



# BIOREMEDIATION SCIENCE AND TECHNOLOGY RESEARCH

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## Acrylamide Toxicity and Its Biodegradation

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### HISTORY

Received: 27<sup>th</sup> July 2017  
 Received in revised form: 2<sup>nd</sup> November 2017  
 Accepted: 5<sup>th</sup> of December 2017

### KEYWORDS

acrylamide  
 pollution  
 biodegradation  
 metabolic pathway  
 microorganism

### ABSTRACT

Acrylamide is a synthetic monomer that has been classified as toxic and carcinogenic apart from its diverse application in the industry. Its application is in the formation of polyacrylamide. Polyacrylamide usage is diverse and is found as herbicide formulation, as soil treatment agent and in water treatment plants. Deaths and sickness due to the accidental exposure to acrylamide have been reported while chronic toxicity is also a source of the problem. This review highlighted the toxic effect of acrylamide to various organisms like human, animal and plant. This review also discusses on the potential use of biological technologies to remediate acrylamide pollution in the environment and the degradation pathways these microorganisms utilize to assimilate acrylamide as a nitrogen, carbon or both as carbon and nitrogen sources.

### INTRODUCTION

Widespread use of acrylamide by the industry led to the environmental pollution that results from the indiscriminate discharge of acrylamide. The presence of acrylamide in the environment is a major threat due to its neurotoxic, carcinogenic and teratogenic properties. Acrylamide is widely used in the industry as a synthetic vinyl monomer that can be utilised in numerous products. Due to this, the demand for acrylamide production keeps on increasing year by year. This has led to the indiscriminate discharge of acrylamide causing the contamination of soil and water [1]. Acrylamide has a variety of applications in industry. Its major use is as a vinyl monomer in the production of high molecular polymer polyacrylamide [2,3]. In 2014, 37% of global acrylamide production was used in waste water treatment [4]. It is usually used as a flocculating agent in many fields such as in municipal water treatment, sewage treatments and mineral water production [5,6].

Acrylamide is classified as a carcinogen by the International Agency for Research on Cancer (IARC). It is highly toxic to human, plant and animal [7–11]. Because of this, the need to understand acrylamide degradation is vital as it can lower the potential of acrylamide as a pollutant that contaminates the environment. In recent years, the number of studies on microbial degradation has increased due to its sustainability ways of cleaning up contaminated areas [1,12–

14]. Acrylamide degradation depends on the nature of microbes that can utilise acrylamide as its energy sources.

### Acrylamide

Acrylamide is an unsaturated amide compound with the chemical formula of  $C_3H_5NO$ . It has two functional groups; an amide group and a reactive double bond with a molecular weight of 71.08 g/mol. Acrylamide is also known as prop-2-penamamide and appears white to colourless white crystal solid at room temperature. Furthermore, it is soluble in water, methanol, dimethyl ether and acetone but insoluble in benzene and heptane. It is unstable and easily decomposes at temperatures higher than 120°C, producing toxic and corrosive fumes that contain nitrogen oxides [15].

Acrylamide was first produced in Germany in 1893 but began to be commercially produced in 1954. Since then, the global market demand for acrylamide has continued to rise. In 2013, the global capacity for acrylamide stood at 1.16 m tonnes/year with 53.7% being produced by the Asia Pacific followed by the United States with 16.9%, Western Europe with 15.6% and 9.3% in Japan [4]. Acrylamide can be commercially manufactured via two ways either by sulphuric acid hydration or copper catalyst process. The sulphuric acid hydration process involves saponification of acrylonitrile to yield acrylamide with the presence of sulphuric acid monohydrate [16]. This traditional method is no longer used by the industry for the

commercial production of acrylamide as it results in the production of sulphate by product and waste streams [17].

