Acrylamide Toxicity and Mitigation Strategies: A Summary of Recent Reports

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Author’s contribution
The sole author designed, analyzed and interpreted and prepared the manuscript.

ABSTRACT
Acrylamide is a potential carcinogen, with proven neurotoxicity and genotoxicity. In the current scenario, neurotoxicity and reproductive toxicity of acrylamide have not been conclusively established for humans; however, the same has been established in laboratory animal species. In this review, we summarize the factors dictating the exposure of acrylamide to humans and subsequently caused toxicity to humans. Further, we review the neurotoxic and genotoxic effects of acrylamide on animal models, with a particular emphasis on reproductive toxicity. We also talk about various strategies such as physical, chemical, and biological approaches, employed for acrylamide. Overall, we discuss that consumption of acrylamide through food products has toxic effects on the endocrine system, and it is deleterious for human health. A novel aspect of this review is that we provide a molecular mechanism of action in conjunction with clinical data on acrylamide toxicity along with relevant examples. This review also highlights the requirement of further research on the consequences of acrylamide toxicity, molecular modes of action, and the overall impact on the human body.

Keywords: Acrylamide; reproductive toxicity; central nervous system; carcinogenesis; neurotoxicity syndromes; occupational diseases.

1. INTRODUCTION
Acrylamide (AA) or acrylic amide is a colourless, odourless, water-soluble crystalline solid, commonly used in the production of dyes, organic compounds, and other industrial purposes.[1-4] This is a potential carcinogen, and the nervous system and the reproductive system

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are severely affected by acrylamide toxicity.[5-12] However, there has been much evidence of acrylamide toxicity, and acrylamide is still consumed in a dietary form wherein it is formed in several food products, rich in carbohydrates when cooked at high temperatures.[13-16] According to recent reports, acrylamide has been found in many commonly consumed foods and has shown to cause hazardous effects on humans and animals.[1,2] Acrylamide levels in food differ based on the food content, the cooking duration, and the technique employed. Studies on acrylamide toxicity, risk assessment, and mitigation have been extensively carried out, which have provided great insight into the current level of understanding of this health hazard.[6,9,15,17,18] According to the Agency for Toxic Substances and Disease Registry (ATSDR), acrylamide is mostly carcinogenic to humans, predominantly based on studies on laboratory animals,[19] and also has been declared as a 2A Group carcinogen by the International Agency for Research on Cancer (IARC).[20] However, one must note that the absorption rate of acrylamide in humans and rodents is different, and also they metabolize acrylamide in a different biochemical manner.[21,22] The No observed adverse effects level (NOAEL) for reproductive toxicity was assessed to be 2–5 mg/kg bw/day among rats, based on the endpoint of fertility or embryonic death.[23] This amount is sufficiently (nearly 2000-fold) higher than the estimated levels of human dietary exposure to preclude any possibility of reproductive toxicity in humans.[6] Furthermore, exposure to high concentrations of acrylamide has resulted in reproductive toxicity in rodents and other laboratory animals. In this review, we will discuss the factors dictating acrylamide exposure to the human body and the harmful effects caused after that. We also shed light on recent research on the neurotoxicity and genotoxicity caused by acrylamide on animal models, with a special focus on reproductive toxicity.

2. FACTORS RESPONSIBLE FOR ACRYLAMIDE EXPOSURE

Acrylamide is a highly reactive organic compound that can polymerize and has wide applications in many industries.[1-3] Acrylamide is widely used for wastewater treatment in cosmetic industries and molecular biology research.[24] Its exposure can be either through the diet we take or our surrounding environment which is discussed herein afterward.[9,25]

2.1 Dietary Exposure

Consumption of acrylamide in our daily diets or food is of significant concern. Acrylamide formation can be due to overheating, pH, water content and the reactivity of the various components.[24,26] Elevated temperature increases the formation of acrylamide along with the time of heating individually or jointly. Generally, no acrylamide is detected in the unboiled food, but the acrylamide content increases as the water content or pH of the food rises. The formation of acrylamide is highest at the temperature 190 degrees or above, an example of which is the increase in acrylamide concentrations in French fries upon heating.[27] For instance, boiling or autoclaving of starch generates the production of acrylamide.[28] Higher acrylamide content is observed in processed foods such as chips, fried potatoes, corn flakes, bread, etc.[29] Gingerbread and coffee also have been found to contain a high amount of acrylamide.[30] Surprisingly, acrylamide is also present in breast milk, and 10-50% of it is transferred from a pregnant woman to the developing fetus via the placenta.[31] Females who consume alcohol are exposed more to acrylamide than the abstainers. Acrylamide exposure is not only because of the consumption of acrylamide containing food but also the amount of the food consumed.

