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Acrylamide in health and disease

Kaci N. Pruser[1] and Nick E. Flynn[1]

[1]Department of Chemistry and Biochemistry, Angelo State University, San Angelo, TX 76909

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1. ABSTRACT

Acrylamide has been classified as a probable carcinogen and can be ingested, inhaled (e.g. tobacco smoke), or absorbed. Fried, starchy foods are the most prominent sources of exposure. The reaction between asparagine and fructose typically produces the most acrylamide in foods from plant sources. Preparation methods shown to affect acrylamide production include temperature and cooking oil. Hemoglobin adducts present a reliable short term measurement of acrylamide exposure; a variety of methods, predominately LC/MS-MS, have been used for acrylamide detection. Health effects of acrylamide include neurotoxicity and genotoxicity. It is believed that the electrophilic nature of acrylamide will allow it to adduct to thiol groups on nerve axons and proteins that regulate neurotransmitter exocytosis. Presynaptic nitric oxide (NO) may also play a role here. Reproductively, males demonstrate a decrease in sperm count, motility and morphology. Acrylamide produces clastogenic effects while glycidamide (GA), its metabolite, produces mutagenic effects. A number of protective measures against the effects of acrylamide are possible including probiotics, increased use of compounds known to decrease acrylamide production and bioengineering of precursor foods such as potatoes.

2. INTRODUCTION

In 1994, the International Agency on Research on Cancer classified acrylamide as "probably carcinogenic in humans" and likely a causative agent in damage to the nervous system when administered at very high levels (1). This has developed into a major concern in humans because of the demonstration of mutations in laboratory animals (2). Acrylamide is a white, crystallizable, water soluble monomer used in the production of a variety of industrial compounds. It is a low molecular weight compound containing an alpha, beta unsaturated double bond. Acrylamide can be metabolically converted to GA, a metabolite, shown to have deleterious health effects. In this respect, it is metabolized partially through the cytochrome p450 system to produce mercapturic acid and GA (3). In rats, acrylamide and GA have half-lives of 5 hours in which they bind to different proteins and DNA (4). These compounds are then detoxified via glutathione conjugation and hydrolysis and subsequently excreted through the urine (5). Acrylamide can also undergo a Michael-type reaction in which the beta-carbon reacts with a nucleophile, typically proteins (6). Acrylamide can be ingested, inhaled, or absorbed through the skin and, due to its solubility, is distributed throughout all body tissues, through passage in the blood.

Because acrylamide has been found to form in a variety of foods, a great deal of interest has developed in regard to understanding its formation as well as in identifying means to decrease acrylamide production in foods. Fried, starchy foods are the most prominent proprietors of acrylamide exposure (7). Asparagine, a nonessential amino acid, in combination with various carbonyl compounds at temperatures greater than 120°C, has been identified as the amino acid precursor for acrylamide formation in food (8). The exact mechanism and contributing factors to its formation, however, are unknown; yet pH and moisture content are probable suspects. Research has demonstrated that acrylamide could be produced through the Maillard Reaction (8). While the amino group of asparagine initially reacts with the carbonyl group of a sugar to form acrylamide (9), it is the amide group nitrogen that is incorporated into acrylamide.

In 1996, acrylamide was determined to be consumed at levels higher than the 0.5 µg/L recommended by the World Health Organization for drinking water (1microg/day for 2 liter daily consumption) (10). In fact, food was estimated to contribute a total exposure for the average person of 0.3 to 0.8 µg acrylamide/kg body weight/day. This totals 21-56 µg/day for a 70 kg person. For children, exposures are typically higher due to a lower body weight and different dietary habits, thus putting children at a higher risk of developing health problems associated with acrylamide exposure (11). Acrylamide has not only been demonstrated as a carcinogen in rodents, but it as well as its metabolite, GA, have been shown to exhibit a neurotoxic effect (12). Other negative health risks associated with acrylamide include genotoxicity (13). Reproductive effects, most prominently in male rodents, have also resulted from exposure to acrylamide (14). These critical effects have promoted many studies regarding protective measures that might be useful in reducing acrylamide formation in foods. With the numerous detrimental effects and prevalence of foods containing acrylamide in the Western diet, it is important to study how acrylamide is formed and to understand the biological effects of acrylamide. It is also important to identify what measures may be taken to decrease both the production and effects of acrylamide in foods.