In the catalytic process, acrylonitrile is hydrated to acrylamide with the presence of copper as a catalyst. In this process, acrylonitrile solubility is increased in the presence of acrylamide solvent in the feed solution. This process is preferable as the yield is near to 100% and the final product is in the form of a solution and can be dried to crystal solid [4,18]. This method also allows the use of a variety of a solid heterogeneous catalyst other than copper such as manganese dioxide [19]. Biocatalyst application can also be used to synthesise acrylamide as it has many advantages such as low energy consumption, milder reaction and higher in safety process [20]. This process involves the use of enzyme nitrile hydratase (NHase) extracted from various microorganisms that are able to catalyse the conversion of acrylonitrile to acrylamide [21,22].

### Uses of acrylamide

Acrylamide has a variety of applications in industry. Its major use is as a vinyl monomer in the production of high molecular polymer polyacrylamide [2,3]. In 2014, 37% of global acrylamide production was used in waste water treatment [4]. It is usually used as a flocculating agent in many fields such as in municipal water treatment, sewage treatments and mineral water production [5,23]. This is because acrylamide copolymer like acrylate-acrylamide has a high molecular weight that helps in oil removal and the lumping of particles [24]. In the oil industry, acrylamide is also being used to stimulate the oil well production by fracturing and forcing the oil to the surface [25]. Acrylamide is being widely used in research industry in the production of polyacrylamide gel for electrophoresis. It is also being used in many other processes like in the synthesis of dye agent, as a thickener and as a copolymer in contact lenses productions [26].

### Toxicity of acrylamide

Acrylamide is a three toxic carbon molecule, that has been categorized as "likely to be carcinogenic to human" by the United States Environmental Protection Agency (EPA) [25]. It contains an amide group and  $\alpha$ ,  $\beta$ -unsaturated olefin bond in which may exert its toxic effects when exposed to nucleophilic attacks of others molecule [27]. It has also been classified as a possible carcinogen by the International Agency for Research on Cancer (IARC, 2014). Despite all this, only the monomeric form of acrylamide is toxic whereas the polymerised form is harmless [27,28].

Upon its administration into an animal cell, acrylamide stimulates the release of intracellular  $\text{Ca}^{2+}$ . High  $\text{Ca}^{2+}$  level activates protein degrading protease that results in cellular damage and decreases the rate of protein synthesis [28]. As it is highly soluble in water, it is rapidly absorbed and distributed throughout the animal body. After absorption, acrylamide was rapidly metabolised, primarily by conjugation with glutathione allowing the serum concentration of acrylamide to return to zero following a 24 h administration [27,29].

Nevertheless, the neurotoxic effects of acrylamide persist after elimination of the compound. At low concentration, it is harmless, but as the concentration increases, it becomes hazardous. Due to this, the level of acrylamide that is allowed is being limited to  $0.3 \text{ mg/m}^3$  in the air by the National Institute for Occupational Safety and Health (NIOSH) for 8 h work day [30]. This "not-to-exceed" level might differ among organisations because of the difference in exposure time. As

continued exposure may be harmful, the EPA has limited that only  $0.3 \text{ mg/L}$  of acrylamide is allowed in drinking water for 10 days as it is expected to not cause any adverse effect in a child [30].

### Acrylamide toxicity in animal model

Acrylamide might enter the human body through ingestion of water or food that contained acrylamide. Human is greatly exposed to acrylamide as it may be produced during cooking of food that is rich in starch as a result of exposure to a high temperature  $> 120 \text{ }^\circ\text{C}$  [31][32]. Human exposure to acrylamide can cause acute toxicity. Human exposure to acrylamide causes it to be absorbed through ingestion, inhalation and through skin absorption [33]. Acrylamide is rapidly absorbed by humans as it is highly permeable and enabling it to cross the cell monolayer via passive diffusion in both directions. It can also be passed to fetus through the placenta and blood barrier [9,34].

