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Acrylamide and Male Infertility: Exploring the Implication for Reproductive Health

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Abstract

Acrylamide, a chemical compound found in various foods and industrial products, has become a topic of growing concern in recent years. Research has shown that this substance has an impact on male reproductive health, potentially contributing to infertility issues. As scientists delve deeper into understanding the effects of environmental factors on human health, the relationship between acrylamide and male reproductive function has emerged as a crucial area of study. Here the key insight into how acrylamide affects male infertility explores. It examines the nature of acrylamide and its presence in our daily lives, as well as its specific effects on the male reproductive system. Also, the mechanisms behind acrylamide-induced male infertility, highlighting studies that shed light on its impact on sperm and testis function. Additionally, it offers practical advice to reduce acrylamide exposure, providing readers with valuable information to safeguard their reproductive health.

Keywords: Acrylamide, Infertility, Reproduction, Sperm, ROS

Introduction

Acrylamide (ACR) is a chemical compound that forms naturally in certain foods during high-temperature cooking processes, such as frying, roasting, and baking. This substance has gained attention due to its potential health effects, particularly its classification as a probable human carcinogen by the International Agency for Research on Cancer (1). ACR is primarily found in plant-based foods that are cooked at high temperatures. The major sources of ACR in the diet include French fries, potato chips, crackers, bread, cookies, breakfast cereals, and coffee (2). It's important to note that ACR does not typically form in dairy, meat, or fish products. Additionally, ACR is present in cigarette smoke, with smokers having three to five times higher levels of ACR exposure markers in their blood compared to non-smokers (3).

The formation of ACR in foods occurs through a chemical reaction known as the Maillard reaction. This reaction occurs between an amino acid, primarily asparagine, and reducing sugars such as glucose or fructose. The process requires high temperatures, typically above 120°C (248°F), and peaks between 160°C and 180°C (320°F to 356°F) ACR formation is closely linked to the browning or crisping of foods during cooking.

Foods that undergo longer cooking or are cooked at higher temperatures tend to accumulate more ACR. For instance, the crispy edges of French fries and the golden-brown color of toasted bread are indicators of ACR formation (4).

It's worth noting that ACR does not form in foods that are boiled, steamed, or microwaved. In the case of coffee, ACR forms during the roasting of coffee beans rather than when the coffee is brewed.

The estimated average daily intake of ACR for adults is approximately 0.3 to 0.6 μg/kg of body weight. Children and adolescents tend to have higher ACR intake per body weight basis, which may be due to their higher caloric intake relative to body weight and greater consumption of certain ACR-rich foods like French fries and potato chips (5). The foods that contribute most to ACR intake vary across countries according to national dietary patterns. However, potato products, breads, and coffee are generally significant contributors across populations. In the United States, foods containing ACR contribute to 38% of total daily energy intake, 47% of total daily iron intake, and 42% of total daily folate intake among adults (5). While ACR exposure through food has been a concern, it's important to note that the levels found in food are much lower than those used in animal studies that showed a clear link to cancer.

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Human studies have not consistently found a direct link between dietary ACR intake and cancer risk. However, research in this area continues, and efforts to reduce ACR levels in food are ongoing.

Acrylamide's Effects on Male Reproductive System

ACR, a chemical compound found in various foods and industrial products, has been shown to have significant effects on the male reproductive system. Research has revealed that exposure to ACR can lead to various adverse outcomes, impacting sperm parameters, testicular cells, and hormonal balance (6-8). (Figure 1)

Impact on Sperm Parameters

Studies have demonstrated that ACR exposure can result in a decline in sperm quality and functionality. In ACR-treated mice, researchers observed significantly lower sperm concentration, viability, and motility compared to control groups. The compound's detrimental effects extend to sperm chromatin quality, potentially affecting male fertility potential (6). ACR has been found to interfere with sperm motility by affecting the kinesin motor proteins in sperm flagella. This interference can lead to reduced sperm motility and, consequently, decreased fertility rates. Additionally, ACR exposure has been associated with abnormal sperm morphology and reduced sperm count (6, 9).