3. UTILIZATION OF ACRYLAMIDE

Acrylamide is used in a number of industrial applications. It is utilized as a cement binder (15) and in the synthesis of polymers and gels, more specifically, for the synthesis of polyacrylamide (PA) (6). In 2000, demand for acrylamide was approximately 400,000 tons annually and the demand is expected to increase yearly (16). Acrylamide is not a natural compound, but it can be produced both enzymatically and chemically. A major method used to produce acrylamide enzymatically is through the use of microbes that produce enzymes which catalyze the synthesis of acrylamide. A specific enzyme, nitrile hydratase, produced by a number of bacteria found within soil and organic matter, such as *Nocardia* cells and *rhodococcus rhodochrous* (I), catalyzes the degradation of acrylonitrile to acrylamide (17-19). Acrylamide can also be produced through the hydration of acrylonitrile using sulfuric acid (20). A common use of acrylamide following its production is the formation of PA.

PA is a polymer produced from acrylamide using acrylamide as the monomer base unit. It is used as a soil conditioner to reduce soil erosion. It is also used in wastewater treatments as a flocculant to enhance sludge thickening and dewatering processes. PA is also mixed with pesticides to serve as a thickening agent (21). PAs are found in cosmetics, textiles, papers, and in ore processing (22). It is used in research laboratories to separate proteins by electrophoresis. PA is hazardous and is capable of producing acrylamide through depolymerization under certain conditions such as heat and light (21). Apparently, pH does not serve as a substantial effector of acrylamide production through PA depolymerization. It is comforting to know that when PA is used as a soil conditioner at a 1% concentration, it does not contaminate soil through depolymerization to acrylamide (23). Furthermore, the small amount of acrylamide that was produced under tested conditions was found to degrade within eighteen hours.

4. ACRYLAMIDE EXPOSURE IN FOODS

In 2005, the World Health Organization and the Food and Agriculture Organization announced that certain foods, primarily those high in starch content, when processed or cooked at high temperatures produce substantial levels of acrylamide (http://www.who.int/ipcs/food/jecfa/summaries/summary_report_64_final.pdf) (24). The time period associated with heating appears to directly affect the amount of acrylamide that is produced in these foods (25). A number of amino acids and sugars produce acrylamide, but the reaction between the amino acid asparagine and the sugar fructose, typically produces the highest amount of acrylamide (26). During processes such as baking, frying, and roasting, the amide group of the asparagine reacts with the carbonyl group of carbohydrates to form acrylamide (27). In 2005, the World Health Organization estimated a daily intake of dietary acrylamide for a typical human to range from 0.3-2.0 microg/kg/body weight (28). Foods that produce extensive amounts of acrylamide are largely from plant sources such as potatoes and grains (barley, rice, and wheat). Processed foods containing large amounts of acrylamide include french fries, potato and tortilla chips, bread crust, crispbreads, and other baked items, including cereals (25, 27, 29). Processed foods exhibit varying acrylamide levels due to a number of factors including: hydration status (unpublished results) amount of asparagine present (30), level of reducing sugars, and cooking methods (25). Depending on tuber species, asparagine has been demonstrated to be a dominant amino acid in potatoes (31). Asparagine has a high C:N ratio (32) and several experiments have shown that over 97% of the nitrogen found in acrylamide comes from asparagine while all 3 of the carbons come from asparagine (33). Furthermore, many of the other naturally occurring amino acids have been tested for acrylamide production and subsequently demonstrated to not affect acrylamide production. Interestingly, it is believed that the amino group of

asparagine initiates the reaction between asparagine and carbonyl groups of reducing sugars (6). Asparagine, however, does not provide a strong correlation with acrylamide production further supporting the belief that another agent, reducing sugars, is involved (27, 34). As mentioned previously, fructose is thought to be the predominant carbohydrate responsible for reacting with asparagine to produce acrylamide (26, 30, 35).

Preparation methods shown to affect acrylamide production include the cooking temperature and type of frying oil used (25, 36). Additionally, culture and geography apparently affects acrylamide intake. A study by Vesper comparing the acrylamide and GA adduct values of individuals in different countries found that the region or environment that one lives in plays a direct role in determining the extent of acrylamide exposure. In this study, Dutch and British populations have higher hemoglobin adducts of acrylamide values (which correlates with acrylamide values) than other countries (37). This could indicate a higher exposure to acrylamide through food consumption due to the Dutch and British culture's relatively high potato diet compared to other countries that were included in the study (38).

