe corrosive of the gastrointestinal tract [28, 51]. Chronic exposure to mercury cause toxic effects to the central nervous system and the kidneys [51].

REGULATORY STANDARDS

Exposure Limits - Mercury		
	Mercury, Alkyl Compounds	Mercury, Inorganic Compounds
OSHA 8-Hour TWA	0.01 mg/m3	0.1 mg/m3
OSHA Ceiling	0.04 mg/m3	-
NIOSH 8-Hour TWA	0.01 mg/m3, Skin	0.05 mg/m3, Skin
NIOSH ST/Ceiling	0.03 mg/m3, (ST) Skin	0.1 mg/m3, (Ceiling) Skin
NIOSH IDLH	2 mg/m3	10 mg/m3
ACGIH 8-Hour TWA	0.01 mg/m3, Skin	0.025 mg/m3, Skin
ACGIH Short Term	0.03 mg/m3, Skin	-

Exposure Limits – Acrylamide		
	Acrylamide	
OSHA PEL	0.3 mg/m3 TWA [skin]	
NIOSH REL	0.03 mg/m3 TWA [skin]	NIOSH considers acrylamide to be a potential occupational carcinogen as defined by the OSHA carcinogen policy [29 CFR 1990].

The regulatory exposure limit for Acrylamide in food is currently not available. The Food and Drug Administration recommends food manufacturers to reduce or minimize the present of Acrylamide in starch based food. The European Commission (EC) has introduced 'indicative values' for those food groups considered to contribute the most to consumer dietary exposure to acrylamide. These are not maximum limits and are intended only as a guide to prompt investigation when higher levels occur so that enforcement authorities can gain more data to understand the problem [18].

MECHANISMS OF ACTION

Acrylamide (ACR) is a water-soluble alkene used in the production of polymers and gels that have various commercial applications. Polyacrylamide compounds are used in the textile, cosmetic and, paper industries [9]. Polyacrylamide is used in ore processing; and as flocculants for wastewater treatment. First, it was discovered that ACR was an electrophile that preferentially formed adducts with soft nucleophilic sites on certain macromolecules [26]. Next, it was noted that the protein catalytic triads were relevant molecular targets of soft, highly nucleophilic thiolate states of cysteine residues. It was also noted that thiolate sulfhydryl groups found on proteins regulate the acceptors for electrophilic mediators of NO signaling[26]. It was concluded that ACR reduced neurotransmission at central and peripheral synapses by disrupting these signaling pathways. It is a potentially significant because the type-2 alkenes are a specific group of structurally related unsaturated derivatives of carbonyl, aldehyde, and ketones. All these are well-documented environmental toxicants and/or found endogenously as mediators of the disease/injury processes associated with cellular oxidative stress[26].

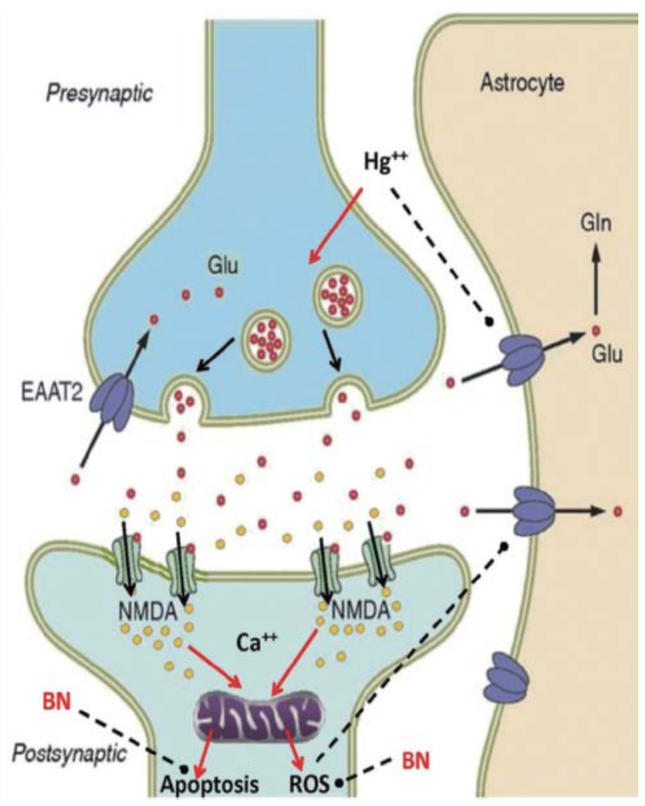
Methyl Mercury produces toxic effects on the central nervous system The lipid solubility of MeHg makes it easy to accumulate in the brain[6]. Both elemental mercury and methyl-mercury exhibit detrimental effects on cognitive and motor neuron systems. Inorganic mercury (Hg++) disrupts the differential pathways of neural stem cells. Mercury interacts mainly with thiol-based-proteins (-SH) or type-2 alkenes such as glutathione[50]. L1 retro-elements comprise 17% of the human genome and can cause mutations, gene disruptions, and genomic instability. It has been shown that mercury increased the expression of L1 RNA, the activity of the L1 5UTR, and L1 retrotransposition exclusively in the neuroblastoma cells. We conclude that non-toxic levels of the neurotoxic agent mercury could influence DNA by increasing L1 activities, specifically in neuronal cells, and may make these cells susceptible to neurodegeneration over time[6].

