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Contaminant acrylamide in food: toxicity, detection methods, mitigation measures and risk assessment for humans

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ABSTRACT: Food safety is related to all aspects of human life, and the quality of food has a profound impact on people's lives and health. Acrylamide is a chemical pollutant produced by the Maillard reaction in baked goods such as potato chips, bread, and cookies. Studies have shown that acrylamide has neurotoxicity, carcinogenicity, reproductive toxicity, genotoxicity, and hepatosplenic toxicity in humans. However, the carcinogenicity of acrylamide in humans is still controversial, and it is unclear whether there is a significant correlation between human exposure to acrylamide and cancer incidence. This review aims to explore the latest research on the human health hazards of acrylamide and prevent or reduce the hazards of acrylamide to humans by detection methods, risk assessment, and mitigation measures to ensure people's food safety.

1. INTRODUCTION

Food safety is a public health issue of global concern and is related to people's life and health. Chemical contaminants in food are an essential factor affecting food safety. A variety of chemical contaminants such as acrylamide (AA), polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines (HAAs), 3-monochloropropane-1,2-diol esters (3-MCPDE) and N-nitroso compounds (NOCs) are produced during the thermal processing of food (C. Li et al., 2021). Among them, AA is mainly found in baked goods such as potato chips, bread, cakes, and cookies and is a compound produced by the Maillard reaction during high temperatures (Andačić et al., 2020). During this reaction, free asparagine in the food is condensed with reducing sugars to produce Schiff base, which can be further reacted to produce the intermediate product 3-APA and finally of AA (Figure 1) (Schouten et al., 2020).

When people consume cakes, cookies, and bread, the AA in them is absorbed into the body by the small intestine's villi. AA is metabolized in the body by two pathways: (1) Under the action of cytochrome P450CYP2E1; AA is metabolized to glycidamide (GA), which is subsequently bound to glutathione and degraded to N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA) and the tautomeric N-acetyl-S-(1-carbamoyl-2-hydroxyethyl)-cysteine (iso-GAMA). (2) Under the action of

glutathione-S-transferase (GST), AA binds to glutathione and degrades to produce N-acetyl-S-(2-carbamoyl-ethyl)-cysteine (AAMA), which in humans AAMA is converted to sulfonlated AAMA (AAMA-SO) (Figure 2) (Chen et al., 2020).

AA and GA can be covalently bound to the N-terminal valine of hemoglobin (Hb) to form stable adducts AA-Hb and GA-Hb (Figure 3), which can remain in the blood for a longer time, which is the reason for the accumulation of AA in the body (Ou et al., 2020). Since 2002, when the Swedish National Food Agency (SNFA) first published the chemical contaminant AA in baked and fried foods, the study of AA toxicity to human health has attracted significant interest from researchers. Existing studies have shown that AA has neurotoxicity, carcinogenicity, reproductive toxicity, genotoxicity, and hepatosplenic toxicity in humans. This paper reviews the latest research progress on the effects of AA on human health in the past three years, describes the formation and metabolic processes of AA *in vivo*, explores the toxic effects and molecular mechanisms of AA, and clarifies the exposure of AA in humans by risk assessment, and uses detection methods and mitigation measures to detect and reduce AA.

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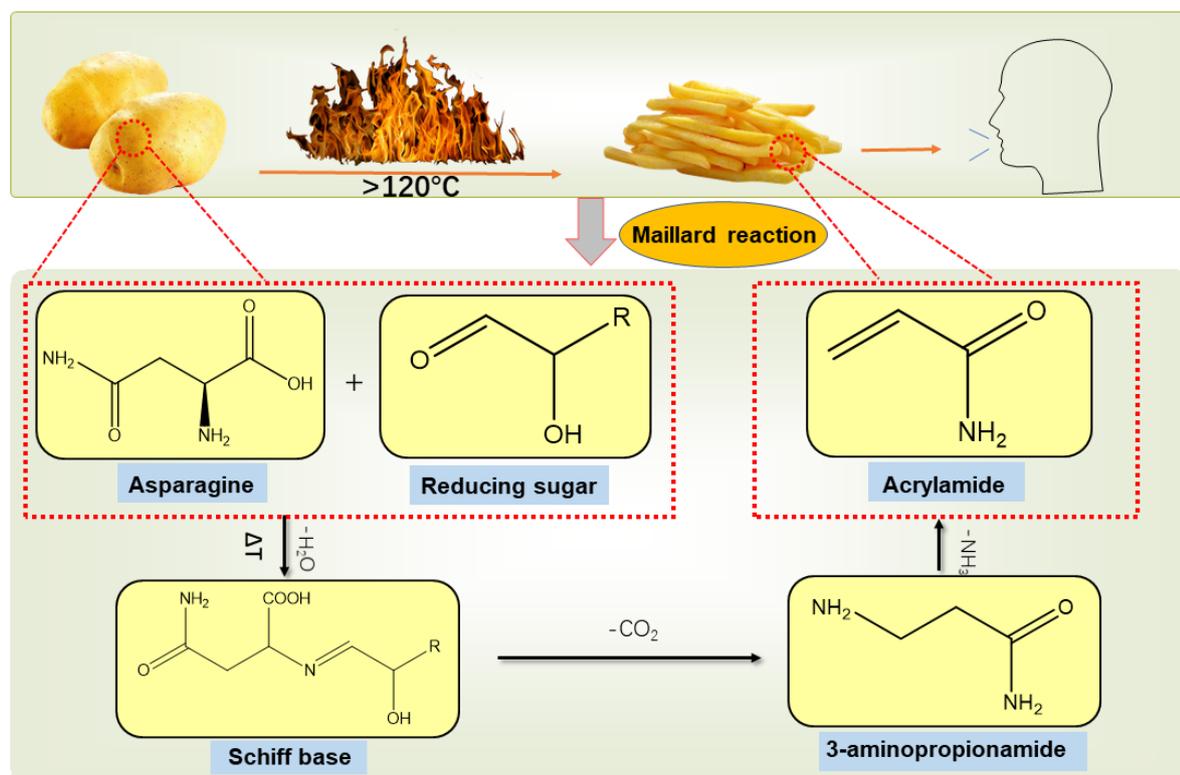