5. ACRYLAMIDE MEASUREMENTS

Exposure to acrylamide can be estimated by measuring the amount of hemoglobin adducts in the bloodstream or performing a urinalysis. Upon entrance into the body, acrylamide and GA react with hemoglobin in the bloodstream to form an adduct (39). This adduct is relatively stable, thus allowing one to monitor acrylamide exposure within the past four months (40). Because acrylamide and GA react with hemoglobin, adduct values correlate with the relative levels of acrylamide and GA in the body during this timeframe (39). Another method of measuring acrylamide exposure is by evaluating urinary components. Upon oral administration of acrylamide, it is absorbed and distributed throughout the body. Acrylamide is then conjugated to glutathione. Upon degradation and acetylation, the resulting molecule, mercapturic acid N-acetyl-S-(2-carbamoylethyl)-L-cysteine is subsequently excreted in the urine. This compound is detectable and its value is directly proportional to the amount of acrylamide in the body. GA is also detectable and can be differentiated from acrylamide through the measurement of regioisomeric mercapturic acids rac-N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine and rac-N-acetyl-S-(1-carbamoyl-2-hydroxyethyl)-L-cysteine excreted in urine. These compounds are produced following the conjugation of GA with glutathione (39).

In foodstuffs, acrylamide can be detected using gas chromatography/mass spectrometry, liquid chromatography/tandem mass spectrometry, or high performance liquid chromatography/UV-Visible detection. A multistep preparation process must be performed prior to detection through use of these instrumental methods (6). This analysis typically involves the use of an aqueous extract from homogenized samples followed by a clean-up procedure involving centrifugation, or solid-phase extraction. Several reviews have described the preparation of acrylamide from foods (6, 41).

6. ACRYLAMIDE IN TOBACCO SMOKE

Acrylamide is a known component of tobacco smoke, thus increasing exposure of smokers to this compound. Acrylamide, as stated previously, is used extensively to prepare PA gels for electrophoresis in research laboratories. A study was performed on smoking and non-smoking personnel who handle these gels on a daily basis (42). Acrylamide adducts were detected in every individual, but smokers had a significantly increased adduct level compared to nonsmokers. The amount of detected adduct was directly proportional to the exposure associated with inhalation of acrylamide from three cigarettes per day. In another study, urinary mercapturic acids were utilized for the measurement of acrylamide and GA in smokers and nonsmokers over a twenty-four hour period (43). Approximately 2.5 times more N-acetyl-S-(2-carbamoylethyl)-L-cysteine and 1.7 times more rac-N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine was detected in the urine of smokers as compared to nonsmokers. Presence of these two compounds is indicative of acrylamide and GA exposure, respectively. These results directly correlate with the rate of daily cigarette consumption as measured by other parameters including nicotine equivalents in body fluids (urine or saliva) and carbon monoxide levels in the expired breath of smokers (43). This again indicates an increased inhalation of acrylamide in smokers, and, therefore, a possible increase in developing health problems due to acrylamide exposure.

7. NEUROTOXICITY DUE TO ACRYLAMIDE

Exposure to acrylamide has been shown to produce peripheral neuropathy in humans (44). Acrylamide has exhibited effects on both the peripheral and central nervous systems of rats producing symptoms including hindlimb foot splay, ataxia, skeletal muscle weakness, and axonal degeneration (34). Other symptoms include weak legs, loss of sensation, diminished reflexes, and peripheral extremity numbness (45). Additionally, prolonged acrylamide exposure due to inhalation or dermal exposure has been shown to cause more severe symptoms of cerebella dysfunction and neuropathy. Alzheimer's disease is known to be caused from a number of different factors, such as nerve terminal damage (46). Because acrylamide exposure causes nerve-terminal damage, it is legitimate to assume that acrylamide may indeed contribute to an increase in development of Alzheimer's in certain populations. More research in this area is certainly warranted.

