

## MINI REVIEW

# Review on Chronic Exposure to Acrylamide Causes a Neurotoxicity Risk

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**Abstract:** The exposure and inhalation of acrylamide (ACR) are not safe to the human health leading to the potential neurotoxicity. ACR is widely used in biochemical techniques and highly occurs in processing foods such as potato chips prepared at high temperatures. ACR is formed from reducing sugars and asparagine through the Maillard reaction. It exerts various harmful and toxic effects such as neurotoxicity both in humans and animal studies. The extensive damage of synaptic proteins, the formation of ACR-DNA adducts, degeneration of motor neurons, neurofilament reduction, are the most common neurological symptoms. The main metabolite of ACR metabolism is glycidamide, and it causes harmful effects as same as ACR. The main purpose of this study is to analyze the neurotoxic effects of ACR on various regions of the brain and its different mechanistic pathways that are involved in ACR neurotoxicity. The consumption of ACR-containing foods and its exposure are reduced by the human, leading to the reduction of toxic effects associated with ACR.

**Keywords:** Acrylamide, human, animal, neurotoxicity.

## 1. INTRODUCTION

Packed food items are commonly used as being more energy dense and fewer nutrients dense than foods consumed at meals due to the attractive nature. Consumers have beneficial effects for consumption of packed foods to provide with a required energy balance [1]. Acrylamide (ACR) occurs in greater amounts with potato chips and augments a health concern worldwide due to its carcinogenicity [2]. As the ACR molecule is small and hydrophilic, it passively disperses throughout the body [3]. The application of ACR in different industrial and laboratory purposes depends on the polar nature [4]. Potato chips are constructed by frying thin potato slices in hot oil and contain unique qualities of crispy, texture, color, and flavor [5]. Snack items are widely consumed in South India, Asian countries and ACR occurs in higher levels in potato chips, which indicated the general risk of consumer exposure [6]. At the high temperature, the ACR is formed from the precursors present in potatoes [7]. ACR is manufactured from the sources of asparagine, glucose, and fructose through the process of Maillard reaction pathway [8].

ACR is extensively preferred in the paper and textile industries, wastewater treatment, ore processing, and cosmetics [3,11]. The potato chips contain higher amounts of ACR than any other foodstuffs (Table 1). ACR and acrylonitrile act as a neurotoxic agent for prolonged and chronic exposures [12,13]. The fast-food restaurant workers found to be higher levels of ACR due to occupational hazards and ACR inhalation [14]. Tobacco smoke products are the significant source of ACR and chronic smokers have reported that increased concentrations of ACR in comparison with non-smokers [15]. Radiofrequency post-processing may be an effectual procedure for lessening the amounts of ACR in the potato chips without inauspicious attributes [5]. The aim of the present study was to determine the effects of ACR exposure and its neurotoxic effects.

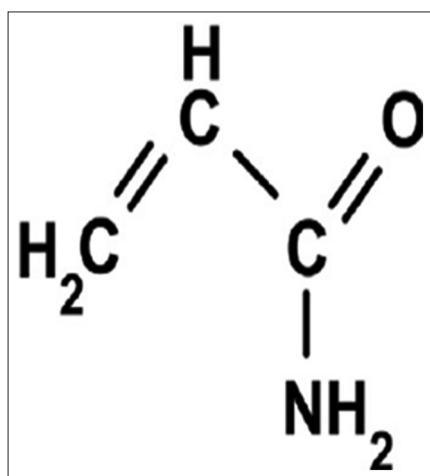
## 2. NEUROTOXICITY OF ACR

### 2.1. ACR and Brain

The ACR molecule consists of two principal functional groups: An amide group and a vinyl group (Fig. 1). ACR has

**Table 1. Concentration of acrylamide content in different food stuffs [9,10]**

Food items	Concentration of acrylamide (µg/mg)
	Median
Potato chips	1200
French fries	450
Biscuits and crackers	410
Pan fried potatoes	300
Breakfast cereals	160
Corn chips	150
Crispbread	140
Soft bread	50
Coffee	25

**Fig. (1). Structure of acrylamide [72].**

been revealed as a carcinogen to humans [16,17]. The ACR is absorbed through the intact skin, mucous membranes, and lungs and acts as neurotoxic agent [18]. ACR exerted chronic damage throughout the ascending somatosensory system of the nervous system [19]. The common features of ACR exposure produce a central-peripheral distal axonopathy in human and some animal species. The main aspects of ACR neurotoxicity are an abnormal sensation, decreased motor strength, and ataxia [20]. Lopachin and Lehning reported that the ACR could be able to diminish axolemmal Na/K-ATPase activity leading to the aberrant cell body processing and deficient axonal transport. The membrane depolarization and distal axon degeneration are the common neurological effects of ACR [21].