Figure 1. Simplified mechanism of acrylamide formation in food

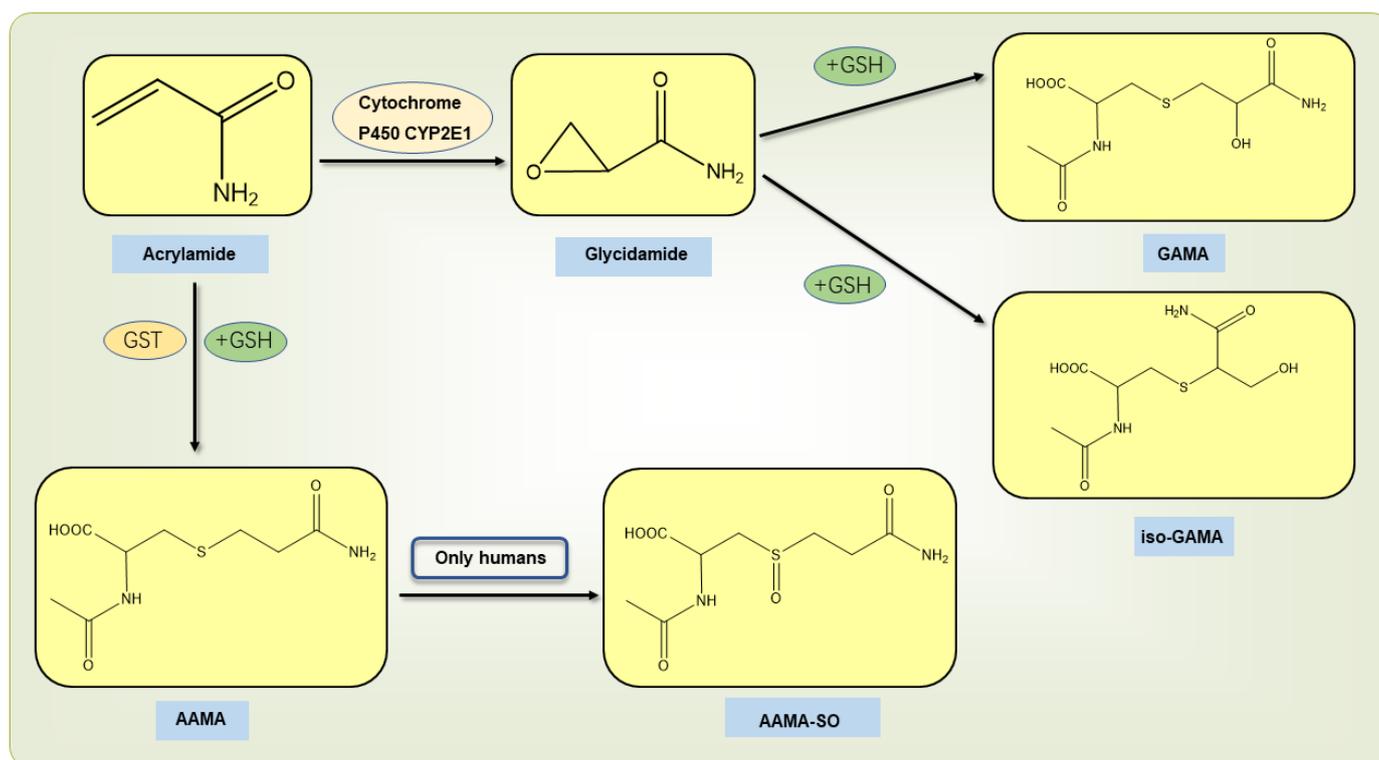


Figure 2. The metabolic process of acrylamide *in vivo*

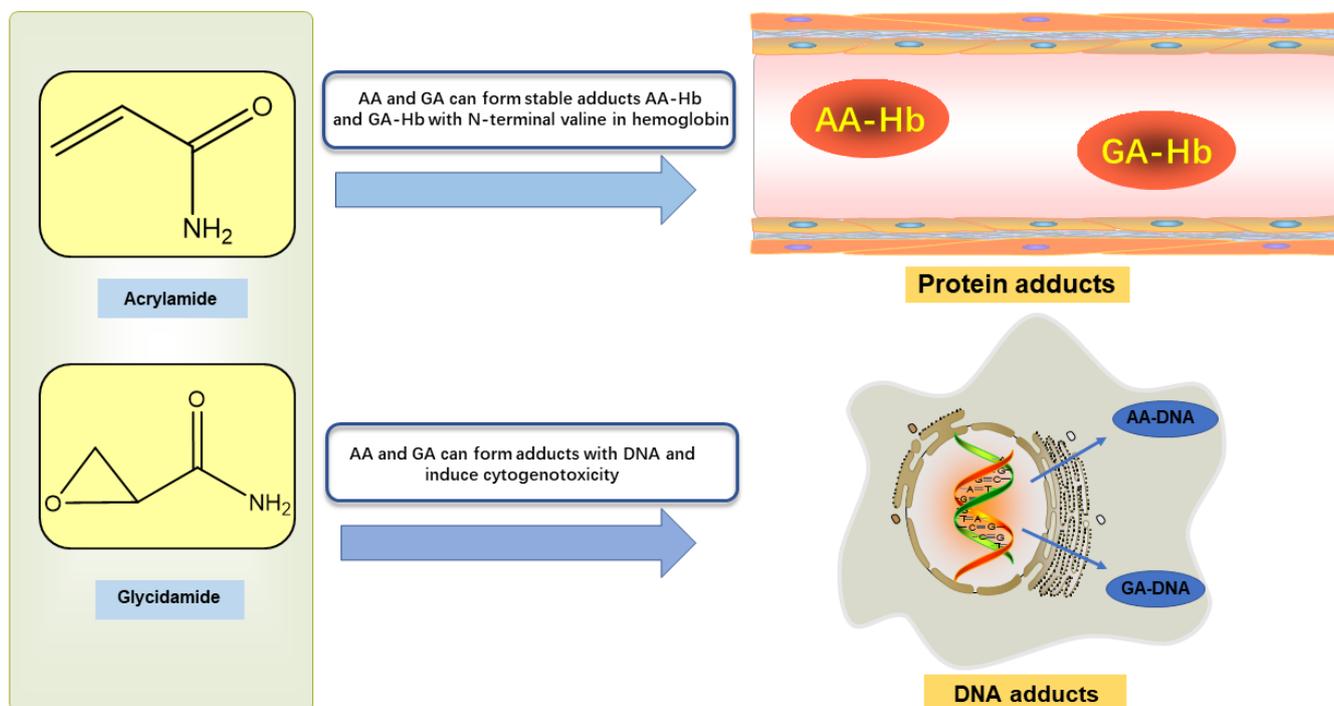


Figure 3. Acrylamide and glycidamide can form adducts with hemoglobin and DNA *in vivo*

2. DETECTION METHODS OF ACRYLAMIDE CONTENT IN FOOD

It is crucial to detect AA in foods because of its potential toxic effects on humans. AA, a small molecule compound, is more difficult to detect in complex food matrices. Carbohydrate-rich foods often produce large amounts of AA during thermal processing, so many methods for AA detection have been developed in various fields. GC-MS (Wawrzyniak & Jasiewicz, 2019), LC-MS (Jozinovi' et al., 2019), and CE (Mollakhalili-Meybodi et al., 2021) are all commonly used technologies for detecting AA in food. Due to its low volatility and polarity, AA is determined by GC-MS derivatization with potassium bromate and potassium bromide. However, direct GC-MS analysis of AA has a number of drawbacks: the lack of characteristic ions and matrix interference in the mass spectrum of underivatized AA increased background noise and poor retention on conventional GC columns. LC-MS is now widely used by research institutions in its derivatization-free and sensitive detection of AA, and the method can also be used to simultaneously detect AA and other toxic compounds in a sample (Desmarchelier et al., 2020). In addition, CE has also been applied to detect AA content, in which compounds with different charges can be detected by applying a high voltage that allows them to dissolve in the electrolyte and move at different rates (Mollakhalili-Meybodi et al., 2021). In addition, with the development of the times, classical chromatographic methods have been refined to adapt to more

complex analytical conditions. In the analysis of AA in coffee, the cumbersome sample pretreatment leads to signal interference from interfering peaks in detecting AA by LC-MS. In contrast, AA was extracted from coffee brewing samples using dispersive liquid-liquid microextraction (DLLME) and detected by liquid chromatography-high resolution mass spectrometry (LC-HRMS) for the content of AA in coffee, which can effectively exclude the interference of impurities and improve the detection efficiency and accuracy (Galuch et al., 2019). Furthermore, Zhang and colleagues applied UPLC-MS / MS to determine AA in human urine and found higher AA levels in men than in women after a short-term diet, providing methodological support for assessing dietary exposure to AA in the short term (Y. Zhang et al., 2020).