Neurotoxicity from acrylamide is thought to be cumulative in that severity of neurological deficit and progression of symptoms are based upon the dose rate and concentration (47). For instance, a high acrylamide dose rate of approximately 30-50 mg/kg/day produces acute neurotoxicity over short exposure duration, from 10-30 days. In comparison, lower dose rates, approximately 1-20 mg/kg/day over a period of 60 days to 2 years produces

similar neurotoxic effects (47, 48). Although neurotoxicity is developed upon exposure, results from one study demonstrated that the neurotoxicity of acrylamide was less than predicted based on Haber's law of dose x time relationship, thus suggesting that the extent of cumulative effects of acrylamide is based upon a multifactorial process (dose, amount of tissue damage and self-repair processes). The nerve-terminal damage due to acrylamide is thought to be associated with a direct effect of acrylamide rather than secondary damage, such as tissue damage (49). Results of recent studies support the claim that *in vitro* exposure of isolated brain synaptosomes to acrylamide will decrease neurotransmitter release (50-52).

Over the history of acrylamide research, the perception as to how acrylamide produces neurotoxic effects has changed. The current belief is that the electrophilic nature of acrylamide will allow it to adduct to thiol groups on the axon of a nerve (52), specifically to proteins that regulate exocytosis of neurotransmitters. This action consequently, inhibits neurotransmitter release from nerve terminals thus affecting both the central and peripheral nervous system. The proteins that regulate exocytosis are typically cysteine rich and thus provide a mechanism for acrylamide to form adducts (50). Additionally, studies have demonstrated that these proteins have a long half-life and thus can have a significant effect on axonal degeneration (50). Acrylamide has been shown to affect the cerebellum as well (53) by affecting Purkinje cells (54). In this instance, acrylamide was demonstrated to accelerate degeneration of these cells. As these cells are responsible for maintaining balance and other motor skills, the effect is dramatically visible.

Moreover, a number of studies agree that presynaptic NO plays a role in acrylamide's neurotoxic effects. NO is synthesized from L-arginine by NO synthase and functions as a "neurotransmission modulator" (55). NO synthase is found in three different forms in the central nervous system. These three isozymes have been found in a number of regions throughout the brain, but in large quantities in the striatum and cerebral cortex. Kim *et al* demonstrated that the caudal area of the brain is more vulnerable to acrylamide neurotoxicity regulated by NO than the rostral area of the striatum. Upon treatment with acrylamide, the caudal area produced more NO than other regions (56) thus demonstrating that acrylamide is also effective in this area of the brain. According to LoPachin, NO functions to inhibit fusion of the synaptic vesicle membrane of a neuron and subsequently decreases neurotransmitter uptake and vesicular storage (57). With these functions in mind, their studies implied that acrylamide mimics neurophysiological effects of NO signaling (57) thus also causing an increased inhibition of neurotransmitter uptake as the result of acrylamide exposure. Alternatively, NO possesses other functions such as, triggering soluble guanylate cyclase (58, 59), inducing synaptic vesicle exocytosis, and, most importantly, modulating neurotransmission (55). Ultimately, neurotransmission is dependent on NO. While viewing NO as a neurotransmitter modulator, other possible effects of acrylamide in relation to NO have been proposed. In this aspect, rather than mimicking NO, acrylamide was shown to impair synaptic function and ultimately to decrease neurotransmitter release (52). Despite the differing perspectives on the interaction between NO signaling and acrylamide, an over-arching concept is that acrylamide plays an inhibitory role in this particular signaling pathway.

8. GENOTOXIC AND REPRODUCTIVE EFFECTS OF ACRYLAMIDE

Genotoxic and clastogenic effects of acrylamide have been demonstrated in research performed on rodents. Genotoxicity is exceedingly prevalent in the associated reproductive effects of acrylamide on males, and acrylamide has demonstrated less prominent genotoxic effects on females. Offspring of these mice also experience genotoxicity. Clastogenicity due to acrylamide is also noteworthy and will be discussed.