The abnormal sensation of decreased motor strength, Rombergism, and skin abnormalities are the major and chronic disease conditions in ACR exposed human subjects [22]. The group of ACR-treated rats exhibited a significant decline in neurobehavioral and electrophysiological responses [23]. The subacute exposure of ACR in the rats contributes to the neuropathy through the functional damage of synaptic proteins and vesicles [24]. The toxic nature of ACR is synthesized from the precursors

such as glucose, fructose, and asparagine (Fig. 2). The animal model of zebrafish impersonates the pathophysiological disease conditions as same as humans and mammalian species. It exhibited the alterations of motor function and presynaptic nerve terminals at the neuromuscular junction. Analysis of neurotransmitter profile showed a significant effect on cholinergic and dopaminergic systems due to the chronic effects of ACR [25]. Faria *et al.* [11] reported that the development of psychological disorders was observed in response to ACR exposure.

## 2.2. ACR and Cerebellum

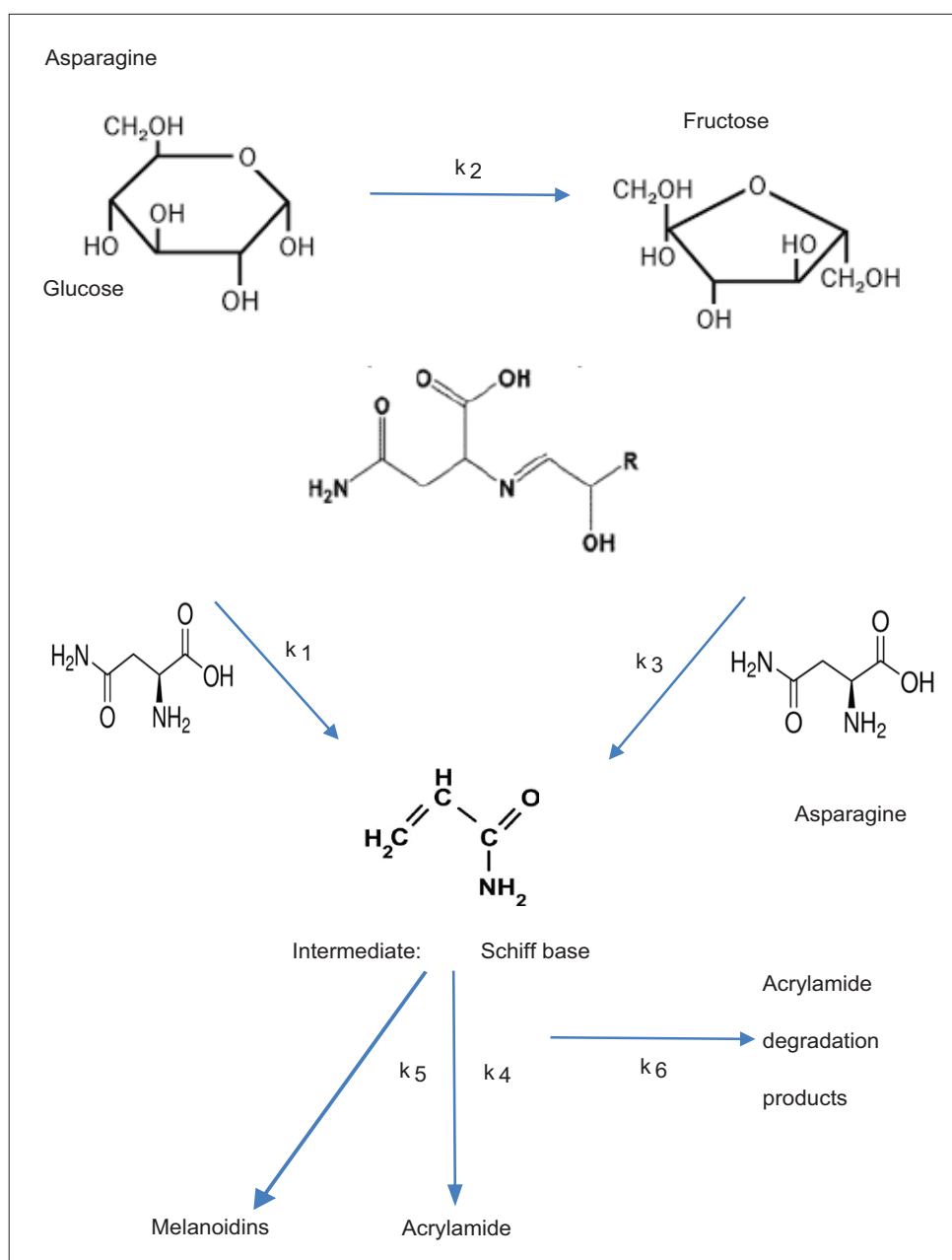
The occupational exposure of ACR to human exerted chronic neurotoxicity symptoms are characterized by ataxia, weakness of skeletal muscles, and numbness of hands and feet [27, 28]. The distribution of ACR could develop the lesions of pyknotic granule cells which present in anterior portions of the cerebellum and small neurons of lamina II and III which occur in the cerebral cortex [29].

