Dietary Source, Mechanism, Toxicity of Acrylamide: A Review

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Abstract- Acrylamide (AA) is an industrial chemical used primarily in the production of dyes and polymers. It forms in foods during high-temperature cooking techniques (such as frying, toasting, roasting, or baking) of foods heavy in carbohydrates at temperatures exceeding 120ºC, it has recently acquired attention. It is important to comprehend its hazardous consequences because of the large exposure potential. Research has demonstrated that Acrylamide can be immunotoxic, neurotoxic, and reproductively toxic. The precise processes are yet unknown, however oxidative stress and apoptosis are thought to be important contributors to its toxicity. It was shown that the main harmful consequence following occupational exposure was neurotoxicity. AA is carcinogenic to multiple organs, genotoxic through a reactive metabolite called Glycidamide, and toxic to male germ cells as well as reproduction and development in rats and mice. Neither dietary nor occupational exposure was linked to an increased risk of cancer, according to epidemiological research. Reducing Acrylamide production and related health hazards may be possible by altering food processing techniques.

Keywords: Acrylamide, Polyacrylamides, Hazardous, Immunotoxic, Neurotoxic, Oxidative stress, Apoptosis, Carcinogenic, Genotoxic, Glycidamide, Epidemiological.

INTRODUCTION

Acrylamide, commonly referred to as 2-propenamide (C3H5NO), is a white, odorless, water-soluble, crystalline, highly reactive solid with a molecular weight of 71.08 gmol−1 [1]. The vast majority of thermally processed foods high in carbs include it, which has made it a serious concern. In 1994, the International Agency for Research Cancer (IARC) identified it as a possible human carcinogen, neurotoxicant, and genotoxicant.

Physicochemical properties of Acrylamide:

IUPAC name : prop-2-amide
Molecular Formula : C3H5NO
Molecular Weight : 71.08 gmol−1
Density : 1.122g/L (25ºc).
Boiling point : 125ºc at 3.3kPa.
Melting point : 84.5ºc.

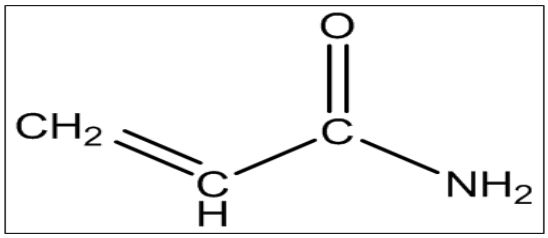

Figure 1: Schematic representation of Acyrlamide structure.

Dietary source of acrylamide:

Figure2: Dietary sources of acrylamide

The Joint Expert Committee on Food Additives (JECFA) reported that key sources of acrylamide in daily meals across the world include potato chips, crisps, coffee, baked goods, and sweet biscuits, particularly in carbohydrate-rich foods cooked at temperatures over 120 °C [2].

After consumption, ACR is readily absorbed in the gastrointestinal system and proceeded to several tissues, including the heart, brain, liver, kidney, and even the blood-brain and blood-placenta barriers (Fennell, 2004; Fennell et al., 2005). After intake, the liver converts ACR to glycidamide (GA), which can subsequently pair with glutathione (GSH) or create adducts with proteins and DNA, potentially leading to a variety of harms (Pernice et al., 2009; Von Tungeln et al., 2012). Epidemiological and investigative studies have shown that dietary exposure to ACR has a significant association with a higher likelihood of ovarian cancer (Adani et al., 2020), chronic renal failure (Chien-Ning et al., 2020), hypertension (Liang et al., 2022), and diabetes (Guangli et al., 2021). The International Agency for Research on Cancer has classified ACR as a potential human carcinogen. Neurotoxicity, hepatotoxicity, genotoxicity, and development toxicity are among the toxicities of ACR that have also been proven in animal and culture studies (Rifai and Saleh, 2020). ACR's toxicological mechanism is still not entirely understood. Additionally, it is critical to identify preventative measures for toxicities linked to ACR. In thermally processed foods, it is well known that certain phytochemicals can inhibit the production of ACR. More intriguingly, these phytochemicals have been found to reduce oxidative stress damage by scavenging free radicals and altering signaling pathways. This may offer significant opportunities to prevent toxicities caused by ACR and to promote health [3].