The previously developed chromatographic methods such as cumbersome sample pre-treatment, expensive instrumentation, and high detection costs have many limitations. Hence, the immunoassay has been developed based on antigen-antibody specificity. It is normally possible to cross-link AA with immune-responsive carrier proteins such as BSA and OVA to generate incomplete antigens and then obtain polyclonal antibodies with particular recognition ability by immunising animals since AA lacks antigenic determinants and immunogenicity. The requirement for real-time and rapid detection of AA can be met by immunochromatographic test strips (ICS) (J. Li et al., 2019; Wu et al., 2019). In addition, as an emerging analytical technology, electrochemical sensing analysis based on biomolecules has been intensively developed

in the environment, medicine, and food. Fe³⁺/hemoglobin electroactive groups are found in each of the four polypeptide chains that make up haemoglobin. When Fe³⁺ and Fe²⁺ are reversibly converted from each other, Hb's electroactivity is increased. AA can form a stable adduct AA-Hb with hemoglobin, so the biosensor can modify Hb on the surface of the transducer to detect AA (Asnaashari et al., 2019). Electrochemical sensors can detect AA with high specificity, high sensitivity, and excellent reproducibility because they are not affected by the presence of other food components. Therefore, with the continuous improvement of analytical methods, more superior analytical tools will undoubtedly be applied to the future detection and analysis of AA in food.

3. TOXIC EFFECTS OF ACRYLAMIDE ON HUMAN HEALTH

3.1. Neurotoxicity

Studies have found that AA causes neurotoxicity and neurodegenerative disorders in experimental animals and humans, causing ataxia (Sui et al., 2020). Neurotoxicity caused by AA in experimental animals might manifest as hind limb dysfunction, skeletal muscle weakness, and weight loss in rats. In humans, on the other hand, AA's neurotoxicity is primarily evidenced by sensory or motor neuropathy, sleepiness, or cerebellar ataxia (Bin-Jumah et al., 2021). Zong et al. (2019) found that five weeks of exposure to AA in rats induced neuroinflammatory response in the brain, manifested by upregulation of IL-1 β , IL-6 and IL-18. Microglia are the most common cells in the central nervous system's macrophage population and are involved in a variety of neurodegenerative disorders and neurological traumas. AA has been demonstrated to activate microglia, as evidenced by increased expression of the microglial markers CD11b and CD40. A study by Nagashima et al. (2019) believes that the brain's hippocampal region may be the site of neurotoxicity produced by the AA. Protein analysis of hippocampal tissue taken from rats after five weeks of gavage revealed a decrease in triosephosphate isomerase, mitochondrial creatine kinase U-type, creatine kinase β -type and proteasome subunit α type-1 activity. L. Zhang et al. (2020) also found that AA caused degeneration of rat nerve terminal axons and decreased noradrenergic axon density in rat prefrontal cortex, hippocampus, and posterior pontine cortex. Therefore, AA-induced noradrenergic neuropathy may be a significant cause of cognitive dysfunction caused by AA poisoning in patients. AA-induced neurotoxicity is also closely related to oxidative stress. Because of the lower activity of antioxidant enzymes in the central nervous system than in other tissues, nerve cells are vulnerable to reactive oxygen species (ROS) attacks, causing oxidative damage to brain tissue. AA is a soft reagent that preferentially reacts with soft nucleophiles such as glutathione or sulfhydryl groups in proteins, interfering with cellular redox signalling pathways and causing neuronal damage (Faria et al., 2019). Activation of cellular signalling pathways eventually leads to changes in various signalling regulators. During cellular oxidative stress, AA reduced the activity of SOD and GSH-Px and increased the content of ROS and MDA. NF-E2-related

factor 2 (Nrf2) was rapidly dissociated from Kelch-like ECH-associated protein 1 (Keap1) and subsequently translocated to the nucleus. Simultaneously, the genes hemoxygenase 1 (HO-1) and quinone oxidoreductase 1 (NQO-1) downstream of Nrf2 were also increased in expression in the nucleus. Activation of the Nrf2 signalling pathway attenuated AA-mediated cellular oxidative damage but was insufficient to reverse AA-induced cellular damage (Figure 4) (Pan et al., 2018). Thus, the neurotoxic mechanisms of AA include induction of neuroinflammation, inhibition of key cellular enzymes, damage to nerve cells, inhibition of neurotransmission and reduction of nerve terminal axon density.

3.2. Carcinogenicity

Animal experiments have shown that exposure of rats to high concentrations of AA can lead to testicular sphincter tumors and thyroid and mammary fibroadenomas (G. Jiang et al., 2021). In light of its rodent carcinogenicity, the IARC has classified AA as a potential carcinogen for humans. Nevertheless, the carcinogenicity of AA in humans has been much debate so far (Zhivagui et al., 2019). Giorgia Adani et al. found that AA in foods increased the risk of ovarian and endometrial cancers in premenopausal women (Adani et al., 2020). For studies related to breast cancer incidence, AA was not significantly associated with the risk of breast cancer in the postmenopausal women population. However, exposure to high AA was associated with a significantly increased analysis of the premenopausal women population risk of breast cancer (Adani et al., 2020). Therefore, the carcinogenicity of AA may be related to the secretion of sex hormones. There was no correlation between AA intake and lung cancer incidence in both men and women who participated in a prospective analysis of 85,303 Japanese participants (Liu et al., 2020). Esophageal, gastric, and colorectal cancers were not linked to dietary exposure to AA in this author's previous research (Liu et al., 2019). There were also studies showing that the intake of AA was not associated with renal cell carcinoma (F. Jiang et al., 2020) and pancreatic cancer (Kito, Ishihara, Kotemori, et al., 2020). In conclusion, AA in food has not been directly related to human cancers in current studies. We may subsequently explore the correlation and specific molecular mechanisms between AA and human cancers in conjunction with hormone levels to further elucidate the carcinogenic risk of AA.

3.3. Reproductive toxicity

According to a study conducted by (Zhu et al., 2021) AA hindered osteoblast differentiation and increased osteoclast maturation in rat embryos, resulting in inadequate skeletal development, decreased body size, and cartilage deformity in rat offspring. Additionally, AA exposure increased foetal resorption considerably and lowered foetal body weights in mice (D. Yu et al., 2020). AA also causes ovarian dysfunction in female rats by altering steroid hormone release and causing death in the cell (Aldawood et al., 2020). In a study of 468 male subjects aged over 12 years in the United States,

stress by NLRP3 inflammasomes. The NLRP3 inflammasome is activated by oxidative damage and endoplasmic reticulum stress (ERS). IRE1 interacts with TRAF2 to activate ASK1, then JNK and p38MAPK. The MAPK signalling pathway can activate the NLRP3 inflammasome, and Caspase-1 increases IL-18 and IL-1 production (Bo et al., 2020). JNK stimulates the expression of pro-apoptotic proteins Bax and cytochrome c while inhibiting anti-apoptotic proteins Bcl-2 and Bcl-xL. IRE1 boosts the NF- κ B signalling pathway and causes NF- κ B nuclear translocation, as well as INOS and NO generation (Figure 4) (Sun et al., 2018). In addition, Komoike et al. (2020) found that AA can cause splenic toxicity. They exposed adult zebrafish to AA, and after one month, their spleen was severely swollen with symptoms such as haemorrhage and inflammation (Komoike et al., 2020). The latest toxicity studies of acrylamide in vivo are summarized in Table 1. Based on the potential health hazards of AA in humans, there is a growing interest in the degradation of AA and toxic metabolites in current studies. Zilli et al. (2021) found that UV could degrade AA with hydrogen peroxide (H₂O₂) into less toxic by-products. The researchers found that microalgae *Desmodesmus quadricauda* are very sensitive to the presence of contaminants such as acrylamide. They irradiated a solution containing AA (1.5 mg/L) in H₂O₂ (0.034 g/L) with UV for 10 min and then used the solution to culture *D. quadricauda*. The growth rate of *D. quadricauda* was almost unaffected, and the absence of AA in the solution was detected by HPLC (Zilli et al., 2021). This suggests that we can develop more efficient methods to reduce the toxicity of AA in the future and ensure people's health safety.