ACR treatment retarded the proliferation of the granular layer leading to consequences of cell migration and differentiation. The ACR-treated animals showed that increased loss of purkinje cells. The prenatal and perinatal ACR or its metabolites may interrupt the biochemical machinery through the formation of oxidative stress and induced alterations in rat cerebellum [30]. ACR and its metabolites induced abnormalities through its toxic effects of elevated heel splay, decreased grip strength, and locomotor activity in the cerebra of neonatal rats [31].

## 2.3. ACR and Biochemical Studies

ACR may able to block the intracellular transport of gamma aminobutyric acid (GABA) receptor resulting in the downregulation of the microtubular system and deterioration of neurofilaments [32]. ACR showed higher rates of reduction in the number of neurites per cell, protein synthesis, and intracellular calcium concentration [33]. The adduction of cysteine residues on N-ethylmaleimide-sensitive factor (NSF) and SNARE proteins are involved in the nerve terminal dysfunction enhanced by ACR [34]. The ACR displayed the raised inhibition of kinesin-based fast axonal transport, alterations in the amount of neurotransmitters, and neurotransmission [35]. Al-Gholam *et al.* reported that the ACR experimental group has been shown to induce apoptosis and oxidation, degeneration of motor neurons, myelin sheath, and neurofilaments [36]. ACR had shown the inhibitory effects on human neuroblastoma, and glioblastoma cellular differentiation leads to disturbances in the nervous system [37,38].

The decrease in the potential amplitude, neurogenic abnormalities, and prolongation of the ankle tendon reflex latency are of greater importance in the early detection of ACR neurotoxicity in occupationally exposed workers [12]. The hind limb splay test is a more sensitive indicator of peripheral neuropathy and displayed a significant effect at the higher dose of ACR [39]. The vibration threshold is potentially useful for screening peripheral nerve dysfunction