In addition to dietary sources, other ways that acrylamide can be exposed include inhalation, tobacco use, and skin absorption. Because the skin serves as a barrier and inhibits the absorption of acrylamide, dermal exposure is less significant. On the other hand, food exposure is still a major worry [4,5]. Furthermore, a recent advancement in the detection of dietary acrylamide in food and other sources is the application of novel methods for the design and development of processes, such as the use of electronic devices for biosensors [4]. Nevertheless, there aren't many evaluations that go into great detail regarding how acrylamide is formed, mitigated, and detected.

Table1: Acrylamide levels in various diets

Category	Samples Tested	Samples Positive	Level of Acrylamide (µg/kg)			
			Mean	SD	Min	Max
Soybean paste	4	4	13.70	8.39	4.08	24.40
Processed meat	6	6	22.62	20.10	2.31	49.06
Rice roll and noodle	11	9	23.22	15.19	9.12	52.09
Cooked meat	5	5	25.03	21.97	2.71	78.57
Sauted nut	8	7	25.14	19.09	4.04	54.66
Roasted bread	5	5	36.72	26.54	10.50	67.19
Wafer biscuit	6	5	44.92	33.86	10.36	86.76
Roasted rice cake	6	6	68.34	65.75	16.82	196.46
Pancake	8	7	70.33	127.86	1.88	352.90
Roasted biscuit	24	23	97.57	103.71	0.41	484.17
Crisp	11	9	137.91	119.68	17.39	398.23
Fried flour snack	8	8	131.73	122.75	39.12	432.92
Fried rice crust	8	8	201.51	122.62	100.46	491.76
Fried prawn strips	4	4	341.40	122.95	166.25	439.44
Fried potato	9	9	604.27	1,327.87	58.40	4,126.26
Total	123	115	94.16	54.74	0.41	4,126.26

Mechanism of acrylamide:

First of all, acrylamide is not included in food ingredients. But it is created when a food ingredient is thermally processed—such as by broiling, baking, frying, or roasting—to a temperature of 120 °C or higher [6]. Reducing sugar and asparagine (C4H8N2O3) are the main precursors for the synthesis of acrylamide. This event, called the "Maillard reaction," occurs when free asparagine and reducing carbohydrates like glucose or fructose combine during food heating, forming acrylamide [6, 7]. When exposed to a high temperature, the reducing sugars (glucose and fructose) and the free asparagine in the food ingredient undergo a complex series of reactions that are not enzymatic. This process changes the food's color and flavor and is also referred to as browning. When acrylamide is formed, reducing sugars become extremely reactive due to the aldehyde group of glucose and the keto group of fructose [8]. Figure 3a shows the typical reaction for the synthesis of acrylamide from the asparagine precursor.