4. RISK ASSESSMENT OF DIETARY EXPOSURE TO ACRYLAMIDE

As researchers continue to delve into the toxic effects of AA, we wonder how much AA is consumed daily from food or the environment. AA's risk assessments have found that people are inevitably exposed to AA's toxic substance in their daily lives, including adults and children. For the literature review in the last three years, we examined some of the literature reporting people's intake of AA daily. In the 2002 FAO/WHO report, the general population's daily dietary exposure to AA was established to be 0.3-0.8 μ g/kg (Andačić et al., 2020). Basaran and Aydin (2020) found that among 263 Turkish people, the average daily AA exposure was 0.11 ± 0.084 μ g/kg for coffee drinking consumers and 0.057 ± 0.037 μ g/kg for non-coffee drinking consumers, with an average daily exposure of 0.10 ± 0.065 μ g/kg for men and 0.12 ± 0.097 μ g/kg for women. According to the findings, it is possible that the typical intake of Turkish coffee (small size due to the cup size) will restrict individual exposure to AA in the long term. The consumption of AA is reduced as a result of factors such as the type of coffee, how it is processed, and where it is grown, which is a positive development (Basaran & Aydin, 2020). The USFDA assessed the daily dietary exposures of the US population to AA in food for those >2 years old and those 2 years old based on 2011-2015 data. The average daily dietary exposure to AA was 0.36 μ g/kg

for those >2 years old, and 1.42 μ g/kg for those 2 years old, with cereal-based infant cereals and infant cookies accounting for 27% of AA intake. Additionally, the JECFA estimates that the average adult's daily dietary consumption of AA is between 0.2 and 1.0 μ g/kg. According to JECFA, children consume twice as much AA than adult consumers, in part because children consume more AA-containing foods (e.g., chips, fries, and cookies) and have a lower average body weight than adults (Abt et al., 2019). In Japan, a study involving 240 participants (aged 40 to 74 years) from five locations (Yokote, Saku, Chikusei, Murakami, and Uonuma) discovered that men had an average daily AA intake of 0.27 μ g/kg while women had an average daily intake of 0.32 μ g/kg (Kito, Ishihara, Yamamoto, et al., 2020). In addition to the effect of dietary habits, Goerke K and colleagues studied twenty healthy non-smoking Caucasian volunteers (21-31 years). It was assigned to two groups: ten (half of each sex) who did not declare any dietary preference and ten (half of each sex) who followed a vegan lifestyle by abstaining from animal products. The researchers found that the daily dietary AA exposure for all volunteers during the 10-day study was 0.32 ± 0.19 μ g/kg, with an intake of 0.29 ± 0.18 μ g/kg for men and 0.35 ± 0.20 μ g/kg for women. The vegan volunteers had a higher AA intake of 0.38 ± 0.23 μ g/kg than the omnivorous volunteers at 0.26 ± 0.10 μ g/kg (Goerke et al., 2019). This suggests that a vegan lifestyle may be more susceptible to AA exposure under certain circumstances, especially when consuming thermally processed vegan foods such as meat substitutes.

In addition, AA dietary exposure is a significant safety risk for children in their developmental years. Mesias et al. (2020) found that children are most exposed to AA through diet. By detecting potato chips in 31 elementary school cafeterias in Spain, the average AA level was 329 μ g/kg (Mesias et al., 2020). On average, semi-industrial sangak bread contained 135 grammes of AA per kilogramme, making it the most dangerous for youngsters to consume (Eslamizad et al., 2019). In addition, the researchers collected 143 different meals from companies providing school canteens in the Umbria region of central Italy. When it came to school-age children's AA consumption, the researchers found that the mean value for potatoes and bakery items was 2.16 μ g/kg, while the highest values were found to be in meat (222 μ g/kg) and the egg products were 1.51 μ g/kg (Branciarri et al., 2020). Therefore, dietary exposure to AA due to school cafeteria food should also be considered a health concern and taken seriously. The ANSES recommends an AA benchmark value of 0.2 μ g/kg for children under three years of age, while a survey of 705 French children under three years of age found an average daily exposure of 0.141 μ g/kg for children aged 1-4 months and 0.708 μ g/kg for children aged 13-36 months. Extrapolating from age classes, 26% to 98% of children exceeded the baseline value of 0.2 μ g/kg, which may be related to the initiation of exposure to potato products and cookies in children aged one year (Sirot et al., 2019). In addition, a study by Hsu CN et al. noted that the higher the concentration of AA detected in the urine of children with chronic kidney disease, the greater the likelihood

Table 1
Toxic effects of acrylamide *in vivo*

Toxicity	Effects	References
Neurotoxicity	People with sensory or motor neuropathy, drowsiness, and ataxia	Bin-Jumah et al. (2021)
	Hind limb dysfunction, skeletal muscle weakness and weight loss in rats	Bin-Jumah et al. (2021)
	Neuroinflammatory response, pro-inflammatory cytokine upregulation and microglia activation in rat brain	Zong et al. (2019)
	Decreased activity of phosphoprostanes isomerase, mitochondrial creatine kinase type U, creatine kinase type β and proteasome subunit alpha-1 in rat hippocampal tissue	Nagashima et al. (2019)
	Axonal degeneration of nerve endings and reduced density of noradrenergic axons in rats	L. Zhang et al. (2020)
Carcinogenicity	Oxidative damage to brain nerve cells	Faria et al. (2019)
	The risk of testicular sphincter tumors and thyroid and mammary fibroadenoma is increasing in rats	G. Jiang et al. (2021)
	The risk of breast, ovarian and endometrial cancers is increasing in pre-menopausal women	Adani et al. (2020)
	No significant association between AA and breast cancer in post-menopausal women	Adani et al. (2020)
	No association between human exposure to AA and lung cancer	Liu et al. (2020)
	No association between human exposure to AA and esophageal, gastric, and colorectal cancers	Liu et al. (2019)
	No association between AA intake and renal cell carcinoma	F. Jiang et al. (2020)
Reproductive toxicity	No association between AA intake and pancreatic cancer	Kito, Ishihara, Kotemori, et al. (2020)
	Incomplete skeletal development and cartilage malformation in rat offspring	Zhu et al. (2021)
	Imbalance of steroid hormone release and ovarian dysfunction in female rats	Aldawood et al. (2020)
	Decreased DNA repair function of Sertoli cells in the testis, increased serum inhibin B levels and decreased sperm production in men	Chu et al. (2003)
	Altering the secretion of sex hormones to affect female reproductive function	Chu et al. (2003)
	Morphological and functional defects in spermatozoa, resulting in reduced male fertility	Ivanski et al. (2020)
	Placental atrophy, reduced number of vasa vasorum and defective embryonic development in pregnant mice	D. Yu et al. (2019)
Genotoxicity	AA induces cellular oxidative stress, mitochondrial dysfunction and DNA damage leading to genotoxicity	Salimi et al. (2021)
	GA forms adducts with DNA and increases micronucleus formation in Sertoli cells to mediate genotoxicity	Yilmaz et al. (2020)
	AA reduces glutathione levels and damages DNA to induce oxidative damage in the liver, kidney, and brain of <i>Clarias gariepinus</i>	Ibrahim and Ibrahim (2020)
	AA induces cellular DNA damage and lipid peroxidation to mediate genotoxicity	B. Wang et al. (2020)
Other toxicity	AA damages rat liver tissue leading to vascular congestion, cellular infiltration, and cellular necrosis	Donmez et al. (2020)
	AA disrupts glucose homeostasis and blocks insulin release to affect liver function in rats	Yue et al. (2020)
	AA induces splenic toxicity in zebrafish, resulting in splenic swelling, haemorrhage, and inflammatory response	Komoike et al. (2020)

Table 2
Dietary exposure to acrylamide ($\mu\text{g}/\text{kg}$) through food consumption