**Fig. (2).** The formation of acrylamide from sugars and asparagine groups [26].

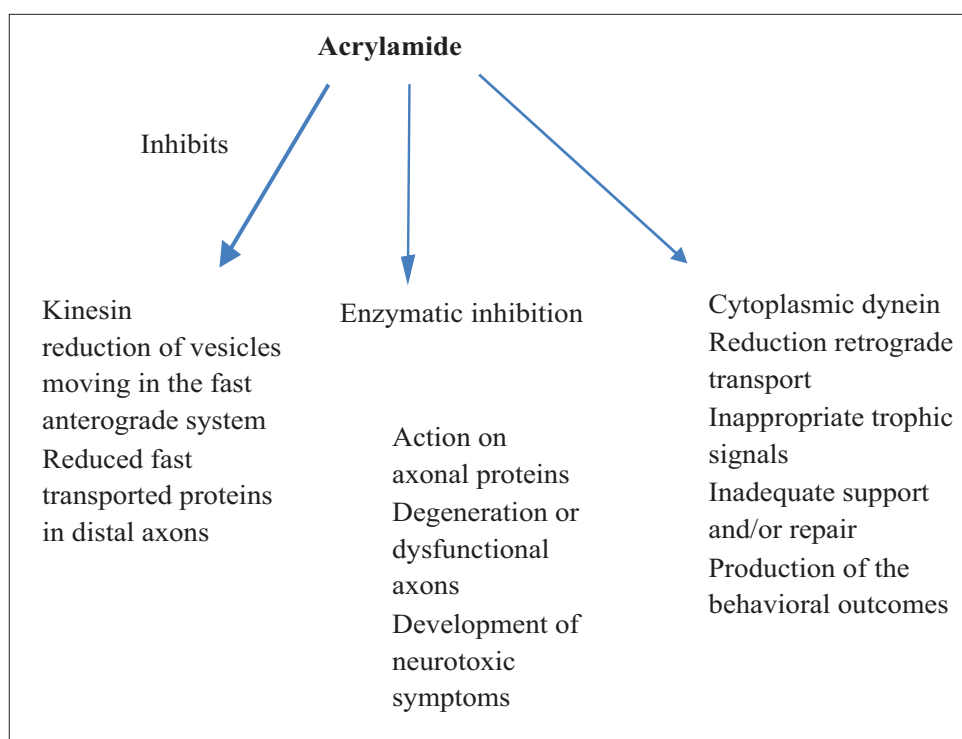
and explained higher levels in experimental subjects than normal controls [27]. The major histological findings described that axons swelling and decreased diameter of axons in the tissues are the consequences of the ACR exposure [40]. The lower concentrations of plasma testosterone on ACR injection in rat brain have been demonstrated [41,42].

The effect of the repeated doses of ACR results in the alterations of functional integrity of the pain fibers following the surgical lesioning of the sciatic nerves impaired sensory-motor performance in rats [43]. In weaning rats, ACR is positively correlated with neurotoxicity and upregulation of GABA leads to the neuronal degeneration in a dose-dependent manner [44]. The oral administration of ACR causes a significant decrease in catecholamine contents and brain-derived neurotrophic factor (BDNF) in brain tissue with a concomitant significant decrease

in the serum activity of creatinine kinase-BB. The brain levels of malondialdehyde,  $\beta$ -amyloid, activities of acetylcholinesterase, and caspase-3 were enhanced in ACR-induced rats [45]. The ACR showed various neurotoxic effects through the inhibition/reduction of retrograde transport, anterograde transport, and degeneration of axons (Fig. 3).

#### 2.4. ACR and Oxidative Stress

ACR-induced neurotoxicity may be associated with the elevated levels of malondialdehyde, and reduction of the antioxidant status by depleting the levels of neural glutathione is the primary event in ACR-induced neuropathy [46]. The frequent exposure of neuronal cells to the free radicals leads to the development of neurodegeneration [47].



**Fig. (3). The different neurotoxic effects of acrylamide [4].**

Environmentally derived ACR and endogenously generated unsaturated aldehydes might act synergistically to increase cellular damage through the oxidative stress, thereby enhancing the human disease progression [48]. Nitroxidative damage through the upregulation of iNOS enzyme leads to microglial and astroglial activation results in the disturbances between neuron-glia interactions [49].

The formation of hemoglobin adducts is useful for the prediction of peripheral neuropathy due to the hazardous exposure of ACR [50]. In response to reactive oxygen species (ROS), production in the endoplasmic reticulum is the marker for the induction of apoptotic neuronal cell death [51]. The ACR-treated mice group found to be decreased concentrations of albumins and thiols with the concomitant increase in the process of lipid peroxidation results in the development of redox imbalance [52]. ACR found to lower the BDNF with ROS production leads to necrotic death and hemorrhagic damages in fetal brain tissue [53].

### 2.5. ACR and Protein Damage

The rat brain shown to have decreased expression of mRNA with the neurofilament protein subunits on ACR exposure [54]. The ACR could conjugate with cysteine of presynaptic membrane proteins leading to the consequences of the inhibition of nerve impulses associated with the following deterioration of neurons [55]. The ACR interacts with sulfhydryl groups of proteins through the defective neurotransmitter transport into the synaptic vesicles leading to the impaired presynaptic release [56]. The ACR- induced process of apoptosis by binding with kinesin-related motor proteins and fusion proteins at the nerve terminus [57]. Theneurotoxicologically, the relevant targets of

ACR are in the formation of specific proteins such as v-ATPase, dopamine transporter, and NSF [58].