2.2 Environmental Exposure

The external source of acrylamide is mostly from industrial wastewater, drinking water, cosmetics and textile industry, tobacco smoke, etc.[32,33] Ingestion, inhalation, or skin contacts are the means of exposure to acrylamide. Single cigarette smoke contains approximately 1 µg of acrylamide.[7] Other tobacco products such as snuff, tobacco strips, etc. contain acrylamide in the range of 100 to 367 ng/g of dry weight.[7] Also, the drinking water is often contaminated with acrylamide, which is used as a flocculating agent for treating the wastewater. Exposure to acrylamide also occurs in scientific labs while casting the polyacrylamide gels. Occupational exposure mainly affects miners or workers of coal preparation plant laboratory workers, chemical plant workers, and construction industry workers.[25]

3. ACRYLAMIDE INDUCED TOXICITY AND MECHANISMS

Acrylamide toxicity manifests itself in the form of peripheral neurotoxicity, mutagenicity, male
3.1 Acrylamide Causes Oxidative Stress

Oxidative stress conditions arise when there is an imbalance in the amount of free radicals (or reactive oxygen species, ROS such as hydroxyl radicals, superoxide anion, hydroperoxide) and antioxidants in our body. Free radicals are molecules that contain an uneven number of electrons and, hence can react with various other molecules in our body causing their oxidation.[40,43,44] Under normal physiological conditions, these ROS molecules are scavenged and controlled by anti-oxidative system of our body including enzymatic as well as non-enzymatic reactions.[11,15]

During oxidative stress conditions, these reactive oxygen species can oxidize biomolecules such as protein, lipid, DNA, which make up most of the body leading to protein oxidation, lipid peroxidation, DNA fragmentation, cell death, etc.[9,15] thereby creating stress and diseased condition (Fig. 1). Antioxidants are protectants in our body that protect us from oxidative stress by providing electrons to ROS without getting affected. Ascorbic acid, tocopherol, flavonoids, and beta-carotene are some non-enzymatic antioxidants that assist in mitigating the effects of oxidative stress.[45] Enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) have antioxidant capacity. Glutathione (GSH) is an integral part of the anti-oxidative defense system and the third line of defense. It participates in the repair of damaged cell components.[44]

There are reports which suggest that animals exposed to acrylamide produce enhanced levels of reactive radicals and hydroperoxides.[46] An increase in thiobarbituric acid reactive substances was found in the rats that were orally administered acrylamide.[47] Additionally, these rats exhibited deterioration in the anti-oxidative enzymes and lipid peroxidation in a dose-dependent manner.[47] The exposed rats also showed increased levels of SOD activity in liver, kidney, testes, and brain in response to the increased rate of superoxide anion in the whole organism.[47] Reduction in the GSH levels is commonly found in animals exposed to acrylamide. The depletion of GSH is majorly seen higher when consumptions involve reactions, including hydrogen peroxide.[48] These studies imply that there is an enhanced activity of anti-oxidative defense system, which is activated by acrylamide and furthermore, increasing the exposure of acrylamide causes oxidative stress in animals.[7]

3.2 Acrylamide Induced Neurotoxicity and Genotoxicity

World health organization (WHO) has already declared that acrylamide is neurotoxic to humans.[49] Neurotoxicity is due to the cumulative effect of acrylamide exposure.[8,34,46] Usually, the people regularly affected are industrial workers, mine workers, people working in flocculating industries.[25] It is noted in several animal studies that acrylamide exposure affects the central nervous system. It is found in reports that rat pups born to mothers who were exposed to acrylamide and fed milk from the lactating rats exposed to acrylamide, had damaging cerebral cortex malfunctions, which included the death of Purkinje cells and granular neuronal cells, enhanced apoptosis.[50] Acrylamide is also present in breast milk, and a significant proportion of it is transferred to the developing fetus via the placenta.[31]