Country	Research Subjects	Age (years)	Food Type	Concentration ($\mu\text{g}/\text{kg}$)	References
Turkey	Male; Female; Coffee drinkers; Non-coffee drinkers	18-65	Coffee	0.10 \pm 0.065 0.12 \pm 0.097 0.11 \pm 0.084 0.057 \pm 0.037	Basaran and Aydin (2020)
United States	Children and adult	>2 <2	French fries; Potato products; Breakfast cereal; Cookies; Chips; Coffee; Pretzels	0.36 1.42	Abt et al. (2019)
Japan	Male; Female	40-74	Bread;Biscuits; Cookies; Coffee; Toast; Potato; Fried batter	0.27 0.32	Kito, Ishihara, Yamamoto, et al. (2020)
Caucasus	Male; Female; Vegan Volunteers; Omnivore Volunteers	21-31	Potato products; Crisps; Snacks; Meals; Coffee; Vegetarian; Meat surrogates; Bread;sandwiche	0.29 \pm 0.18 0.35 \pm 0.20 0.38 \pm 0.23 0.26 \pm 0.10	Goerke et al. (2019)
Italy	Children	3-13	Pasta; Cereals; Egg products; Legumes; Fish; Bread; Meat; Potatoes; Bakery products	2.16	Branciari et al. (2020)
France	Children	1-4 months 13-36 months	Vegetable; Meat; Eat; Potato; Biscuits	0.141 0.708	Sirost et al. (2019)

of cardiovascular disease, indicating that excessive intake of AA in children may lead to exacerbation of the disease or lesions of other organs (Hsu et al., 2020). Table 2 summarizes the daily intake of AA in specific national populations, providing a more intuitive understanding for assessing AA dietary exposure. Thus, for the risk assessment of AA, we found that the dietary intake of AA in children is at least twice as high as that of adults, and in the future, researchers should pay more attention to the dietary exposure to AA and find ways to reduce the AA content in foods to ensure people's food safety.

5. MEASURES TO REDUCE ACRYLAMIDE IN FOOD

5.1. Application of plant antioxidants

Based on the toxic effects of AA on human health, we should take the initiative to find more techniques and methods to reduce the formation of AA in food and reduce the health risk of people. It was found that some antioxidant substances exist in natural plants to reduce AA formation. P. Wang et al. (2019) found that Blueberry anthocyanins extract (BAE) inhibited the formation of the GA and reduced the accumulation of GA-DNA adducts in the kidney, liver, and lung of rats. S. Yu et al. (2020) found that To prevent the generation of AA, lipophilic grape seed proanthocyanidin (LGSP) reduced lipid oxidation in the acrolein pathway and Schiff base levels in the asparagine process Yang et al. (2021) also found that the polyphenols of apple root bark glycoside phlorizin in apple significantly reduced the amount of AA in French fries after soaking potato fries and preserved the color and flavour of the food itself. There are no examples of antioxidant applications for AA protection and whether we should enhance the development of new plant

antioxidant-based drugs or nutraceuticals related to protecting against AA contaminants.

5.2. Application of asparaginase

Asparagine is one of the precursors for AA formation, and the asparagine content in food ingredients directly affects AA production. Because asparaginase is stable in food and does not cause toxic reactions in humans, asparaginase can be added to food as a food additive to reduce the amount of AA in food (da Cunha et al., 2019). Wang Y et al. found that a novel recombinant Asparaginase produced by *Palaecoccus ferrophilus* retained more than 98% of its initial activity after three months of storage at 4°C. In addition, enzyme treatment of French fries (10 U / mL, 85°C, 15 min) resulted in a significant 79% reduction in AA content compared to untreated fries (Y. Wang et al., 2021).

5.3. Optimization of baking conditions

In the process of baking food, roasting parameters can affect the formation of AA. Bertuzzi et al. (2020) found that baking Arabica and Robusta varieties at an elevated temperature from 90 °C to 215 °C resulted in a maximum AA content when the temperature reached 175-177 °C after 10 min of baking. However, when the temperature reached 203-205°C after 14 min, the AA content decreased rapidly, along with decreased asparagine and reduced sugar content (Bertuzzi et al., 2020). AA is produced above 120°C during frying and baking but undergoes degradation at temperatures above 180°C (Esposito et al., 2020). Therefore, we should determine the appropriate baking temperature and time to reduce the

AA content during food processing. In addition, the moisture content of food ingredients also affects the production of AA. For example, potatoes, coffee, and cereals with low water content (<5% moisture content) are more favourable for AA formation (Andačić et al., 2020). Food ingredients with pH between 7-8 are more likely to form AA, while changes in the pH of processed foods may result in changes in the content of AA. These changes in baking parameters undoubtedly increase the food safety risks for people, so accurate control of food baking conditions is also an effective measure to reduce the production of AA.

6. CONCLUSION AND FUTURE PROSPECTS

The exposure of AA in food is an unavoidable public health problem for humans. AA can cause neurotoxicity, carcinogenicity, reproductive toxicity, genotoxicity and hepatosplenic toxicity, detrimental to human health. Although there is controversy in current research about whether dietary exposure to AA increases the risk of cancer in humans, animal studies have shown that high levels of AA can lead to an increased risk of cancer, suggesting that we should be more vigilant about dietary exposure to AA in humans. In addition, with the development of modern analytical techniques, we can detect AA and its metabolites in food or human urine by LC-MS/MS, GC-MS and CE. However, the detection of AA and its metabolites is limited in routine and clinical applications due to the expensive analytical instruments, high cost and tedious sample handling. Therefore, novel assays that are rapid, inexpensive, and accurate also need to be developed. Risk assessment of human exposure to AA has revealed that with the improvement of quality of life and the introduction of baked goods such as French fries, cookies and bread into people's daily life, adults and children have been exposed to the risk of AA, especially for children, whose bodies are still developing and more vulnerable to the toxic effects of AA. Therefore, it is also crucial to find effective mitigation measures to reduce the formation of AA in food. Government authorities should enact relevant laws and regulations to set minimum residue limits of chemical contaminants AA in food, and food manufacturers should take responsibility to optimize the process conditions to reduce AA production in food. In the future, we should also conduct more research to explore the toxic effects of AA and elucidate the specific molecular mechanisms of AA poisoning, to prove the correlation between AA and human diseases from clinical data, and to establish effective detection methods and mitigation measures to protect people's health and food safety.

ABBREVIATIONS

AA; acrylamide
 GA; glycidamide
 3-APA; 3-aminopropionamide
 NOCs; N-nitroso compounds
 HAAs; heterocyclic aromatic amines
 Hb; hemoglobin
 GST; glutathione-S-transferase

PAHs; polycyclic aromatic hydrocarbons
 3-MCPDE; 3-monochloropropane-1,2-diol esters
 GAMA; N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine
 iso-GAMA; N-acetyl-S-(1-carbamoyl-2-hydroxyethyl)-cysteine
 AAMA; N-acetyl-S-(2-carbamoylethyl)-cysteine
 SNFA; Swedish National Food Agency
 GC-MS; gas chromatography-mass spectrometry
 LC-MS; liquid chromatography-mass spectrometry
 CE; capillary electrophoresis
 DLLME; dispersive liquid-liquid microextraction
 LC-HRMS; liquid chromatography-high resolution mass spectrometry
 BSA; bovine serum albumin
 OVA; ovalbumin
 ICS; immunochromatographic test strips
 ROS; reactive oxygen species
 SOD; Superoxide dismutase
 GSH-PX; Glutathione peroxidase
 MDA; malondialdehyde
 Nrf2; nuclear factor erythroid 2-related factor 2
 HO-1; heme oxygenase 1
 Keap1; Kelch-like ECH-associating protein 1
 NQO-1; NAD(P)H Quinone Dehydrogenase 1
 IARC; International Agency for Research on Cancer
 FDA; Food and Drug Administration
 JECFA; Joint Expert Committee on Food Additives
 FSH; follicle-stimulating hormone
 Esx1; Extra-embryonic tissue-spermatogenesis-homeobox gene 1
 bHLH; basic Helix-Loop-Helix
 NO; nitric oxide
 ERS; endoplasmic reticulum stress
 JNK c-Jun N-terminal kinase
 ASK1; activate apoptosis signal-regulated kinase 1
 Bax; BCL2-Associated X
 Bcl-2; B-cell lymphoma-2
 Bcl-xL; B-cell lymphoma-xL
 TNF; Tumor necrosis factor
 TRAF2; Tumor necrosis factor receptor associated factor 2
 INOS; Inducible nitric oxide synthase
 FAO; Food and Agriculture Organization
 WHO; World Health Organization
 BAE; Blueberry anthocyanins extract
 LGSP; lipophilic grape seed proanthocyanidin

CONFLICTS OF INTEREST

The authors of this study have no conflicts of interest to disclose.