In human studies, exposure to acrylamide via inhalation results in muscle weakness as well as numbness in hands and feet [30]. Direct contact of acrylamide to the skin will cause skin redness, irritation and peeling [10,35]. Continual minor exposure to acrylamide may result in respiratory problems like throat and nose irritation [36]. In studies using animal models, acrylamide results in the poor ability of animals to produce offspring and causes several types of cancer in mice and rats model [36]. [18] reported a variation between two different group of workers that are exposed to acrylamide due to occupational activities in acrylamide plant, with the highest level of contaminations found in workers that work in monomer and polymer production areas with acrylamide adduct range was  $15\text{--}1884 \text{ pmol/g}$  and glycidamide adducts ranged from  $9$  to  $1376 \text{ pmol/g}$   $10$  to  $19$  tens fold higher than administrative workers of the same facilities.

Metabolically, acrylamide is oxidized to glycidamide by cytochrome P450 [6,37,38]. [18,34,39] suggest that glycidamide are more toxic to animal when compared to its parent compound acrylamide. Similar result were obtained by [40] in neonatal mouse model that report an increase in the incidence of combined hepatocellular adenoma or carcinoma was  $4.2\%$  and  $71.4\%$  in both  $0.70 \text{ mmol}$  acrylamide and glycidamide respectively when compare to only  $3.8\%$  in the control group. This is because of mutation of nitrogenous base at codon 62. In addition [34] reported a clear mutagenicity effects of glycidamide in Salmonella mutagenicity test while no mutagenicity effect observe in acrylamide. In contrast to this [41] reported that glycidamide is a weak neurotoxicant to rats as the glycidamide plasma concentration level is low in rats although the rate of conversion of acrylamide to glycidamide metabolites is higher in sub-chronic dose. From this, they conclude that glycidamide is unlikely to cause axon degeneration in rats during acrylamide exposure. More additional works are needed to confirm the neurotoxicity effect of acrylamide either it is mediated by the acrylamide itself as parent chemical or by it metabolites glycidamide.

### Acrylamide toxicity on aquatic system

Acrylamide residue was reported to be found in sludge from waste water in sand, gravel mine, water treatment plant, river and agricultural field water [7,8]. Acrylamide toxicity started to gain interest after 'Hallandsas' in Sweden where it is being used for chemical grouting [42]. The neurotoxic effects of acrylamide in fishes were noted in the form of collapse of fins and loss of tails movement in *Heteropneustes fossilis* [11]. In a recent study, [43] reported that acrylamide polyelectrolyte is very toxic to green microalgae that result in affected growth of

that organism. Although some studies report low toxicity of acrylamide in *M. galloprovincialis*, continual exposure to the acrylamide will result in the subsequent formation of reactive oxygen species (ROS) and toxic metabolites [44].

#### Environmental contamination by acrylamide

Acrylamide contamination was frequently found in the environment as a result of the commercial production of acrylamide as effluents. In the United States alone, currently, 76 facilities are involved in the release of acrylamide effluents either on-site and off-site [30]. It may be released to the environment during its production and or involved in the whole process in the formulation [36].

Due to its low vapour pressure and high solubility, acrylamide contamination in the atmosphere are very low. In the atmosphere, it is expected to exist as vapour that will soon degrade photochemical to hydroxyl radicals with a half-life at 1.4 days. Water is the most common area where acrylamide contamination occurs. In England, 0.75 ppb acrylamide was found in tap water from areas that use acrylamide as water treatment [45]. Some industrial effluents in England were also reported to contain 16 µg/L of acrylamide that is equivalent to 1.2 µg/L in receiving stream [46]. Acrylamide is also found as a degradative product of polyacrylamide; some important chemicals used in agriculture as the pesticide additive in glyphosate formulation and as soil treatment agent. Also, in Malaysia, polyacrylamide is used by the tons in water treatment systems [3].