One probable accepted mechanism for acrylamide neurotoxicity is the inhibition of neurotransmitter release (Fig. 2), which happens due to the conjugation of acrylamide to the cysteine amino acids of the presynaptic membrane proteins.[51,52] The neurodegenerative effect of acrylamide is due to its involvement in causing redox imbalance and thereby generating reactive oxygen species. In turn, the activity of acetylcholinesterase neurotransmitter is also affected due to ROS.[53] Degeneration of dopaminergic neurons and the accumulation of alpha-synuclein are manifestations of acrylamide exposure, ultimately leading to Parkinson’s pathology.[54]

3.3 Acrylamide Induced Reproductive Toxicity

Over the past several years, there have been many research projects examining the effects of acrylamide on rodent reproductive performance. There was also found to be a strong correlation...
Table 1. Summary of acrylamide toxicity observed in experimental models

| Model system                              | Objectives                                                                 | Conclusions                                                                                           | References          |
|-------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------|
| BALB/c mice                               | Effect of acrylamide and its metabolite glycidamide on meiotic maturation of mouse oocytes in vitro and in vivo. | Acrylamide exposure causes severe toxicity to mouse oocytes through its metabolite glycidamide.       | Aras et al. [37]    |
| PC12 cells (rats)                         | Characterization of acrylamide neurotoxicity in PC12 cells by determining the roles of apoptosis, and other signaling pathways. | Acrylamide exposure triggered apoptosis, induced oxidative stress and mitochondrial dysfunction.      | Pan et al. [38]     |
| Human                                     | Association between dietary acrylamide intake and the incidence of endometrial or ovarian cancers in Japanese women. | No associations were found between dietary acrylamide intake and endometrial or ovarian cancer risks. | Kotemori et al. [39]|
| Human colon adenocarcinoma (Caco-2)       | Assessment of comprehensive mechanisms of the cytotoxic and genotoxic action of acrylamide on Caco-2 cell line. | Acrylamide has a pro-oxidative effect on Caco-2 cells, which leads to apoptotic cell death.           | Nowak et al. [18]   |
| Male rats                                 | Role of oxidative stress and other signalling mechanisms against acrylamide induced neurotoxicity was examined. | Thymoquinone protected against acrylamide-induced neurotoxicity by means of antioxidant and anti-apoptotic properties. | Tabeshpour et al.[40]|
| Roundworm (C. elegans)                    | Effects of chronic acrylamide exposure on three major neuron classes that regulate motor movement. | Chronic acrylamide exposure leads to locomotor defects by mediating degeneration of specific neuron types. | Murray et al. [34]  |
| Human                                     | Association between exposure levels of acrylamide biomarkers and the prevalence of cardiovascular diseases in general US population. | Acrylamide exposure showed significant association with total and individual cardiovascular diseases in US population. | Zhang et al. [41]   |
| Fruitfly (D. melanogaster)                | Toxic effects of dietary acrylamide exposure and reversal due to antioxidants. | Acrylamide causes developmental and neurological toxicity which is partially rescued by Thymoquinone and Curcumin. | Senthilkumar et al. [35] |
| Female mice                               | Effects of acrylamide on the oocyte maturation, apoptosis and other developmental hallmarks in vitro. | Acrylamide decreased oocyte maturation, increased chromosome misalignment and caused other developmental disorders. | Liu et al. [42]     |
| Clam(M. corallina)                        | Effects of acrylamide exposure on the fatty acid composition and redox status of the bivalve molluscs. | Acrylamide caused genotoxic effects by producing high amounts of oxidized metabolites and alteration in fatty acid composition. | Trabelsi et al. [43]|
between neurotoxicity and male reproductive toxicity in animal models. A detailed report by Tyl and co-workers highlighted the impact of acrylamide toxicity on male reproductive performance in rats.[55] At the dosage rate of 60 mg/kg/day, the mating index and the fertility index showed a significant depression among the tested subjects. In this study, male systemic toxicity was observed at dosage rates of 15, 30, 45, and 60 mg/kg/day, which in turn depended on body weight changes that occurred during the dosing period. They also determined a strong relationship between systemic toxicity and reproductive effects. In another recent study by Rajeh and Al-Shehri,[56] the antioxidant effect of *Ferula* sp. root extract was investigated on the acrylamide-induced testicular toxicity in male rats. The authors found that acrylamide exposure induced histopathological changes in testes and liver of rats. They also found that the *Ferula* sp. root extract can act as a weak antioxidant in response to the acrylamide-induced testicular toxicity. Lastly, a recent study provided novel insights into the repercussions of acrylamide toxicity on female reproduction.[57] It also revealed that when female mice were orally administered varying dosages of acrylamide, a significant reduction in body weights, organ weights, and the number of corpora lutea were observed. This study also deciphered that acrylamide exposure can cause reproductive toxicity in female mice, and most likely, due to Nitric Oxide Synthase (NOS) signaling pathway.