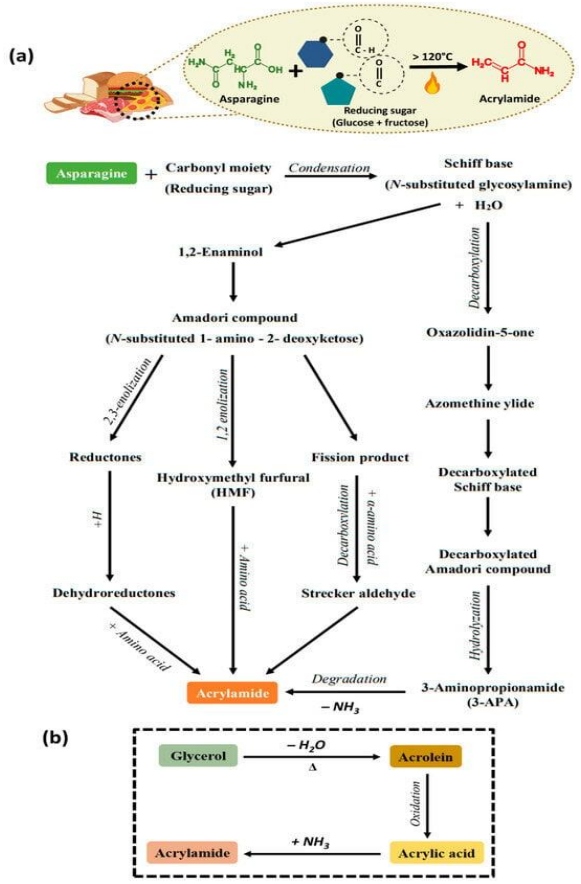

Figure 3: (a) Conversion of asparagine to acrylamide and the overall mechanism of acrylamide formation via the Maillard reaction. (b) Formation of acrylamide via the acrolein pathway.

Schiff bases are created when the asparagine condenses with the reactive carbonyl molecule in the initial stage of the "Maillard reaction" [9]. The Amadori compound is produced when these unstable Schiff bases go through Amadori rearrangement at an acidic pH [8,10]. The Amadori product then passes through enolization to produce reductones and deoxyosones before turning into melanoidin compounds, which give the food its brown hue and scent. "Strecker degradation" is the process by which the dicarbonyl molecules are decarboxylated to produce Strecker aldehyde, which promotes the development of acrylamide in food [11]. The decarboxylation of the Schiff base to Azomethineylide is another mechanism [9]. Following hydrolysis, the decarboxylated product yields 3-Aminopropionamide, which subsequently breaks down to produce acrylamide [12]. Figure 1a illustrates the general process of acrylamide production during the Maillard reaction.

The "Acrolein pathway" is one of numerous minor mechanisms that, in addition to the Maillard reaction, aid in the synthesis of acrylamide in food. The carcinogenicity of acrolein, also referred to by its chemical name 2-propenal, is a major worry [13]. Pyrolysis of glycerols, also known as thermolysis or breakdown of glycerols at high temperatures, can produce acrolein [14]. Following oxidation of acryllein, acrylic acid is created. This acid subsequently reacts with ammonia generated in Strecker degradation to yield acrylamide [15]. Because of the Maillard reaction and the synthesis of acrylamide from asparagine, acrylic acid can also be made from aspartic acid [14]. When fats or oils, especially unsaturated ones, are heated to extremely high temperatures to the point that they release an unpleasant smoke, glycerol dehydrates and becomes acrolein, which in turn produces acrylamide.

In addition to being produced from carbs via the Maillard reaction, acrylamide may additionally be produced from other macromolecules like lipids via the acrolein pathway, proteinogenic amino acids like cysteine and serine via the pyruvic acid pathway, and aspartic acids, β-alanine, and carnosine [17]. Acrylamide has also been discovered to form in meat products through the acrolein pathway when heated to higher degrees, according to Lee et al. [18]. This

occurs when lipid degradation produces acrolein, which oxidizes to produce the acrylamide concentration in meat samples.

Acrylamide and its toxicity:

1) Acrylamide and Oxidative Stress

Research has demonstrated that acrylamide (AA), a chemical frequently present in food preparation (especially in fried or roasted meals), increases oxidative stress in animals. Studies show that acrylamide exposure causes a rise in the production of hydroperoxides and free radicals, which causes lipid peroxidation and other oxidative damage in the brain, liver, kidneys, and testes, among other tissues.

Several studies have documented changes in the antioxidative response in animals exposed to acrylamide:

- SOD activity is elevated in blood plasma, liver, brain, kidneys, and testes of acrylamide-exposed rats, suggesting increased superoxide anion formation.
- GPx activity also increases, alongside depletion of GSH, indicating the antioxidative system is adapting to the higher levels of hydrogen peroxide (H_2O_2) produced during exposure. The depletion of GSH is notably linked to its consumption in detoxifying reactions with H_2O_2 and in conjugation with acrylamide or its metabolite, glycidamide, in phase II detoxification reactions.
- A deficiency in GSH, a key cellular antioxidant, exacerbates redox imbalance, potentially contributing to the pathological effects of acrylamide.

