

Acrylamide Induced Neurotoxicity in Workers

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Abstract

Background: Acrylamide (ACR) are used in many chemical and industrial process. They exposure to human pose some health risk, while some effects are proven, the causal relationship between ACR and neurotoxicity is still unclear, so we would like to look for some evidence regarding this issue. The search for evidence is also complemented with a seven-step occupational disease assessment in order to establish occupational disease diagnosis.

Methods: Searching literature for the evidence-based has been conducted with a clinical question through “PICO” method. Then we continued the searching using electronic databases: “PubMed”, “Google Scholar”, and “Cochrane Library” search engine. The keyword is Acrylamide” “2-Propenamide; Ethylenecarboxamide” “Neurotoxic” combined with Boolean operation. The inclusion criteria are research in human, publication last ten years, and English full text article, while our exclusion criteria are duplicate or not relevant study.

Results: From the three literatures obtained, we could obtain the description of neurotoxicity symptoms induced by acrylamide, the diagnosis and treatment, and also the mechanism how acrylamide could induce neurotoxicity in human.

Conclusion: Acrylamide exposure in workers can cause neurotoxicity depend on the duration and concentration of exposure.

Keyword: acrylamide, neurotoxicity, worker, occupational exposure.

Abstrak

Pendahuluan: Akrilamida (ACR) banyak digunakan dalam proses kimiawi dan industri. Paparan terhadap manusia mempunyai beberapa risiko kesehatan, meskipun beberapa efek buruk sudah terbukti, namun hubungan antara akrilamida dan efek toksisitas terhadap saraf masih belum jelas, sehingga penulis memutuskan untuk mencari beberapa bukti mengenai hal ini. Pencarian bukti ini juga dilengkapi dengan tujuh langkah penilaian penyakit akibat kerja agar didapatkan diagnosis penyakit yang jelas.

Metode: Pencarian literatur berbasis bukti dilakukan dengan menjawab pertanyaan klinis dengan metode “PICO”. Penulis melanjutkan pencarian dengan menggunakan basis data : “PubMed”, “Google Scholar”, dan “Cochrane Library”. Kata kunci yang digunakan adalah Acrylamide” “2-Propenamide; Ethylenecarboxamide” “Neurotoxic” yang dikombinasikan dengan pengoperasian Boolean. Kriteria inklusi berupa studi pada manusia, jurnal dalam sepuluh tahun terakhir, dan jurnah penuh dalam Bahasa Inggris. Sementara itu, kriteria eksklusi dalam studi ini adalah jurnal ganda atau yang tidak berhubungan dengan topik.

Hasil: Dari tiga literatur yang ditelaah, penulis mendapatkan gambaran mengenai gejala toksisitas pada saraf akibat akrilamida, diagnosis dan tatalaksana, serta mekanisme bagaimana akrilamida dapat merusak saraf manusia.

Kesimpulan: Paparan akrilamida pada pekerja dapat menyebabkan toksisitas saraf bergantung pada durasi dan konsentrasi zat yang terpapar.

Kata kunci: acrylamide, neurotoxicity, worker, occupational exposure.

Introduction

Neuronal synapses are mainly used for transmission of sensory input, processing the signal, and motor output, mediated by complexes of neurons interconnected by multiple chemicals, electrical synapses, and structures. All the formation and maintenance of these structures depends on communication of information between neurons in order to keep the nervous systems function properly.¹ Neurotoxicity itself means direct or indirect effect of chemicals that disrupt normal function of nervous systems or damaging their structures. Numerous chemicals have been identified can cause neurotoxic effects, some of which act directly in neural cells, others interfering with metabolic process and damaging the nervous system. One of the chemical substance responsible for causing neurotoxicity is Acrylamide.²

2-Propenamide; Ethylenecarboxamide known as Acrylamide (ACR) is an odorless crystalline solid at room temperature and employed in many chemical and industrial process. It is a vinyl monomer and its industrial application can be associated with health risk. Acrylamide is used in gel chromatography, water waste management, chemical grouts at construction, drilling, mining sites, and also manufacturing flocculators. It is also known that ACR could be a contaminant in foods.^{3,4} In most countries, residue of acrylamide in water treatment are limited to 0.25 µg/litre. Concentration of acrylamide in effluents from polyacrylamide-using factories generally range less than 1 to 50 µg/litre. In their local grouting operations, high level of acrylamide may be found in wells and ground water (a concentration of 400 mg/litre was reported once). Monitoring of acrylamide concentrations in air and soil close to 6 acrylamide-producing plants in the USA failed to demonstrate any acrylamide in the air or in the soil.⁵