In males, exposure to acrylamide has been demonstrated to decrease sperm count, sperm motility, and sperm morphology (60). Peripheral neuropathy caused by acrylamide also plays an indirect effect on reproductive capacity. Because of peripheral paraplegia, reduction of grip strength and penile stimulation dysfunction in the animal, difficulty in mounting and copulation is experienced (60). Furthermore, neurotoxicity can decrease male endurance levels which then leads to an inability to mate long enough for sperm to reach the uterus (61). Acrylamide, therefore, indirectly induces peripheral neuropathy, thus causing a decrease in mating, and therefore, production of offspring. Acrylamide is not only an indirect instigator of reproductive problems, but it can also play a direct role in the toxicological effects of sperm morphology, motility, and production. Studies have shown defects in sperm when male mice are exposed to acrylamide. This demonstrates that acrylamide affects the role of the testes in normal sperm development. According to Sickles, this is thought to be due to acrylamide and GA obstructing the normal function of kinesin-like motor proteins (62). These proteins are found in the nucleus and this therefore leads to disruption of mitosis and meiosis in the cell (63). More specifically, this results in the prevention of separation of daughter chromosomes during both processes, resulting in lower sperm production (63). Kinesin-like motor proteins are also found in flagella of the sperm. Therefore, obstruction of these proteins decreases sperm motility, thus causing an inability to reach the ovum for fertilization as well as a decrease in fertilization and offspring production.

Furthermore, acrylamide has been found to cause germ cell mutations. In a review of literature related to germ line effects of acryladmide and GA, Favor and Shelby suggested that this could be due to the strong affinity of acrylamide for certain sperm proteins (64). Evaluation of heritable translocations and specific-locus mutations seen in the progeny of male mice exposed to acrylamide or GA has been conducted. Experimental results illustrate that exposure of spermatids or spermatozoa to these substances, increases the frequency of mutation (13). In 2006, additional investigations were performed to determine the

in vivo genotoxicity of acrylamide and GA. Groups of male and female Big Blue mice were provided two different doses of acrylamide or GA, 100 and 500 mg/L, in drinking water for 3 to 4 weeks. Tests were conducted following administration assessing the micronucleated reticulocytes in the peripheral blood, and lymphocyte *Hprt* and liver *cll* mutagenesis assays were carried out twenty-one days following final administration. Results indicated an increase in frequency of the micronucleated reticulocytes in males treated with high doses of acrylamide and GA (13). Additionally, both doses of acrylamide and GA produced an increase in lymphocyte *Hprt* and liver *cll* mutant frequencies. This study ultimately indicated that both acrylamide and GA are genotoxic in mice, and that mutation types and mutant frequencies are indicative of acrylamide metabolism to GA.

Lethal mutations can also be generated following intake of acrylamide. This effect was exhibited in offspring when both male and female mates were dosed with acrylamide and, interestingly, when only males were exposed (60, 63). Most likely, the direct effects of acrylamide on sperm function are the cause of mutations exhibited in the spermatid (65). Additionally, evidence was obtained to determine that GA, rather than acrylamide, was the major instigator of these mutations. This hypothesis was confirmed by administering a cytochrome P450 2E1 inhibitor to male rats which presumably inhibited acrylamide conversion to GA thus resulting in an absence of mutations. Additional support to the hypothesis that GA mediates mutation in cells was developed in 2006 by Koyama when it was determined that acrylamide produced clastogenic effects, changes in chromosomes, while GA produced mutagenic effects (66). Upon evaluating behavioral and morphological studies of acrylamide and GA, Costa *et al*, found that acrylamide instigated peripheral neuropathy and GA produced cytotoxic effects on sperm cells (44).

Another effect exhibited in male mice and rats due to acrylamide exposure was a significant decrease in body weight thus suggesting paternal toxicity. An excellent review by Shipp describes the effects of acrylamide dosing on rodent parents and offspring (67). When dosed with acrylamide through drinking water at, 0.5, 2.0, and 5.0 mg/kg/day, male body weight dramatically declined, but upon discontinuation, body weight returned to normal. Additionally, offspring that were weaned onto acrylamide dosed water two weeks following birth exhibited a significant decline in weight. This, however, was only experienced in male pups drinking 5.0 mg/kg/day of acrylamide whereas female pups were unaffected. These findings, therefore, suggest that acrylamide in drinking water results in paternal toxicity in mice. In 1986, Zenick *et al*, made a significant breakthrough in this area when they determined that prenatal survival, in large part, is dependent upon male acrylamide exposure (14). Only male mice exposed to acrylamide-dosed drinking water exhibited a significant decrease in prenatal survival of offspring in comparison to controls. Acrylamide has also been shown to not only produce neurotoxicity in adults, but it has been estimated to affect young offspring more prominently (68). Additionally, *in utero*, transpacental transfer of acrylamide has been demonstrated as well as transfer of acrylamide to maternal milk (69).