In addition to these adaptive responses, acrylamide exposure leads to increased lipid peroxidation, evidenced by elevated levels of malondialdehyde (MDA), a marker of oxidative damage, in the brain. Such oxidative damage can impair cell structures, including membranes, enzymes, and DNA, further compounding the oxidative stress in the body.

Chronic exposure to high doses of acrylamide induces significant oxidative stress. One study found that SOD activity decreased in the neural system of rats after 10 weeks of acrylamide exposure, likely due to oxidative damage of SOD itself by the superoxide anions it is supposed to neutralize. This suggests that prolonged exposure to acrylamide could overwhelm the antioxidative system, leading to more severe oxidative damage.

The doses of acrylamide used in animal studies ranged from 0.5 µg to 40 mg/kg body weight, with the first signs of oxidative imbalance appearing after 10 weeks of exposure to doses as low as 25 µg/kg. These doses are several times higher than what humans might consume through food, raising questions about the potential health risks of typical dietary acrylamide exposure. While the effects observed in animal studies are concerning, it is unclear whether typical human dietary exposure to acrylamide (which is much lower) is sufficient to cause a similar disturbance in redox balance.

2) Genotoxicity of Acrylamide

Acrylamide (AA) is known to induce oxidative stress, which can lead to both cytotoxicity and genotoxicity. The accumulation of free radicals caused by AA exposure may damage cellular components such as mitochondria, DNA, and other organelles, triggering apoptosis and mutations. This oxidative imbalance can result in cell death or even neoplastic (cancerous) transformation. Free radicals contribute to this damage, leading to DNA oxidation, base mutations, and strand breaks, which are hallmark features of genotoxicity.

AA itself can form 7-formamidoethyl adducts with guanine, one of the nucleic acid bases in DNA, which has been shown to be a significant genotoxic event. The adduct formation follows the pattern: guanine > adenine > uracil in terms of stability. However, its metabolite, glycidamide, exhibits a higher affinity for nucleic acids and forms stronger adducts with guanine, particularly at the N-7 position. The primary DNA adduct formed by glycidamide, N7-dG-glycidamide, is mutagenic, promoting G-T transversions during DNA replication, a mutation type that is linked to cancer development. In laboratory studies, embryonic fibroblasts of transgenic mice exposed to 320 µm acrylamide in vitro showed A-G transitions and G-C transversions, which are indicative of mutagenic effects. Similarly, human lymphocytes exposed to AA

exhibited DNA strand breaks, increased caspase-3 activity, and apoptosis. Furthermore, AA exposure disrupted DNA repair mechanisms, compounding its genotoxic effects.

Chronic exposure to low doses of acrylamide has been shown to significantly increase the formation of glycidamide-DNA adducts in the spermatocytes of mice. Even exposure to doses as low as 0.01 µg/ml in drinking water, administered daily over 9-12 months, led to an increase in double-strand breaks in the germ cells' DNA. This suggests that long-term, low-level exposure to acrylamide can accumulate genetic damage, which may have long-term effects on reproduction and genetic stability.

3) Carcinogenic Potential of Acrylamide

Acrylamide's genotoxic effects are linked to its carcinogenic potential. In animal studies, Fischer 344 rats exposed to acrylamide through drinking water over 106 weeks showed an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in males, as well as mesotheliomas in the testes. Females also exhibited a significant rise in mammary gland tumors, including fibroadenomas and adenocarcinomas. Similarly, long-term studies on Swiss-ICR mice exposed to acrylamide doses ranging from 2.5 to 50 mg/kg per body weight (administered orally every second day for one year) revealed the development of skin tumors (squamous cell papilloma's and carcinomas) and increased lung cancer incidence. These findings suggest that acrylamide has the potential to induce tumorigenesis in animal models, pointing to its pro-oncogenic activity.