Human exposure to ACR can occur through occupational exposure or through food (contamination during processing in high temperature). The potential routes of human exposure to ACR are from ingestion, eye contact, dermal contact, and inhalation. Oral route of Acrylamide exposure may also happen via drinking water contaminated or through food.⁴ Acrylamide itself has been recognized as mutagenic, carcinogenic, endocrine disruptor both in humans and experimental animals. Neurotoxic effect of acrylamide is documented, but further research is still needed.^{3,6} The neurotoxic

effects of Acrylamide exposure in humans include skeletal muscle weakness, numbness of extremities, ataxia, polyneuropathy, peripheral or central nervous damage. There is a hypothesis stated that the primary site of action for ACR neurotoxic effects is at the presynaptic part of nerve terminals, and the molecular process is the formation of protein adducts directly impairing synaptic function.⁶ Another hypothesis stated that nerve endings are the site of acrylamide action and long-term effect of acrylamide may cause irreversible changes (Schwann cells without axons or degenerating myelin) in the nervous system and disrupt the transmission of impulses between neuron.^{7,8} general weakness, numbness, tingling in the limbs or ataxia. Numerous scientific studies show the effect of ACR on nerve endings and its close connection with the cholinergic system. The cholinergic system is part of the autonomic nervous system that regulates higher cortical functions related to memory, learning, concentration and attention. Within the cholinergic system, there are cholinergic neurons, anatomical cholinergic structures, the neurotransmitter acetylcholine (ACh

Acrylamide is readily absorbed by ingestion, inhalation, and through the skin. Biotransformation of acrylamide or major detoxification pathway in the body occurs through glutathione conjugation and through decarboxylation, resulting in urinary excretion of N-acetyl-S-(3-amino-3-oxopropyl) cysteine, a mercapturic acid derivative. Another pathway is the CYP2E1 (Cytochrome P450 2E1) oxidation of acrylamide, resulting genotoxic epoxide glycidamide (GA) which may constitute useful biomarkers for the assessment of acrylamide intake. Acrylamide and its metabolites also accumulated in blood by bounding to hemoglobin. Half-life for absorbed acrylamide which bound to blood is about 10 days.^{8,9} Compensation, and Liability Act (CERCLA) Despite many studies have been done, the causal relationship between acrylamide and neurotoxic is still unclear, so we want to look for some evidence regarding this relationship.

Method

A literature review was conducted on March 30, 2022 through a search of PubMed database using the keyword “Acrylamide” OR “2-Propenamide; Ethylenecarboxamide” AND “Neurotoxic”. Under this strategy, 324 articles were found. Another search

strategy was carried out on the same date using Google Scholar database using the same keyword above, which gave 47 articles. A database search of the Cochrane Library was also conducted, using “Acrylamide” OR “2-Propenamide; Ethylenecarboxamide” AND “Neurotoxic” keyword, yielded 64 articles.

Inclusion criteria in this study were : human studies, publication last no more than 10 years, English language articles, and free full text articles, by including this criteria, 27 articles were selected from those three database, and by adding exclusion criteria (i.e. duplicate study and non relevant articles), produce 3 useful review articles relevant to this study. After the selection, the critical appraisal was done using several aspects based on the Centre of Evidence-based Medicine, the University of Oxford for Harm/Aetiology study.

Result

From the online search results, we found three studies which fit our inclusion and exclusion criteria, all of them are literature review articles. The first study is from Pennisi M, et al (2013), the second study is from LoPachin RM and Gavin T (2012), and the last one is from Kopanska M, Lagowska A, Kuduk B, and Banas-Zabczyk A (2022).

In the first article by Pennisi M, et al (2013) is to describe that acrylamide requires multiple exposure to produce neurotoxicity. It is also stated that ACR poisoning usually involved construction industry workers, mine workers, flocculator manufacture workers and tunnel workers. Symptoms of ACR neurotoxicity are weak legs, loss of toe reflexes and sensations, and numb