Unlike male mice, females, upon exposure to acrylamide in drinking water, did not experience such an abrupt weight loss, but, nonetheless did exhibit reproductive effects (67). Although female body weight significantly decreases following exposure to acrylamide in weeks 2, 4, and 7-10, this only occured in the highest acrylamide dosage group (5.0 mg/kg/day). Following delivery of offspring, females in the 5.0 mg/kg/day group also showed a significant reduction in maternal body weight during lactation (61). The number of offspring produced by parents exposed to acrylamide dosed drinking water was also affected. The number of implantations per dam and the number of live pups per litter at birth significantly declined. In contrast, the number of post implantation losses per litter significantly increased in the 5.0 mg/kg/day group of parents. In addition, the group of offspring with parents that were administered 5.0 mg/kg/day acrylamide in drinking water, exhibited a significant decline in postnatal survival from days 0-4, but following day four, survival was unaffected. These tests are indicative of prenatal lethality produced by dosing male and female mice with 5.0 mg/kg/day of acrylamide in their drinking water. Furthermore, Chapin et. al also determined that acrylamide can have a more prominent effect on later generations of mice (70). That is, upon dosing mice with high concentrations of acrylamide in their drinking water, the number of live pups delivered in the F_O generation decline only 11% in comparison to the control. In contrast, the number of live pups delivered in the F_1 generation declined by 47%. This is a significant percentage increase, and therefore, acrylamide mutations and offspring effects are more prominent in future progeny.

9. GLYCIDAMIDE FORMATION AND SIGNIFICANCE

GA is the epoxide metabolite of acrylamide that is formed through oxidation of acrylamide via the cytochrome P450 2EI (71). Cytochrome P450 is part of a large, diverse superfamily of hemoproteins (72). GA has demonstrated a neurotoxic and genotoxic effect following acrylamide intake. Neurotoxic effects of GA though are controversial because the question of which molecule, acrylamide or GA, is responsible for these neurotoxic effects has not been fully answered. In a study performed in 1993 by Abou-Donia *et al*, it was found that GA played a role in producing neurological deficits and axonal degeneration when acrylamide was injected into rats (12). However, in a similar study conducted by Costa *et al* in 1995, evidence was produced suggesting that two separate neurological effects occur due to acrylamide and GA (44). It was determined that acrylamide induced peripheral neuropathy while GA did not. Proof of this was exhibited when GA did not inhibit glyceraldehyde phosphate dehydrogenase, GADPH, in peripheral nerves, thus not producing peripheral neuropathy. In contrast, acrylamide did actually inhibit this enzyme. Although GA did not inhibit GADPH peripherally, it did produce a significant effect on GADPH activity in the brain, therefore indicating

involvement of GA in central nervous system toxicity (44). Because of these studies and a number of conflicting studies regarding the neurotoxic effects of both GA and acrylamide molecules, additional research is needed to fully resolve this issue.

In addition to GA's effect on neurotoxicity, it has been studied to determine its genotoxic effects. In a study performed in 2006, the genotoxic effects of GA and acrylamide in human lymphoblastoid cells was investigated (66). It was determined that while acrylamide had only a slight genotoxic effect on gene mutations at high concentrations, GA demonstrated significant genotoxicity at significantly lower concentrations. Additionally, they determined that the genotoxic effects of acrylamide and GA were different. Acrylamide effects were predominately clastogenic. GA, however, caused mutagenic effects and, more specifically, point mutations (66). Based on species differences in metabolism and toxicokinetics of acrylamide in rats and humans, however, bioactivation of GA from acrylamide is lower in humans in relation to rodents, indicating that humans may have a lower risk of developing cancer due to GA exposure than rats (73). Overall, GA's metabolic production from acrylamide is most likely responsible for the mutagenicity of acrylamide because it is much more reactive with DNA, which is characteristic of a promutagenic molecule (74).