Despite the clear carcinogenic effects in animals, epidemiological studies in humans have not shown a direct correlation between acrylamide exposure and an increased incidence of cancer. For instance, studies have not found a consistent link between dietary acrylamide levels and human cancer rates. Nevertheless, the doses of acrylamide causing genotoxic effects in animals are similar to those consumed by people with high dietary intake of acrylamide, which has led to its classification as a potential carcinogen. The European Union and International Agency for Research on Cancer (IARC) have both classified acrylamide as a possible carcinogen, with IARC placing it in Group 2A, indicating that it is probably carcinogenic to humans.

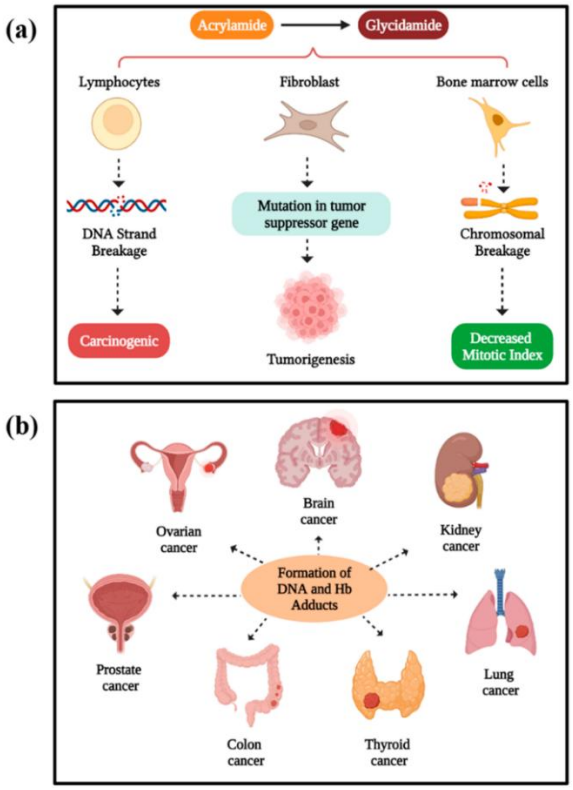

Figure 4: (a) Genotoxic effect of acrylamide and its metabolite glycidamide; (b) carcinogenic effect of acrylamide. Created with BioRender.com.

4) Reproductive Toxicity of Acrylamide

Acrylamide (AA) is a low molecular weight compound that easily dissolves in water, enabling it to pass through biological membranes, including the placenta and breast milk, in both animals and humans. As a result, acrylamide exposure can potentially affect prenatal and postnatal development, particularly during the early stages of pregnancy and infancy. Although human data on the reproductive toxicity of acrylamide is limited, studies suggest that the compound may pose a risk to fetal development, warranting further investigation.

The median acrylamide intake in pregnant women has been estimated to be 33.7 µg/day based on food frequency questionnaires, with urinary metabolites showing a median excretion of 11.2 µg/day. This

corresponds to a median daily exposure of approximately 20.3 µg, with the maximum exposure estimated to be 137.5 µg/day in some cases. It is believed that around 50% of dietary acrylamide crosses the placenta to the developing embryo. The primary dietary sources of acrylamide for pregnant women include potato crisps, biscuits, breakfast cereals, and bakery product

Studies in animals have demonstrated that exposure to high doses of acrylamide during pregnancy leads to significant embryotoxic effects. In rodents, exposure to ≥5 mg/kg body weight/day of AA resulted in increased post-implantation embryo loss and a decreased number of live pups. At higher doses (up to 15 mg/kg body weight/day), reduced pup weight and poor survival rates were observed. Notably, a study by El-Sayyad et al. (2011) found that when pregnant rats were exposed to 30 mg/kg body weight/day from day 6 of gestation until parturition, their offspring exhibited reduced body size, lower brain size, and signs of muscular dystrophy. These pups also showed ultrastructural changes in the cerebral cortex, suggesting that early neurological development was significantly impaired.