#### Acrylamide treatment

As listed by EPA, acrylamide is likely to be carcinogenic and toxic to human. The removal of acrylamide is very important. As most industries were involved in the usage of acrylamide monomer, the degradation of industrial effluents containing acrylamide and their derivatives before being discharge into the environment is important. Currently, there are five major treatments that can be used to degrade acrylamide: thermal, photolytic, chemical, mechanical and biological degradation. The use of chemical treatment to degrade acrylamide is usually involved in waste water treatment.

Polyelectrolytes are being used together with oxidants like chlorine, chloramines, ozone, permanganate and peroxides that results in the degradation of acrylamide [25]. Hydrolysis of acrylamide under acidic or basic condition will also result in its degradation. [47,48] found 10% of the amide group in polyacrylamide monomer is being converted to carboxylic acid residues after 10 days due to hydrolysis of amide side chain. However, under fluorescent light at 95°C polyacrylamide are stable and do not release any detectable level of acrylamide [47,48]. At both basic and acidic condition, nucleophilic addition of water to the protonated amide or hydroxide to the amide carbonyl will result in the elimination of NH<sub>3</sub> and NH<sub>2</sub>.

#### Biological treatment

As an alternative to physical and chemical treatment, bioremediation is one of the alternatives being used to treat acrylamide pollution. The use of remediation technology to treat polluted sites using microbial process has been proven to be effective and reliable [49]. This method requires the use of natural microbial activity mediated by different consortia of microbial strains [50]. More than that, it also more cost-effectiveness when compare to the traditional method as it involves no disturbance to the environment thus causing less ecosystem disruption. Degradation of acrylamide monomer to acrylic acid and ammonia depends on the nature of the microbe

itself that is capable of utilizing acrylamide as its sole carbon and nitrogen source [1].

Apart from that, other criteria like oxygen, nutrients concentrations, temperature, pH and the nature of the pollutants itself are important to determine the success of bioremediation technique [49]. Gao *et al.* [51] reported the use of phytoremediation or the use of the plant as one of the alternatives of bioremediation to treat acrylamide in the soil. The result revealed that *Arabidopsis* could absorb acrylamide as the total content of acrylamide was reduced drastically in soil sample after 5 days but increased slowly in seedlings. The result showed that phytoremediation is effective in removing acrylamide and is a more environment-friendly alternative for removal of toxins from the environment.

#### Advantages of bioremediation

The main advantage of bioremediation is that it is more cost-effective compared to conventional methods as it can be done on-site, thereby eliminating the transfer process of contaminants from one environmental medium to another [49]. More than that, it also involves natural processes and publicly accepted as an alternative treatment to waste contaminants since it brings no harmful effects to the environment and allows the complete destruction of contaminants [50,52]. Besides, its non-invasive technique maintains the ecosystem, thus leaving it intact while producing only non-harmful residual products like carbon dioxide, water and cell biomass [53].

One of the hallmarks of bioremediation is that it can remediate toxicants in the presence of complicated matrices such as soil that form a formidable challenge to existing physicochemical methods. In addition, low concentrations can be remediated while physicochemical methods might not be effective or even economical at low concentrations of toxicant. These important characteristics make bioremediation an alternative technique to physicochemical methods.

#### Acrylamide degradation by bacteria

Biodegradation of acrylamide from the environment using bacterial isolates depends on the nature of microbes that are able to utilize acrylamide as its energy sources. This process is regulated by the action of enzyme amidase that degrades acrylamide monomer to acrylic acid and ammonia. Several numbers of bacterial isolates with the ability to degrade acrylamide monomer have been isolated from various environments. Most of the isolated bacterium that has been reported utilise acrylamide as either carbon source or nitrogen source or as both carbon and nitrogen source [54–57].

Many of the reported works involve isolation using an enrichment culture technique. The media were designed such that they were lacking in elements of nitrogen or carbon or both carbon and nitrogen source respectively. Some bacteria like *Bacillus cereus* EU 439437 and *Bacillus flexu* D837543 is able to use acrylamide as the carbon source while some denitrifying bacteria like *Pseudomonas* sp. C-3 and *Pseudomonas* sp. DRY J7 is able to utilise acrylamide as its sole nitrogen source [57,58].