10. CARCINOGENICITY

Presently, acrylamide is considered a potential carcinogen to humans based upon a number of studies performed on mice and rats. In studies designed to investigate the effect of acrylamide on cell cultures, chromosomal breaks and point mutations were exhibited (1). These mutations could ultimately lead to a proliferation of abnormal cells and subsequently, cancer development. Human and cell mice lines treated with high doses of acrylamide, not typically consumed in the American diet, exhibited an increase in gene mutation rates and these mutations were frequently the exchange of adenine by guanine or cytosine for guanine. Additionally, in mice experiments, an elevated number of tumors were found in the thyroid gland, lungs, clitoral gland, and the brain (1). Because most studies exhibit mutations and tumor formation based upon the administration of abnormally high amounts of acrylamide to animals, a number of epidemiological studies have been conducted to determine the cancer risk for humans (48). In 2003, data was analyzed on a population-based case-control in Sweden. This study compared cases with cancer of the bowel, bladder, and kidney with healthy controls by assessing dietary acrylamide exposure via food frequency data and acrylamide levels in specific ingested foods. A retroactive analysis revealed no correlation between dietary acrylamide and cancer of the bladder, bowels, or kidneys (1). Several other epidemiological studies exhibited no correlation in relation to kidney, colon/rectum, or breast cancers (75-78).

Conversely, a study performed in the Netherlands reported an increased risk of renal cell cancer associated with acrylamide intake (79), thus making reports concerning the effect of acrylamide on these types of cancers inconsistent. Furthermore, studies performed by Hogervorst *et al* (80) and Olesen *et al* (81) did report a linkage between acrylamide intake and cancers of the endometrium and breast in women (80, 81). Consequently, further experiments and analyses should be conducted to resolve these discrepancies.

The influence of acrylamide on lung cancer has recently piqued the interest of investigators. In 2009, a study was published indicating the correlation of dietary acrylamide intake with risk of acquiring lung cancer (82). This case-cohort study was performed among 58,279 men and 62,573 women in the Netherlands, and the intake of acrylamide containing foods and risk factors for cancer were assessed through a questionnaire. The correlation between acrylamide intake and lung cancer development was evaluated. Results indicated the hazard ratio of lung cancer for men was 1.03 signifying that the hazard of acquiring lung cancer in men did not increase with acrylamide consumption. Interestingly, the hazard ratio for women calculated was 0.82, demonstrating that acrylamide inversely affected women's probability of lung cancer.

Although most animal studies indicate a correlation of dietary acrylamide with numerous cancers, some recent epidemiological studies on humans do not fully support these findings. Limitations of the epidemiological studies in the ability to detect moderate increases in tumors that appeared in rat studies, however, has been acknowledged (83). Additionally, due to the rarity of a number of cancers exhibited in these animals such as, thyroid or hormone responsive cancers, a cohort study has not been performed to determine its association, if any, with acrylamide intake. Thus, follow-up studies in relation to the cancers in animals and the correlation with cancer predisposition in humans is certainly warranted.

11. PROTECTIVE MEASURES

A number of protective measures against the effects of acrylamide have been identified. As previously discussed, in addition to producing the enzyme nitrile hydratase that catalyzes the hydrolysis of acrylonitrile to acrylamide, some bacteria such as *Rhodococcus rhodochrous* PA-34, have been shown to produce an acrylamide-degrading amidase. Based upon studies and observations, this bacterium may provide a possible route to reduce acrylamide levels in food and, following probiotic consumption, in the digestive tract (84). In a recent study, Xie *et al* analyzed additional dietary components for their ability to ameliorate acrylamide toxicity. These include tea polyphenols, resveratrol, and diallyl trisulfide (85). Tea polyphenols are components in green tea and reduce cancer risk in tumor prone organs (86). Resveratrol is a phytoalexin found predominantly in grapes. It is also produced by some spermatophytes in response to injury and is housed in the skin of grapes. It has been demonstrated to possess anticancer effects, as well as other properties that benefit major disease prevention (87). Diallyl trisulfide is an ingredient in garlic that inhibits cytochrome P450 2E1 and therefore diminishes the

formation of GA (88). Naringenin, a flavenoid and weak antioxidant that is seen in citrus and tomato, has recently been found to inhibit acrylamide formation likely by reacting with acrylamide precursors (89). These experiments demonstrated that naringenin formed adducts with asparagine degradation products, therefore, inhibiting them from binding and forming acrylamide.