**Fig. 1.** A schematic representation of the connection between calcium signalling and genotoxic effects of acrylamide in animal models. Figure adapted with permission from Kumar et al. [9]
Fig. 2. A diagrammatic representation depicting the mechanism of action of acrylamide causing thyroid tumor in animal models. Figure adapted with permission from Kumar et al. [9]

4. ACRYLAMIDE MITIGATION

An important aspect of acrylamide risk assessment and risk management is the detection of acrylamide and identification of unfavorable health effects and consequences of the exposure to acrylamide so that we can plan for, avoid, or mitigate the repercussions.[6,12] Acrylamide mitigation can be carried out in several ways, including biological, physical, and chemical methods. The optimal biological approach to go about acrylamide mitigation in food is to reduce asparagine and reducing sugars, which are the two main precursors of acrylamide, in the raw material used for food preparation. Another method to reduce the consumption of acrylamide precursors is to employ genetic tools to generate crops that have reduced asparagine and reducing sugar, which are predominantly used in food preparation.[12] We can also carry out acrylamide mitigation using physical methods, whereby one can change the food processing and preparation techniques, focusing specifically on temperature correction, time monitoring, and moisture regulation.[1,2] Reduction in the formation of Maillard reaction products and acrylamide is possible by adjusting physical parameters such as moisture content and temperature. Another approach towards acrylamide mitigation is the use of chemical pre-treatments, which can extract the amino acids and free sugars that subsequently participate in the formation of acrylamide and other by-products.[7,36] It has been observed that acrylamide formation has been reduced in potato-based food products when the procedure is preceded by rinsing, blanching, and soaking treatments. Lastly, antioxidants and other phytochemicals may be present as endogenous secondary metabolites,
or they can be provided as exogenous additives, which can result in the reduction in acrylamide levels by the means of chemical modification.[6,12,15] The use of antioxidants and phytochemicals is the optimal approach for overcoming acrylamide toxicity. In some cases, the treatment of experimental animals with the flavonoid molecule, quercetin appeared to combat the toxicity generated by this noxious chemical agent. For patients exposed to potentially lethal doses of acrylamide (either intentionally or accidentally), therapeutic techniques involve administering antioxidants, vitamin B6, vitamin C, melatonin, and other drugs along with supportive therapies.[25,58,59]

5. DISCUSSION AND CONCLUSION

In this review, we have highlighted the causes and consequences of acrylamide toxicity pertaining to the human body. In contrast to other reviews on this subject, the novel outlook presented here lies in comparing the clinical outcomes and the molecular modes of action in a simultaneous manner.[8,11,17] This study also provides a more recent summary of the cases of acrylamide toxicity observed in experimental models (Table 1). There appears to be a consensus among governing authorities in several countries that sufficient figures regarding acrylamide levels in different foods are not available. Our analysis sheds light on the various modes of exposure to acrylamide and the consumption of acrylamide-containing food products. With a particular focus on reproductive toxicity, we have discussed various forms in which acrylamide toxicity manifests itself.

Since significant levels of acrylamide compounds in the consumed foods products influences various endocrine systems, the requirement of further research is the need of the hour to elucidate the outcomes, molecular mechanisms of action, and the consequences with regards to the human body. Thus, it becomes imperative that more studies are carried out to investigate the absorption, storage, elimination, and metabolic outcome of acrylamide and its metabolites. Furthermore, in cases where acrylamide exposure is an occupational hazard, sufficient precautionary measures must be taken to evade the repercussions of the neurotoxic and genotoxic effects of acrylamide.

DATA AVAILABILITY STATEMENT

No data were used to support this study.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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