NEURAL DISRUPTION

Both Acrylamide and Mercury induce cells to premature cell death (Apoptosis) by depletion of thiol (Glutathione) reserves.

Early research was based on the idea that ACR produced central–peripheral distal axon degeneration and, therefore, research was focused on possible axonal sites of action such as axonal Na+/K+-ATPase.[50]

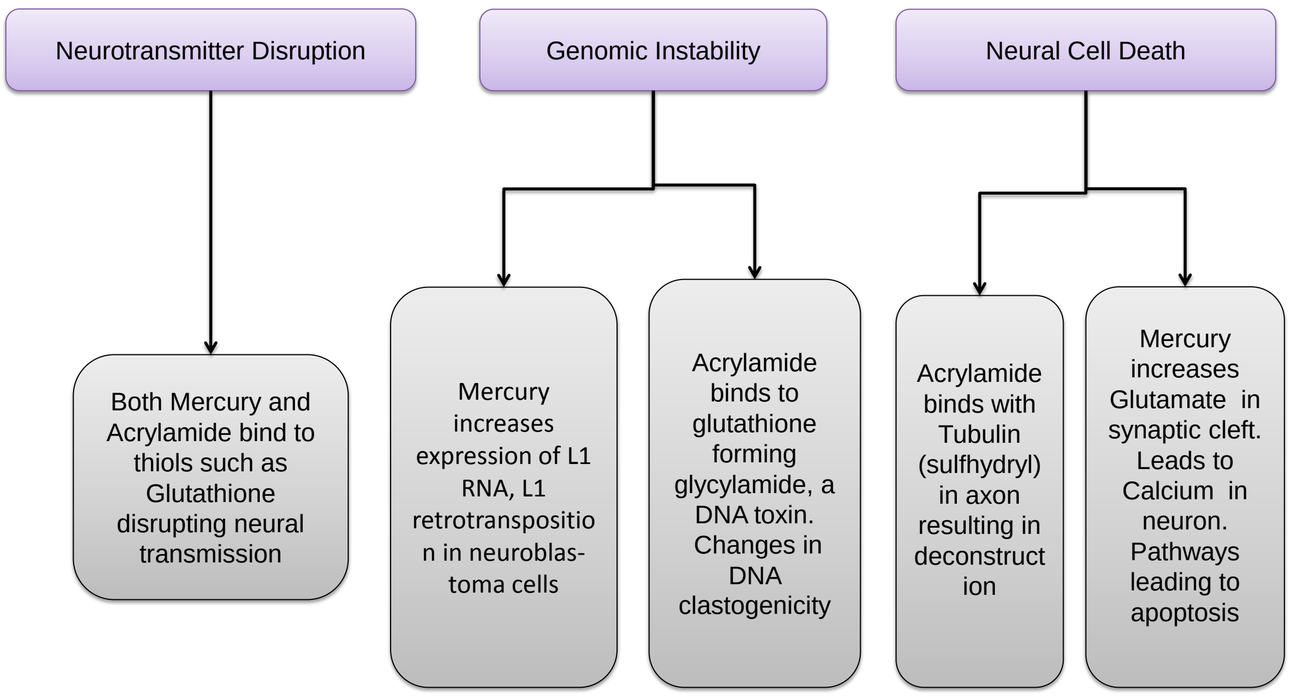
Current knowledge of the chemistry of target – toxicant reactions has led the Testing and development of a systematic neurotoxicity from ACR.



It has been shown that type-2 alkenes like ACR reacting with specific cysteine residues on cellular proteins to impair protein function. Research shows that ACR reacts with Cys342 thus inhibiting presynaptic Na+-dependent dopamine transporter function.

It can be shown that disruption of the NO pathway by ACR will have significant effect on presynaptic function. Cysteine adduct formation will inactivate the presynaptic proteins. These proteins are replaced slowly and damaged cells will accumulate as the rate of removal by protein turnover exceeds the rate of adduct formation.

SIMILAR MECHANISMS OF ACTION



CONCLUSION

It has been shown that both mercury and acrylamide are prevalent in nature. Mercury occurs naturally but has been widely dispersed in its use in industry and is still available as methylated mercury in our food supply.. Acrylamide is not only used in industrial settings but occurs in food preparation. Both molecules are capable of crossing the blood-brain-barrier and accumulating in the cerebral cavity. Both molecules are neurotoxins and bind to thiols such as glutathione disrupting neural pathways. By binding to glutathione it is possible that if the body is exposed to both substances before either can be metabolized by the body then an additive effect can occur. If some other condition exists to limit the production of glutathione then a synergistic effect may occur.

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