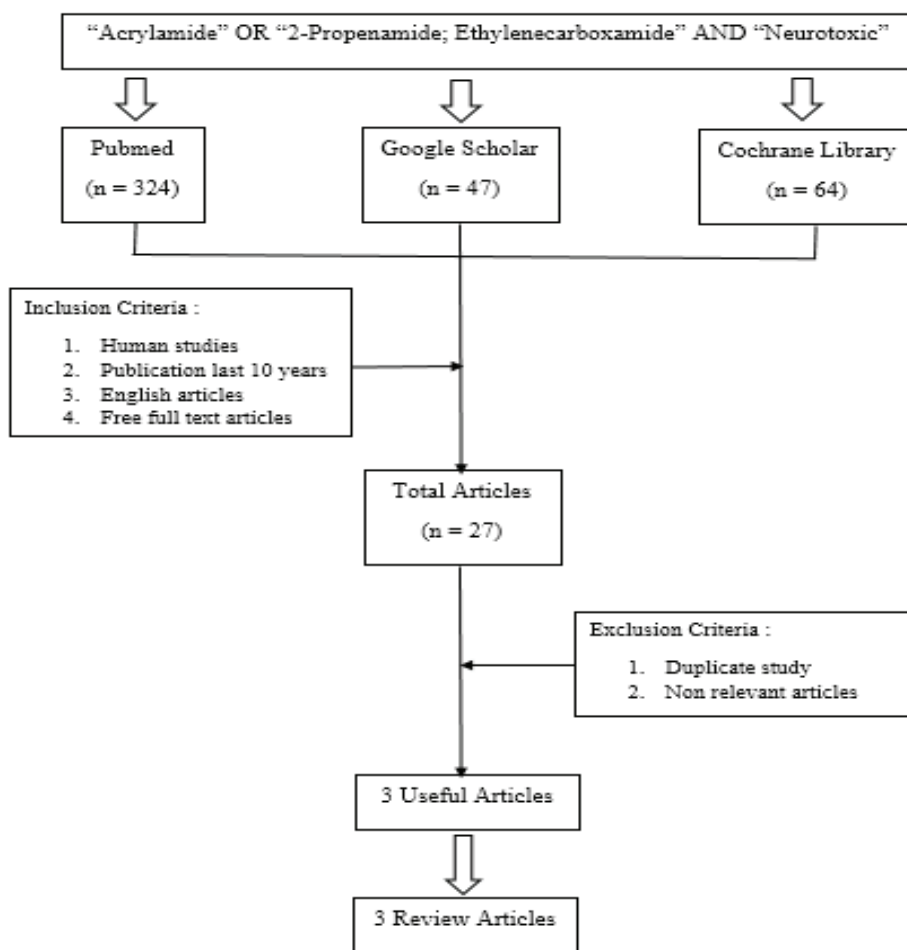


Figure 1. Searching Strategy Flowchart

hands and feet, sometimes preceded by skin peeling. Although symptoms of acrylamide neurotoxicity are known from some human case studies, however, the exact mechanism and the treatment are still unknown.⁴

From the second article by LoPachin RM and Gavin T (2012), we know that the mechanism of neurotoxicity was shifted from observational research to define cell-level sites of action to molecular mechanism. ACR was a soft electrophile which formed adducts with soft nucleophilic sites on macromolecules. This process could disrupt neurotransmission signaling pathway at central and peripheral synapses. It was also stated that exogenous derived toxicants (such as acrylamide) could interact with endogenous unsaturated aldehydes, therefore could accelerate the onset and development of atherosclerosis, diabetes, Alzheimer's disease and other disease caused by oxidative stress.¹⁰

The last article by Kopanska M, Lagowska A, Kuduk B, and Banas-Zabczyk A (2022) stated that there were three types of acrylamide toxicity; neurotoxicity, genotoxicity, and carcinogenicity. And until now,

only the neurotoxic effect of acrylamide on the human body has not been proven yet, but the neurotoxic effect might be caused by reduction in acetylcholinesterase activity. It was also described that acrylamide exposure in human was assessed by measuring adducts, i.e., specific compounds formed by combining acrylamide with hemoglobin or DNA.⁷

Discussion

To establish occupational diagnosis, seven basic principles steps can be taken, namely to determine the relationship between disease and workers if workers with neurotoxic symptoms are found to be exposed to acrylamide.

The first step is to determine the clinical diagnosis. Neurotoxic symptoms such as weak legs, loss of toe reflexes and sensations, numb hands and feet, cerebellar dysfunction, peripheral neuropathy, and abnormal gait can be established by anamnesis, physical examination,

Table 1. The Critical Appraisal of The Study

Articles		Validity							Relevance	Level of Evidence*	
Study Design		Number of Participants	Outcome measure same ways	Similarity treatment and control	Follow-up complete and long enough	Diagnostic test for causation	Dose response gradient	Consistent study to study	Can be extrapolated to patients	Alternative treatments	
Pennisi M, et al (2013)	Literature Review	-	-	-	-	+	-	?	+	+	V
LoPachin RM and Gavin T (2012)	Literature Review	-	-	-	-	+	-	?	?	-	V
Kopanska M, Lagowska A, Kuduk B, and Banas-Zabczyk A (2022)	Literature Review	-	-	-	-	+	+	?	+	-	V

Note : + stated clearly in the article; - not being done; ? not stated clearly
 *based on Oxford Centre for Evidence-Based Medicine (OCEBM)

and additional workup like magnetic resonance imaging (MRI) of the brain or nerve conduction study (NCV) – electromyography (EMG) to know where is the nerve’s lesion.^{4,11}