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Tingdong Yan and Yi Cai created the research concept and design. Chaoming Huang, Shisheng Jiang, and Yantianyu Yang collected and/or assembled data. Yantianyu Yang, Shuhan Gao, Zihan Lin, and Wei Gu analysed and interpreted the data. Chaoming Huang wrote the article. Tingdong Yan and Yi Cai contributed to the article's revision. Tingdong Yan and Yi Cai gave final approval to the article.

REFERENCES

- Abt, E., Robin, L.P., McGrath, S., Srinivasan, J., DiNovi, M., Adachi, Y., Chirtel, S., 2019. Acrylamide levels and dietary exposure from foods in the United States, an update based on 2011-2015 data. *Food Additives & Contaminants: Part A: Chemistry, Analysis, Control, Exposure & Risk Assessment*. 36(10), 1475–1490. <https://doi.org/10.1080/19440049.2019.1637548>
- Adani, G., Filippini, T., Wise, L.A., Halldorsson, T.I., Blaha, L., Vinceti, M., 2020. Dietary Intake of acrylamide and Risk of Breast, Endometrial, and Ovarian Cancers: A Systematic Review and Dose-Response Meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention*. 29(6), 1095–1106. <https://doi.org/10.1158/1055-9965.epi-19-1628>
- Aldawood, N., Alrezaki, A., Alanazi, S., Amor, N., Alwasel, S., Sirotkin, A., Harrath, A.H., 2020. Acrylamide impairs ovarian function by promoting apoptosis and affecting reproductive hormone release, steroidogenesis and autophagy-related genes: An in vivo study. *Ecotoxicology and Environmental Safety*. 197, 110595. <https://doi.org/10.1016/j.ecoenv.2020.110595>
- Andačić, I.M., Tot, A., Ivešić, M., Krivohlavek, A., Thirumdas, R., Barba, F.J., Sabolović, M.B., Kljusurić, J.G., Brnčić, S.R., 2020. Exposure of the Croatian adult population to acrylamide through bread and bakery products. *Food Chemistry*. 322, 126771. <https://doi.org/10.1016/j.foodchem.2020.126771>
- Asnaashari, M., Kenari, R.E., Farahmandfar, R., Abnous, K., Taghdisi, S.M., 2019. An electrochemical biosensor based on hemoglobin-oligonucleotides-modified electrode for detection of acrylamide in potato fries. *Food Chemistry*. 271, 54–61. <https://doi.org/10.1016/j.foodchem.2018.07.150>
- Basaran, B., Aydin, F., 2020. Estimating the acrylamide exposure of adult individuals from coffee: Turkey. *Food Additives & Contaminants: Part A*. 37(12), 2051–2060. <https://doi.org/10.1080/19440049.2020.1819570>
- Bertuzzi, T., Martinelli, E., Mulazzi, A., Rastelli, S., 2020. Acrylamide determination during an industrial roasting process of coffee and the influence of asparagine and low molecular weight sugars. *Food Chemistry*. 303, 125372. <https://doi.org/10.1016/j.foodchem.2019.125372>
- Bin-Jumah, M., Abdel-Fattah, A.-F.M., Saied, E.M., El-Seedi, H.R., Abdel-Daim, M.M., 2021. Acrylamide-induced peripheral neuropathy: manifestations, mechanisms, and potential treatment modalities. *Environmental Science and Pollution Research*. 28(11), 13031–13046. <https://doi.org/10.1007/s11356-020-12287-6>
- Bo, N., Yilin, H., Chaoyue, Y., Lu, L., Yuan, Y., 2020. Acrylamide induces NLRP3 inflammasome activation via oxidative stress- and endoplasmic reticulum stress-mediated MAPK pathway in HepG2 cells. *Food and Chemical Toxicology*. 145, 111679. <https://doi.org/10.1016/j.fct.2020.111679>
- Branciarri, R., Roila, R., Ranucci, D., Altissimi, M.S., Mercuri, M.L., Haoet, N.M., 2020. Estimation of acrylamide exposure in Italian schoolchildren consuming a canteen menu: health concern in three age groups. *International Journal of Food Sciences and Nutrition*. 71(1), 122–131. <https://doi.org/10.1080/09637486.2019.1624692>
- Chen, X., Jia, W., Wang, Q., Han, J., Cheng, J., Zeng, W., Zhao, Q., Zhang, Y., Zhang, Y., 2020. Protective effect of a dietary flavonoid-rich antioxidant from bamboo leaves against internal exposure to acrylamide and glycidamide in humans. *Food & Function*. 11(8), 7000–7011. <https://doi.org/10.1039/D0FO00811G>
- Chu, P.L., Liu, H.S., Wang, C., Lin, C.Y., 2003. Association between acrylamide exposure and sex hormones in males: NHANES. *PLoS One*. 15(6), 234622–234622. <https://doi.org/10.1371/journal.pone.0234622>
- da Cunha, M.C., dos Santos Aguilar, J.G., de Melo, R.R., Nagamatsu, S.T., Ali, F., de Castro, R.J.S., Sato, H.H., 2019. Fungal L-asparaginase: Strategies for production and food applications. *Food Research International*. 126, 108658. <https://doi.org/10.1016/j.foodres.2019.108658>
- Desmarchelier, A., Hamel, J., Delatour, T., 2020. Sources of overestimation in the analysis of acrylamide-in coffee by liquid chromatography mass spectrometry. *Journal of Chromatography A*. 1610, 460566. <https://doi.org/10.1016/j.chroma.2019.460566>
- Donmez, D.B., Kacar, S., Bagci, R., Sahinturk, V., 2020. Protective effect of carnosic acid on acrylamide-induced liver toxicity in rats: Mechanistic approach over Nrf2-Keap1 pathway. *Journal of Biochemical and Molecular Toxicology*. 34, e22524. <https://doi.org/10.1002/jbt.22524>
- Eslamizad, S., Kobarfard, F., Tsitsimpikou, C., Tsatsakis, A., Tabib, K., Yazdanpanah, H., 2019. Health risk assessment of acrylamide in bread in Iran using LC-MS/MS. *Food and Chemical Toxicology*. 126, 162–168. <https://doi.org/10.1016/j.fct.2019.02.019>
- Esposito, F., Fasano, E., Vivo, D., Velotto, A., Sarghini, S., Cirillo, F., T., 2020. Processing effects on acrylamide content in roasted coffee production. *Food Chemistry*. 319, 126550–126550. <https://doi.org/10.1016/j.foodchem.2020.126550>
- Faria, M., Prats, E., Gómez-Canela, C., Hsu, C.-Y., II, M.A.A., Bedrossiantz, J., Orozco, M., Garcia-Reyero, N., Ziv, T., Ben-Lulu, S., Admon, A., Gómez-Oliván, L.M., Raldúa, D., 2019. Therapeutic potential of N-acetylcysteine in acrylamide acute neurotoxicity in adult zebrafish. *Scientific Reports*. 10(1), 16467. <https://doi.org/10.1038/s41598-019-53154-w>
- Galuch, M.B., Magon, T.F.S., Silveira, R., Nicácio, A.E., Pizzo, J.S., Bonafe, E.G., Maldaner, L., Santos, O.O., Visentainer, J.V., 2019. Determination of acrylamide in brewed coffee by dispersive liquid-liquid microextraction (DLLME) and ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS). *Food Chemistry*. 282, 120–126. <https://doi.org/10.1016/j.foodchem.2018.12.114>
- Goerke, K., Ruenz, M., Lampen, A., Abraham, K., Bakuradze, T.,