Lakshmikandan *et al.* [13] reported on *Stenotrophomonas acidaminiphila* MSU12 that could degrade 30 mM of acrylamide as both nitrogen and carbon sources using the same method. The result indicates that the bacterial cell reached death phase completely after 48 h of incubation. In some of the works, the use of immobilization to biodegrade acrylamide have been reported [56,59]. The use of immobilization has been reported

to increase the degradation capability of microbes when compared to the resting cell as the enzymes activities remain for a longer time within the immobilized cell.

Immobilization of cells offers protection against the toxic concentration of acrylamide that must slowly diffuse into the matrix before reaching the cells. This provided a lower dose of toxicity than direct exposure to acrylamide as found in the free cells state. It was reported that immobilized cell *Rhodococcus* sp. that degrade 64 mM acrylamide in 3 h of incubation while free cells use 36 h of incubation to degrade acrylamide of the same concentration [60]. In addition, at 128 mM, immobilized cell took only 5 h to degrade while free cell show growth inhibition at 128 mM. This study indicates that acrylamide degradation by immobilized and free cell influenced by acrylamide concentration. In addition [1] also reported on *Pseudomonas aeruginosa* that utilise acrylamide as both carbon and nitrogen sources isolated from acrylamide contaminated soil. In this work, immobilized cells of *Pseudomonas aeruginosa* degrade acrylamide within 24 h while free cell *Pseudomonas aeruginosa* degradative activity only begin after incubation for 24 h.

#### Degradation pathway of acrylamide in bacteria

Acrylamide can be degraded by bacteria either as a carbon source or nitrogen source or both as carbon and nitrogen sources via different pathways. The biodegradation of acrylamide monomer to acrylic acid and ammonia in bacteria is an amidase enzyme that is responsible for the hydrolysis of acrylamide to acrylic acid and ammonia [1,57,61]

Bacteria that are able to use acrylamide as both carbon and nitrogen sources does not require any carbon or nitrogen supplementation to grow, but this property is rarely reported [11,62]. Wen *et al.* [63] reported that with the addition of glucose as its carbon source, occurs a retarded efficiency of the bacteria to degrade acrylamide. This is because too much conventional carbon source is present in the media, thus decreasing the biodegradation rate as the microorganism will prioritise using the conventional carbon source instead of the toxic compound to satisfy their needs.

#### Acrylamide biodegradative pathway

In bacteria, the degradation pathways of acrylamide to acrylic acid and ammonia is via hydroxylation via amidase [61]. In aerobic condition, once it is converted to acrylic acid and ammonia, there are two possible pathways of acrylamide degradation, one is through hydroxylation of acrylic acid to  $\beta$ -hydroxypropionate before it is oxidized to carbon dioxide [57]. Another pathway is via reduction of  $\beta$ -hydroxypropionate to propionate [64].

While in an anaerobic condition, acrylamide mineralization occurs via formation of acrylyl-CoA which later is converted to lactate as the final product. In bacteria species, degradation of acrylamide involves Omp 36 osmoporin and dipeptide transport protein as their energy source [64]. This outer membrane protein is responsible for acrylamide stress response and degradation in bacterial species.

Shanker *et al.* [57] reported the complete disappearance of acrylamide peak after 5 days of incubation with the emerging of the new peak identified as acrylic acid just after one day of incubation. This new peak area value is reported to increase as the incubation time is longer. This, conclude that as acrylamide degradation happen, the accumulation of acrylic acid as intermediates is increasing. Previously, Acrylic acid as an

intermediate was detected in some of the acrylamide-degrading bacteria in *Pseudomonas* sp. strain DRYJ7 [58], *Pseudomonas stutzeri* [65]. In addition [14,57,66–68] all reported the emerging of acrylic acid as intermediated in acrylamide degradation.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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