The second step is to determine exposure in the workplace or work environment. Exposure to acrylamide could lead to three types of disorder, namely neural disorder (neurotoxicity), genetic disorder (genotoxicity), and cancer (carcinogenicity).⁷ Acrylamide itself is frequently used as a flocculant, textile treatment agent, dispersant, paper strengthener, and also adhesive. There are also many reported cases of neurological disorders among workers who were exposed to an acrylamide-containing grouting agent, whether in Korea, United Kingdom, Sinsang (Chinese City), and in a Norwegian tunnel site. Workers may be exposed to acrylamide through ingestion, skin contact, or vapor/dust inhalation. Because of that, the Korean Ministry of Labor has proposed that acrylamide exposure to be limited at <0.03 mg/m³ and prevention at the workplace is needed. The American Environmental Protection Agency has estimated that respiratory and dermal exposure levels were 0.008-0.12 mg/m³ and 0.6-5.0 mg/h respectively based on a TLV-TWA value of 0.008-0.12 mg/m³ and an acrylamide concentration of 5%.^{3,4,11} Besides that, biomonitoring should also be done to investigate the neurotoxic effects of acrylamide on human, such as mercapturic acid in urine, glycidamide (GA) in blood, resulted from CYP2E1 oxidation pathway for acrylamide, and hemoglobin or DNA-adducts in the body.

The third step is to determine whether there is a relationship between exposure to disease. This relationship is based on the result of previous epidemiological studies (evidence-based studies) combined with the Bradford Hill criteria to determine if there is sufficient evidence enough that acrylamide can cause neurotoxicity:

1. Strength of association

The results of previous studies show that neurotoxicity-induced by acrylamide exposure is still unclear, many hypothesis and molecular studies shown that there were related, even there were cases of workers developed symptoms of neurotoxicity exposed to high concentration of acrylamide.

2. Consistency

Result from this study is consistent that acrylamide could induce neurotoxicity in

human. The outcomes stated that acrylamide disrupts the normal function of nerve transmission, and some case studies also proved the neurotoxic effects.

3. Specificity

All of these studies are literature review, although hypotheses and theories already described that acrylamide could induce neurotoxic event, but clear study is needed to strengthen the theories.

4. Temporality

A case study from Kim H, Lee SG, Rhie J (2017), found that higher concentration of acrylamide used in industry (grouting agent) was positively associated with neurological symptoms caused by toxicity of acrylamide in the nervous system. The symptoms appeared to be independent of another neurological risk factors, whereas the patient’s medical history and previous occupational history were unremarkable

5. Dose response

Worker exposed to higher concentration of acrylamide tends to develop symptoms of neurotoxicity, this is in line with total exposure guidelines from Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) is 0.03 mg/m³/ 8 hours of working. Acrylamide and its metabolites could also be accumulated in blood by bounding to hemoglobin, its half-life is about 10 days.

6. Coherent

Those three studies above support the evidence that acrylamide can cause neurotoxicity in various mechanism, and one study also reported workers developed symptoms of neuropathy induced by acrylamide exposure at high concentration and at longer time.

7. Experiment

None of three studies above conduct experiment.

8. Analogy

Acrylamide does not specifically only cause neurotoxicity.

The fourth step was to determine whether the exposure is sufficient. ACGIH, OSHA, and NIOSH have determined threshold value (TLV) for occupational, which is 0.03 mg/m³/8 hours of working (TWA: 0.03 mg/m³) through skin. Longer duration of exposure could lead to more severe symptoms.

The fifth step was to determine if any individual factors that play a role. There is no study that mention any patients with specific medical conditions are more vulnerable to acrylamide neurotoxicity, since acrylamide also found in high temperature processed food.

The sixth step was to determine whether there are other factors outside work. Acrylamide is used in many industrial processes and also could be found through food contaminated during processing in high temperature. Neurotoxicity-induced by acrylamide could be from not only occupational exposure, but also from food, however, a case study from Kim H, Lee SG, Rhie J (2017), did not found any risk factors apart from occupational exposure of acrylamide.

The seventh step is to determine a working diagnosis. Neurotoxicity or neuropathy occupational disease due to exposure to acrylamide in the workplace can be enforced if it fulfills the seven steps for establishing an occupational diagnosis.

Conclusion

To determine causality, we performed a critical assessment using the Evidence-Based Medicine Harm/Etiology Worksheet and the Bradford Hill criteria, which suggest a relationship between acrylamide exposure to neurotoxic effects or neuropathy.

From the results of a systematic literature search, several studies have shown the mechanism or pathway that acrylamide could induced neurotoxicity, however it depends on the duration and the concentration of exposure. Since there are many hypotheses and theories about acrylamide exposure, further research is needed to strengthen the evidence that acrylamide could induced neurotoxicity in workers.

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Conflicts of Interest

The authors declare no conflict of interest.

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