- Eisenbrand, G., Richling, E., 2019. Biomonitoring of nutritional acrylamide intake by consumers without dietary preferences as compared to vegans. *Archives of Toxicology*. 93(4), 987–996. <https://doi.org/10.1007/s00204-019-02412-x>
- Hsu, C.N., Hou, C.Y., Lu, P.C., Chang-Chien, G.P., Lin, S., Tain, Y.L., 2020. Association between acrylamide Metabolites and Cardiovascular Risk in Children With Early Stages of Chronic Kidney Disease. *International Journal of Molecular Sciences*. 21(16), 5855. <https://doi.org/10.3390/ijms21165855>
- Ibrahim, M.A., Ibrahim, M.D., 2020. Acrylamide-induced hematotoxicity, oxidative stress, and DNA damage in liver, kidney, and brain of catfish (*Clarias gariepinus*). *Environmental Toxicology*. 35(2), 300–308. <https://doi.org/10.1002/tox.22863>
- Ivanski, F., de Oliveira, V.M., de Oliveira, I.M., de Araújo Ramos, A.T., de Oliveira Tonete, S.T., de Oliveira Hykavei, G., Bargi-Souza, P., Schiessel, D.L., Martino-Andrade, A.J., Romano, M.A., Romano, R.M., 2020. Prepubertal acrylamide exposure causes dose-response decreases in spermatid production and functionality with modulation of genes involved in the spermatogenesis in rats. *Toxicology*. 436, 152428. <https://doi.org/10.1016/j.tox.2020.152428>
- Jiang, F., Teng, M., Zhu, Y.X., Li, Y.J., 2020. No association between dietary acrylamide and renal cell carcinoma: an updated meta-analysis. *Journal of the Science of Food and Agriculture*. 100(7), 3071–3077. <https://doi.org/10.1002/jsfa.10339>
- Jiang, G., Lei, A., Chen, Y., Yu, Q., Xie, J., Yang, Y., Yuan, T., Su, D., 2021. The protective effects of the *Ganoderma atrum* polysaccharide against acrylamide-induced inflammation and oxidative damage in rats. *Food & Function*. 12(1), 397–407. <https://doi.org/10.1039/D0FO01873B>
- Jozinović, A., Šarkanj, B., Đurđica Avčar, c, J.P.B., Šubarić, D., c, T.C., c, J.R., Guberac, S., c, J.B., 2019. Simultaneous Determination of Acrylamide and Hydroxymethylfurfural in Extruded Products by LC-MS/MS Method. *Molecules*. 24(10), 1971. <https://doi.org/10.3390/molecules24101971>
- Kito, K., Ishihara, J., Kotemori, A., Zha, L., Liu, R., Sawada, N., Iwasaki, M., Sobue, T., Tsugane, S., 2020. Dietary Acrylamide Intake and the Risk of Pancreatic Cancer: The Japan Public Health Center-Based Prospective Study. *Nutrients*. 12(11), 3584–3584. <https://doi.org/10.3390/nu12113584>
- Kito, K., Ishihara, J., Yamamoto, J., Hosoda, T., Kotemori, A., Takachi, R., Nakamura, K., Tanaka, J., Yamaji, T., Shimazu, T., Ishii, Y., Sawada, N., Iwasaki, M., Iso, H., Sobue, T., Tsugane, S., 2020. Variations in the estimated intake of acrylamide from food in the Japanese population. *Nutrition Journal*. 19(1), 17. <https://doi.org/10.1186/s12937-020-00534-y>
- Komoike, Y., Nomura-Komoike, K., Matsuoka, M., 2020. Intake of acrylamide at the dietary relevant concentration causes splenic toxicity in adult zebrafish. *Environmental Research*. 189, 109977. <https://doi.org/10.1016/j.envres.2020.109977>
- Li, C., Li, C., Yu, H., Cheng, Y., Xie, Y., Yao, W., Guo, Y., Qian, H., 2021. Chemical food contaminants during food processing: sources and control. *Critical Reviews in Food Science and Nutrition*. 61(9), 1545–1555. <https://doi.org/10.1080/10408398.2020.1762069>
- Li, J., Zhao, X., Chen, L.-J., Qian, H.-L., Wang, W.-L., Yang, C., Yan, X.-P., 2019. p-Bromophenol-Enhanced Bioluminescence Competitive Immunoassay for Ultrasensitive Determination of Aflatoxin B1. *Analytical Chemistry*. 91(20), 13191–13197. <https://doi.org/10.1021/acs.analchem.9b03579>
- Liu, R., Sobue, T., Kitamura, T., Kitamura, Y., Ishihara, J., Kotemori, A., Zha, L., Ikeda, S., Sawada, N., Iwasaki, M., Tsugane, S., 2019. Dietary acrylamide Intake and Risk of Esophageal, Gastric, and Colorectal Cancer: The Japan Public Health Center-Based Prospective Study. *Cancer Epidemiology, Biomarkers & Prevention*. 28(9), 1461–1468. <https://doi.org/10.1158/1055-9965.epi-18-1259>
- Liu, R., Zha, L., Sobue, T., Kitamura, T., Ishihara, J., Kotemori, A., Ikeda, S., Sawada, N., Iwasaki, M., Tsugane, S., 2020. Dietary acrylamide Intake and Risk of Lung Cancer: The Japan Public Health Center Based Prospective Study. *Nutrients*. 12(8), 2417. <https://doi.org/10.3390/nu12082417>
- Mesias, M., Delgado-Andrade, C., Holgado, F., Morales, F.J., 2020. Acrylamide in French fries prepared at primary school canteens. *Food & Function*. 11(2), 1489–1497. <https://doi.org/10.1039/C9FO02482D>
- Mollakhalili-Meybodi, N., Khorshidian, N., Nematollahi, A., Arab, M., 2021. Acrylamide in bread: a review on formation, health risk assessment, and determination by analytical techniques. *Environmental Science and Pollution Research*. 28(13), 15627–15645. <https://doi.org/10.1007/s11356-021-12775-3>
- Nagashima, D., Zhang, L., Kitamura, Y., Ichihara, S., Watanabe, E., Zong, C., Yamano, Y., Sakurai, T., Oikawa, S., Ichihara, G., 2019. Proteomic analysis of hippocampal proteins in acrylamide-exposed Wistar rats. *Archives of Toxicology*. 93(7), 1993–2006. <https://doi.org/10.1007/s00204-019-02484-9>
- Ou, J., Ou, J., Huang, J., Ho, C.-T., Ou, S., 2020. Interaction of acrylamide, acrolein, and 5-Hydroxymethylfurfural with Amino Acids and DNA. *Journal of Agricultural and Food Chemistry*. 68(18), 5039–5048. <https://doi.org/10.1021/acs.jafc.0c01345>
- Pan, X., Wu, X., Yan, D., Peng, C., Rao, C., Yan, H., 2018. Acrylamide-induced oxidative stress and inflammatory response are alleviated by N-acetylcysteine in PC12 cells: Involvement of the crosstalk between Nrf2 and NF- κ B pathways regulated by MAPKs. *Toxicology Letters*. 288, 55–64. <https://doi.org/10.1016/j.toxlet.2018.02.002>
- Salimi, A., Baghal, E., Ghobadi, H., Hashemidanesh, N., Khodaparast, F., Mitochondrial, S.E., 2021. Mitochondrial, lysosomal and DNA damages induced by acrylamide attenuate by ellagic acid in human lymphocyte. *PLoS One*. 16(2), 247776. <https://doi.org/10.1371/journal.pone.0247776>
- Schouten, M.A., Tappi, S., Romani, S., 2020. Acrylamide in coffee: formation and possible mitigation strategies – a review. *Critical Reviews in Food Science and Nutrition*. 60(22), 3807–3821. <https://doi.org/10.1080/10408398.2019.1708264>
- Siroto, V., Rivièrè, G., Leconte, S., 2019. French infant total diet study: Dietary exposure to heat-induced compounds (acrylamide, furan and polycyclic aromatic hydrocarbons) and associated health risks. <https://doi.org/10.1016/j.fct.2019.05.009>. 130, 308–316. <https://doi.org/10.1016/j.fct.2019.05.009>
- Sui, X., Yang, J., Zhang, G., Yuan, X., Li, W., Long, J., Luo, Y., Li, Y., Wang, Y., 2020. NLRP3 inflammasome inhibition attenuates subacute neurotoxicity induced by acrylamide in vitro and in vivo. *Toxicology*. 432, 152392. <https://doi.org/10.1016/j.tox.2020.152392>
- Sun, G., Qu, S., Wang, S., Shao, Y., Sun, J., 2018. Taurine attenuates acrylamide-induced axonal and myelinated damage through the Akt/GSK3 β -dependent pathway. *International Journal of Immunopathology and Pharmacology*. 32, 2058738418805322. <https://doi.org/10.1177/2058738418805322>
- Wang, B., Qiu, W., Yang, S., Cao, L., Zhu, C., Ma, J., Li, W., Zhang, Z., Xu, T., Wang, X., Cheng, M., Mu, G., Wang, D., Zhou, Y., Yuan, J., Chen, W., 2020. Acrylamide Exposure and Oxidative DNA Damage, Lipid Peroxidation, and Fasting Plasma Glucose Alteration: Association and Mediation Analyses in Chinese Urban Adults. *Diabetes Care*. 43(7), 1479–1486. <https://doi.org/10.2337/dc19-2603>