Damage to Testicular Cells

ACR has been shown to cause damage to various testicular cells, including those in the seminiferous tubules and Leydig cells. Histopathological studies have revealed degeneration of epithelial cells in the seminiferous tubules, formation of multinucleated giant cells, and vacuolation in the testes of ACR-exposed animals (8). The compound's toxicity extends to Leydig cells, which are responsible for testosterone production. Research has indicated that ACR can reduce Leydig cell viability, leading to decreased testosterone levels and diminished spermatogenesis. This damage to testicular cells can significantly impact male reproductive function (10).

Hormonal Disruptions

ACR exposure has been linked to hormonal imbalances within the male reproductive system. Studies have shown that ACR can disrupt the hypothalamic-pituitary-gonadal (HPG) axis, leading to alterations in hormone levels. In ACR-treated animals, researchers observed decreased levels of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. These hormonal disruptions can have far-reaching effects on male reproductive function, including impaired spermatogenesis and reduced fertility (11). Furthermore, ACR has been found to affect the expression of genes involved in testosterone synthesis. Studies have shown that exposure to ACR can lead to the downregulation of steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase (3β-HSD), both of which play crucial roles in testosterone production (12, 13). The impact of ACR on male reproductive hormones appears to be more pronounced during puberty. Research has indicated that prepubertal exposure to ACR can lead to more significant decreases in serum testosterone and estradiol levels in pubertal mice compared to adult mice (14). In conclusion, ACRs effects on the male reproductive system are multifaceted, impacting sperm parameters, testicular cells, and hormonal balance. These findings underscore the importance of understanding and mitigating ACR exposure, particularly during critical developmental periods such as puberty, to safeguard male reproductive health.

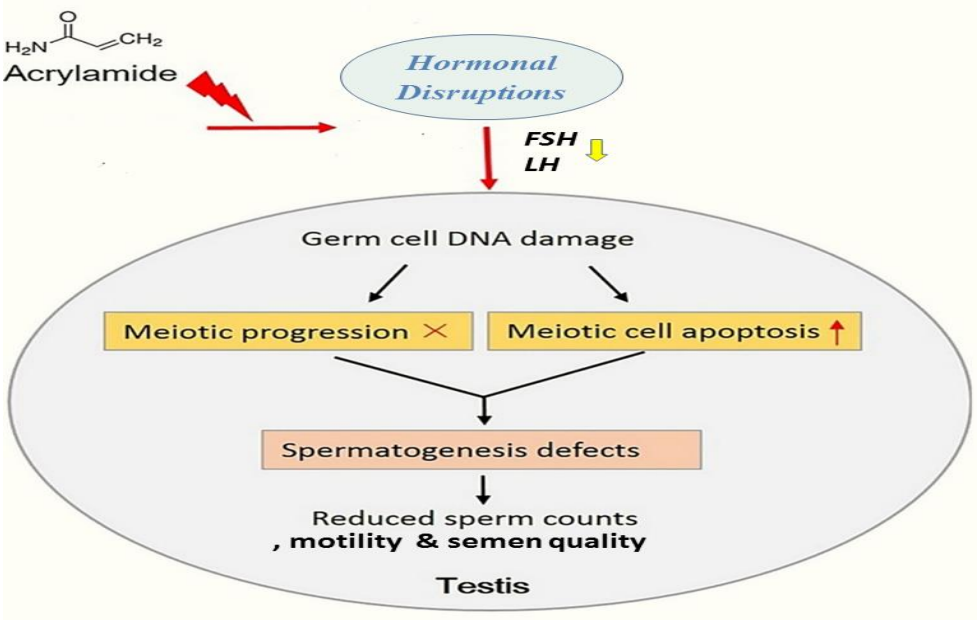

Figure 1: An illustrative figure showing the toxic effects of ACR on testicular cells.