### 2.6. ACR and Gene Expression

Previous reports revealed that the carcinogenicity and neurotoxicity of ACR on animal models suggested that ACR could enhance the rate of mutation, the common feature in the development of carcinogenesis in the brain [59]. Oral ingestion of ACR at higher doses enhanced neither marked changes in gene expression nor neurotoxicity in the motor and somatosensory areas of the central nervous system [60]. The ACR induced the rate of DNA damage and gene mutation through their genotoxic and neurotoxic effects [61]. ACR decreased the Ikaros DNA-binding activity through the CK2 pathway, resulting in a reduction of neuronal cell adhesion molecule expression in human neuroblastoma cells [62]. ACR has shown the properties of neurotoxic, genotoxic, cancerogenic, and physiological and significant influence on the signal propagation in peripheral nerves [63].

### 2.7. ACR and Mortality

The male and female rats of Fischer 344 rats were found to be significantly higher chance of the development of tumor incidence in scrotal mesothelioma and mortality rate [64]. The ACR showed greater chances of mortality from numerous types of malignant tumors [65].

### 2.8. Actions of ACR and Glycidamide

ACR could exert chronic damage to peripheral nerves than glycidamide and confirmed that nerve tissue was more

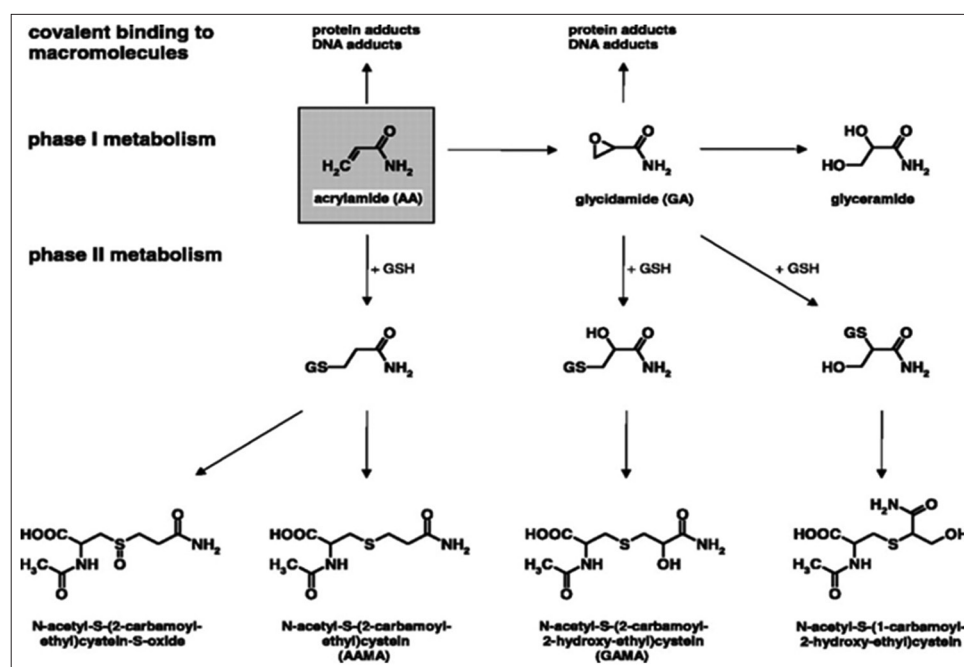


Fig. (4). The metabolic pathway of acrylamide [66].

vulnerable to ACR [67]. Glycidamide showed more active than ACR metabolite and involved in axon degeneration during the subchronic route of ACR [68]. The primary metabolite of ACR metabolism is glycidamide and it exhibited greater mutagenic activities than ACR [69]. The glycidamide is the major and specific metabolite, and both ACR and glycidamide exhibited similar toxicity (Fig. 4).

## 2.9. Toxicity Reduction by Phytoextracts and Low Exposure

The plants and their derivatives found to have pharmacological activities exhibited the beneficiary effects against ACR-induced neurotoxicity [70]. The lower levels and exposure of ACR have been directly proportional to the attitudes and reduction of consumption ACR containing diet [71].

## CONCLUSION

The ACR from various sources and its metabolite glycidamide expose a threat to human and animal. The reduced consumption of ACR-containing diet is the only factor for decreasing the effects of toxicity associated with ACR.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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