Acrylamide also appears to negatively impact male fertility. Sperm count and motility are both affected by acrylamide exposure, and DNA damage in male reproductive cells has been demonstrated in animal studies. The formation of glycidamide-DNA adducts and DNA fragmentation in the germ cells of male mice exposed to low, chronic doses of AA was observed by Nixon et al. (2012). These DNA lesions in sperm can lead to genetic damage being transmitted to the zygote during fertilization, potentially increasing the risk of developmental abnormalities in offspring. Furthermore, Sakamoto and Hashimoto (1986) showed that male rats exposed to 19 mg/kg body weight of acrylamide for eight days had reduced fertility rates and a higher incidence of embryo resorption when mated with unexposed females. Additionally, Zenick et al. (1986) found that exposure to 100 ppm of acrylamide impaired mating performance, ejaculatory processes, and sperm transport in rats.

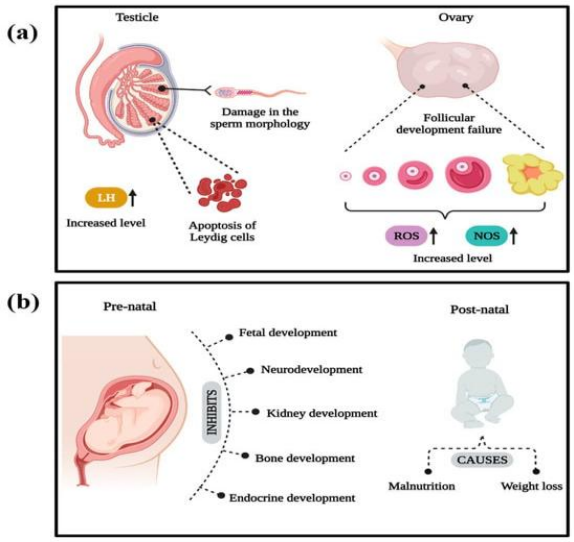

Figure 5: (a) Reproductive toxicity of acrylamide. (b) Prenatal and postnatal effects of acrylamide. Created with BioRender.com.

5) Neurotoxicity of Acrylamide

Acrylamide (AA) is known to induce neurotoxic effects in both humans and animals, primarily manifesting as peripheral neuropathy and, in some cases, central nervous system (CNS) damage. While the human neurotoxic effects of acrylamide have been documented through occupational exposure, where peripheral neuropathy was the most common symptom, more detailed animal studies have further elucidated the mechanisms and broader spectrum of neurotoxic effects.

Human studies have shown that occupational exposure to acrylamide, typically at high levels, leads to peripheral neuropathy, characterized by muscle weakness and ataxia. Similarly, in animal studies, chronic oral exposure to acrylamide has produced clinical signs of peripheral neuropathy. For example, monkeys exposed to 10 mg/kg body weight/day for up to 12 weeks exhibited signs of muscle weakness and ataxia (SCF, 2002). In rats, exposure to 40 mg/kg body weight every second day for 10 weeks caused hind limb paralysis, abnormal gait, and foot splay. These motor impairments were linked to alterations in the electrophysiology of the sciatic nerve, possibly due to damage to the myelin sheath and/or disruption in the Na/K-ATPase function (Zhu et al., 2008).

Acrylamide exposure also causes damage to the central nervous system. Studies involving rat pups exposed to acrylamide in utero (at doses of 30 mg/kg body weight) and via lactation showed significant ultrastructural changes in the cerebral cortex. These included pyknotic neuronal cells, apoptotic cell death, and the loss of Purkinje cells and granular neuronal cells (El-Sayyad et al., 2011). These structural changes suggest that acrylamide exposure during development can lead to both immediate and long-term effects on brain function, likely affecting neurocognitive and motor functions.