Mechanisms of Acrylamide-Induced Male Infertility

The mechanisms through which ACR affects male infertility are complex and multifaceted. Research has identified several key pathways through which this chemical compound exerts its detrimental effects on the male reproductive system.

Oxidative Stress induction

ACR has a significant impact on oxidative stress levels in the male reproductive system. Studies have shown that exposure to ACR leads to an increase in reactive oxygen species (ROS) production and a decrease in antioxidant capacity in germ cells. This imbalance results in oxidative stress, which has an impact on sperm quality and function (7, 15).

The sperm cell is particularly vulnerable to oxidative attack due to its low volume of cytoplasm and, consequently, low levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (16). Additionally, the high levels of polyunsaturated fatty acids in sperm make them susceptible to free radical attacks (17). Lipid peroxidation caused by ROS leads to the formation of malondialdehyde (MDA), a stable peroxidation product in seminal plasma (18). MDA is a biomarker for measuring the level of oxidative stress in the cell and is a well-known indicator of reduced fertility and sperm dysfunction (19). The oxidative stress induced by ACR has an impact on sperm motility, membrane integrity, and DNA integrity. This can result in reduced motility, inhibition of the acrosomal reaction, and decreased sperm ability for fertilization (20).

DNA Damage

ACR and its metabolite, glycidamide, have been shown to induce DNA damage in male reproductive cells. Glycidamide, formed through the metabolism of ACR by cytochrome P450 enzyme CYP2E1, is known to be more reactive toward macromolecules such as DNA than the parent ACR compound (21).

Studies have demonstrated that ACR exposure leads to an increase in DNA damage in sperm cells. This damage has been observed through various methods, including the formation of micronuclei in sperm cells and increased chromatin damage in testicular cells (6, 7, 22). The DNA damage induced by ACR and glycidamide can have significant consequences for male fertility (23). Sperm with damaged DNA may have reduced fertilization potential and may lead to early embryonic loss or developmental abnormalities.

Endocrine Disruption

ACR has been identified as an endocrine disruptor, affecting the hypothalamic-pituitary-gonadal (HPG) axis and disrupting hormonal balance in the male reproductive system (24). Research has shown that ACR exposure can lead to decreased levels of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. These hormonal disruptions can have far-reaching effects on male reproductive function, including impaired spermatogenesis and reduced fertility (24). ACR has also been found to affect the expression of genes involved in testosterone synthesis. Studies have shown that exposure to ACR can lead to the downregulation of steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase (3β-HSD), both of which play crucial roles in testosterone production (25, 26). The impact of ACR on male reproductive hormones appears to be more pronounced during puberty. Research has indicated that prepubertal exposure to ACR can lead to more significant decreases in serum testosterone and estradiol levels in pubertal mice compared to adult mice (14, 27).

In conclusion, the mechanisms of ACR-induced male infertility involve a complex interplay of oxidative stress, DNA damage, and endocrine disruption. These processes collectively contribute to the detrimental effects of ACR on male reproductive health, highlighting the importance of understanding and mitigating ACR exposure to safeguard male fertility.

Studies on Acrylamide and Male Fertility

Animal Studies

Numerous animal studies have shed light on the effects of ACR on male fertility. One study investigated sperm chromatin quality and testosterone levels in ACR-treated mice (6). The results showed significantly lower sperm concentration, viability, motility, and testosterone levels in ACR-treated mice compared to control groups. Additionally, the study revealed a higher proportion of spermatozoa with less condensed chromatin in ACR-treated mice. Another study examined the impact of ACR on the testicular antioxidant system in rats exposed during the prepubertal period (27-29). The findings indicated that prepubertal oral exposure to relevant doses of ACR impaired the testicular antioxidant system in adulthood, leading to increased protein carbonylation and lipid peroxidation. This suggests that ACR exposure during critical developmental periods may have long-lasting effects on male reproductive health.