Reducing the accumulation of asparagine, a precursor to acrylamide formation has also been investigated as a protective measure. In 2008, a genetically engineered potato possessing a reduced concentration of free asparagine was developed. Researchers metabolically modified the tubers of the potato through silencing two asparagine synthetase genes. This produced a decrease in acrylamide production of approximately 95% in french fries and potato chips. Processed potato product consumption provides approximately one-third of the average dietary intake of acrylamide, and so replacing current potato varieties with bioengineered ones could significantly reduce acrylamide intake (24).

In recent years, certain compounds have been shown to induce some level of protection against or recovery from acrylamide induced neuropathy. These compounds include vitamin B_6 and B_3 (90), 4-methylcatechol (91) and α and β-asarones present in an ethanol-water extract of rhizomes of the *Acorus calamus plant* found in India (92). Vitamin B_6 plays a role in the function of neurotransmitter synthesis, making it a plausible protectant against neurotransmitter degeneration. In a study done by Zeng *et al* the effect of fifteen different vitamins in the inhibition of acrylamide formation in model systems was studied. It was found that two vitamins, vitamins B3 and B6, inhibited acrylamide production by over 70% in the model chemical systems and a 50% inhibition in the model food systems, fried potato crisps (90). 4-methylcatechol is known to be a stimulator of endogenous nerve growth factor synthesis, which is important for the growth and survival of neurons. When administered with acrylamide to rats in a study performed by Saita *et al*, in comparison to rats given only acrylamide, a significantly larger amount of nerve growth factor was present in the sciatic nerves. A faster motor nerve conduction velocity, and a higher density of myelinated fibers was also exhibited. This suggests that 4-methycatechol can prevent the progression of acrylamide induced peripheral neuropathy (91).

As previously discussed, acrylamide produces a number of neurobehavioral problems in rodents. In 2002, Shukla, *et al* found that rhizomes of Acorus calamus help to decrease these effects (92). Upon treatment of rhizomes with ethanol and water the glutathione content and the glutathione-S-transferase activity in the corpus striatum of the brain increased. Additionally, a decline in the number of dopamine receptors was seen. This is substantial because glutathione helps to detoxify xenobiotics and carcinogens; therefore, an increase of this compound would help to prevent cancer development in animals. A Glutathione-S-tranferase aids in ridding the body of xenobiotics and therefore, its presence is important in health. In the study, acorus calamus was administered to rodents in conjunction with acrylamide. A decline in lower limb paralysis was seen in comparison with those just given acrylamide. A drop in dopamine receptors was also detected. This is favorable because acrylamide acts as a dopamine agonist (93). This agonist activates certain signaling pathways and ultimately alters the process of gene transcription—acrylamide as an agonist prohibits the normal function of these cells. With a decline in this agonist's efficacy due to Acorus calamus, however, normal function can be sustained.

12. CONCLUDING REMARKS

Understanding the effects and causes of acrylamide exposure is very important, particularly considering the amount of acrylamide that individuals are being exposed to on a daily basis. It is therefore vital to identify methods to reduce acrylamide formation and subsequent effects of exposure. This task, however, is a complicated one since several factors such as heat, temperature and hydration status are known to contribute to acrylamide formation in foods. Furthermore, individual differences in enzyme capacities, such as cytochrome P450, make it difficult to precisely determine the effects of acrylamide and its metabolite, GA on specific individuals. There is, however, sufficient evidence to indicate that acrylamide most likely exerts neurotoxic, genotoxic, carcinogenic and reproductive effects.

We are, however, lacking sufficient information in certain areas of acrylamide research. More research is specifically needed in understanding the effect of acrylamide on NO metabolism in addition to drawing correlations between acrylamide exposure and incidence of Alzheimer's disease. Distinguishing what genotoxic and neurotoxic effects can be attributed to acrylamide and its metabolite GA will also be helpful in developing methods to ameliorate the health effects of acrylamide. Furthermore, investigators need to look toward obtaining a better understanding of the aforementioned protective measures in addition to developing new methods.

13. ACKNOWLEDGEMENT

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Abbreviations: GADPH: glyceraldehyde phosphate dehydrogenase; GA: glycidamide; NO: nitric oxide; PA: polyacrylamide

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Send correspondence to: Nick Flynn, Department of Chemistry and Biochemistry, Angelo State University, San Angelo, TX 76909, Tel: 325-942-2181, Fax: 325-942-2184, E-mail: Nick.Flynn@angelo.edu

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