Acrylamide exposure has been found to affect acetylcholinesterase activity, an enzyme essential for cholinergic neurotransmission. In mice exposed to acrylamide doses of 20-40 mg/kg body weight, a decrease in acetylcholinesterase activity was observed in the cerebrum, cerebellum, and medulla oblongata. This suggests prolonged residence of acetylcholine in synapses, which could lead to excessive cholinergic stimulation. Such changes could disrupt memory formation, muscle control, and autonomic functions (Kopańskaetal.,2015).

The neurotoxic effects of acrylamide are thought to involve several mechanisms. One significant mechanism is the conjugation of acrylamide with cysteine residues on presynaptic proteins involved in neurotransmitter release, which can impair nerve impulse transmission and lead to neuronal degeneration (LoPachin and Barber, 2006; Pingot et al., 2013). Another important contributing factor is oxidative stress. Acrylamide exposure has been linked to redox imbalance, which is associated with the production of free radicals. These free radicals can contribute to lipid peroxidation, which in turn leads to neurodegeneration. Studies by Zhu et al. (2008) showed that peripheral neuropathy in rats was accompanied by redox imbalance, and in a similar fashion, Kopańska et al. (2015) observed malondialdehyde (a product of lipid peroxidation) accumulation in the brains of acrylamide-exposed mice, further supporting the role of oxidative stress in neurotoxicity.

The link between oxidative stress and neurodegeneration is well-documented. Malondialdehyde, a marker of lipid peroxidation, has been found to be elevated in Alzheimer's disease patients, both in their erythrocytes and neurofibrillary tangles in the brain (Matveychuk et al., 2011). Given the evidence that oxidative stress is a major contributor to neurodegenerative diseases, it is plausible that chronic exposure to acrylamide, which induces redox imbalance, could play a role in the etiology of neurodegenerative conditions, including Alzheimer's disease.

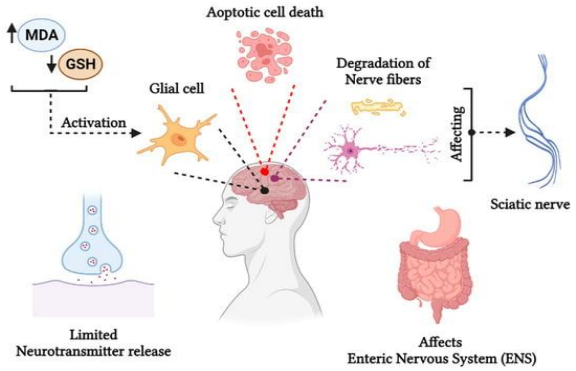

Figure 6: Neurotoxic effect of acrylamide created with BioRender.com.

CONCLUSION

Acrylamide is one of the main harmful substances produced by the Maillard reaction in thermally cooked food. Acrylamide consumption that is too high may pose health hazards. A lot of research has been done on the causes of acrylamide in food. Nonetheless, most studies have focused on general factors like pH, moisture content, and temperature and aim to focus more on the effects of specific/particular components that cause food to brown. According to the Joint Expert Committee on Food Additives (JECFA), coffee, baked goods, potato chips, crisps, and sweet biscuits are major sources of acrylamide in everyday meals worldwide, especially in carbohydrate-rich foods prepared at temperatures higher than 120 °C. Many international organizations, including the Food and Drug Administration and the World Health Organization, currently recognize AA as a food-borne toxicant. This review also includes the toxic effects caused by the acrylamide such as neurotoxicity, genotoxicity, reproductive toxicity, carcinogenicity. People should also be made aware of the possible

health risks connected to consuming foods that contain acrylamide. It is still very difficult to comprehend the molecular process and the variables that contribute to the production of dietary acrylamide.

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[19] M. SEMLA1, Z. GOC1, M. MARTINIAKOVÁ2, R. OMELKA2, G. FORMICKI1 1 Pedagogical University of Cracow, Institute of Biology, Kraków, Poland, 2 Constantine the Philosopher University in Nitra, Faculty of Natural Sciences, Nitra, Slovak Republic Acrylamide: a Common Food Toxin Related to Physiological Functions and Health