- Wang, P., Ji, R., Ji, J., Chen, F., 2019. Changes of metabolites of acrylamide and glycidamide in acrylamide-exposed rats pretreated with blueberry anthocyanins extract. *Food Chemistry*. 274, 611–619. <https://doi.org/10.1016/j.foodchem.2018.08.058>
- Wang, Y., Wu, H., Zhang, W., Xu, W., Mu, W., 2021. Efficient control of acrylamide in French fries by an extraordinarily active and thermo-stable l-asparaginase: A lab-scale study. *Food Chemistry*. 360, 130046. <https://doi.org/10.1016/j.foodchem.2021.130046>
- Wawrzyniak, R., Jasiewicz, B., 2019. Straightforward and rapid determination of acrylamide in coffee beans by means of HS-SPME/GC-MS. *Food Chemistry*. 301, 125264. <https://doi.org/10.1016/j.foodchem.2019.125264>
- Wu, M.-F., Wang, Y., Li, S., Dong, X.-X., Yang, J.-Y., Shen, Y.-D., Wang, H., Sun, Y.-M., Lei, H.-T., Xu, Z.-L., 2019. Ultrasensitive immunosensor for acrylamide based on chitosan/SnO₂-SiC hollow sphere nanochains/gold nanomaterial as signal amplification. *Analytica Chimica Acta*. 1049, 188–195. <https://doi.org/10.1016/j.aca.2018.10.041>
- Yang, Y., Shen, H., Liu, T., Wen, Y., Wang, F., Guo, Y., 2021. Mitigation effects of phlorizin immersion on acrylamide formation in fried potato strips. *Journal of the Science of Food and Agriculture*. 101(3), 937–946. <https://doi.org/10.1002/jsfa.10701>
- Yilmaz, B.O., Yildizbayrak, N., Aydin, Y., 2020. Vitamin C inhibits glycidamide-induced genotoxicity and apoptosis in Sertoli cells. *Journal of Biochemical and Molecular Toxicology*. 34, e22545. <https://doi.org/10.1002/jbt.22545>
- Yu, D., Liu, Q., Qiao, B., Jiang, W., Zhang, L., Shen, X., Xie, L., Liu, H., Zhang, D., Yang, B., Kuang, H., 2020. Exposure to acrylamide inhibits uterine decidualization via suppression of cyclin D3/p21 and apoptosis in mice. *Journal of Hazardous Materials*. 388, 121785. <https://doi.org/10.1016/j.jhazmat.2019.121785>
- Yu, D., Xie, X., Qiao, B., Ge, W., Gong, L., Luo, D., Zhang, D., Li, Y., Yang, B., Kuang, H., 2019. Gestational exposure to acrylamide inhibits mouse placental development in vivo. *Journal of Hazardous Materials*. 367, 160–170. <https://doi.org/10.1016/j.jhazmat.2018.12.061>
- Yu, S., Chen, Z., Meng, H., Chen, M., 2020. Addition of lipophilic grape seed proanthocyanidin effectively reduces acrylamide formation. *J Sci Food Agric*. 100(3), 1213–1219. <https://doi.org/10.1002/jsfa.10132>
- Yue, Z., Chen, Y., Song, Y., Zhang, J., Yang, X., Wang, J., Li, L., Sun, Z., 2020. Effect of acrylamide on glucose homeostasis in female rats and its mechanisms. *Food Chem Toxicol*. 135, 110894. <https://doi.org/10.1016/j.fct.2019.110894>
- Zhang, L., Hara, S., Ichinose, H., Nagashima, D., Morita, K., Sakurai, T., Ichihara, S., Ichihara, G., 2020. Exposure to acrylamide decreases noradrenergic axons in rat brain. *Neurotoxicology*. 78, 127–133. <https://doi.org/10.1016/j.neuro.2020.03.001>
- Zhang, Y., Wang, Q., Jia, W., Cheng, J., Zhu, L., Ren, Y., Zhang, Y., 2020. Rapid Simultaneous Determination of Cascade Metabolites of Acrylamide in Urine for Toxicokinetics Profiles and Short-Term Dietary Internal Exposure. *Journal of Agricultural and Food Chemistry*. 68(24), 6748–6758. <https://doi.org/10.1021/acs.jafc.0c01685>
- Zhivagui, M., Ng, A.W.T., Ardin, M., Churchwell, M.L., Pandey, M., Renard, C., Villar, S., Cahais, V., Robitaille, A., Bouaoun, L., et al., 2019. Experimental and pan-cancer genome analyses reveal widespread contribution of acrylamide exposure to carcinogenesis in humans. *Genome Research*. 29(4), 521–531. <https://doi.org/10.1101/gr.242453.118>
- Zhu, F., Wang, J., Jiao, J., Zhang, Y., 2021. Exposure to acrylamide induces skeletal developmental toxicity in zebrafish and rat embryos. *Environmental Pollution*. 271, 116395–116395. <https://doi.org/10.1016/j.envpol.2020.116395>
- Zilli, S.C., Grehs, B., Carissimi, E., Pizzolato, T.M., Silva, W.L.D., Silvestri, S., 2021. Toxicity of acrylamide after degradation by conjugated (UV/H₂O₂) photolysis in microalgae. *Environmental Science and Pollution Research*. 28(28), 38085–38093. <https://doi.org/10.1007/s11356-021-13355-1>
- Zong, C., Hasegawa, R., Urushitani, M., Zhang, L., Nagashima, D., Sakurai, T., Ichihara, S., Ohsako, S., Ichihara, G., 2019. Role of microglial activation and neuroinflammation in neurotoxicity of acrylamide in vivo and in vitro. *Archives of Toxicology*. 93(7), 2007–2019. <https://doi.org/10.1007/s00204-019-02471-0>