Research has also shown that ACR can induce DNA damage in male reproductive cells. Studies have demonstrated an increase in DNA damage in sperm cells following ACR exposure, observed through the formation of micronuclei and increased chromatin damage in testicular cells. This DNA damage has significant implications for male fertility, as it may lead to reduced fertilization potential and early embryonic loss (7, 21, 30).

Human Studies

While animal studies have provided valuable insights into the effects of ACR on male fertility, human studies have been more limited. However, some research has been conducted to explore the relationship between ACR exposure and reproductive health in human males.

A cross-sectional analysis of the general US population found associations between ACR exposure and sex hormone alterations in male participants. The study revealed that hemoglobin adducts of ACR (HbAA) levels were positively associated with serum levels of inhibin B and sex hormone-

binding globulin (SHBG). Additionally, hemoglobin adducts of glycidamide (HbGA) levels were associated with an increase in serum anti-Müllerian hormone (AMH) levels (11). These findings suggest that ACR exposure may affect hormone homeostasis in human males, particularly sex hormones. However, it's important to note that no associations were found between ACR exposure and other sex hormones, including testosterone, estradiol, and androstanedione glucuronide (11, 22).

Dose-Response Relationships

Understanding the dose-response relationship between ACR exposure and male fertility is crucial for assessing potential risks. Animal studies have provided some insights into this relationship, but extrapolating these findings to humans requires caution. In one study, mice were exposed to ACR at a dose of 10 mg/kg dissolved in drinking water for 35 days. This exposure resulted in poor sperm parameters, including reduced sperm count, motility, and normal morphology, compared to control animals. However, it's important to note that this dose is significantly higher than typical human exposure levels (6). Human dietary exposure to ACR is estimated to range between 1 μg/kg/day and 4 μg/kg/day. While these levels are lower than those used in animal studies, the long-term effects of chronic low-dose exposure on male fertility remain a subject of ongoing research (31).

In conclusion, studies on ACR and male fertility have provided valuable insights into the potential reproductive toxicity of this compound. Animal studies have consistently shown detrimental effects on sperm parameters, testicular function, and hormone levels. Human studies, while more limited, suggest potential associations between ACR exposure and alterations in sex hormones. However, further research is needed to fully elucidate the dose-response relationships and long-term effects of ACR exposure on male fertility in humans.

Strategies to Reduce Acrylamide Exposure

Dietary Changes

To reduce exposure to ACR, individuals can make several dietary changes. The U.S. Food and Drug Administration (FDA) recommends adopting a healthy eating plan consistent with the Dietary Guidelines for Americans. This plan emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk products while limiting saturated fats, Tran’s fats, cholesterol, salt, and added sugars (32, 33).

ACR is primarily found in plant-based foods cooked at high temperatures, such as potatoes, grain products, and coffee. To lower ACR intake, individuals can reduce consumption of foods known to have high ACR levels, including French fries, potato chips, crackers, biscuits, and wafers. However, it's important to note that the FDA does not recommend reducing the intake of healthful grain products that are good sources of whole grains and fiber (33-37).

Food Preparation Methods

The way food is prepared can significantly impact ACR formation. When cooking potatoes, frying causes the highest ACR formation, followed by roasting and baking. Boiling potatoes and microwaving whole potatoes with skin on do not produce ACR (38, 39). To reduce ACR formation during cooking, individuals can:

Soak raw potato slices in water for 15-30 minutes before frying or roasting.

Store potatoes outside the refrigerator in a dark, cool place to prevent increased ACR formation during cooking.

Cook cut potato products, such as frozen French fries, to a golden yellow color rather than a brown color.

Toast bread to a light brown color, avoiding very brown areas that contain the most ACR.

For the food industry, the Food Drink Europe (FDE) has developed an "ACR toolbox" that serves as a comprehensive guide for reducing ACR in various food products. Some strategies include:

Selecting potato varieties low in ACR precursors.

Optimizing potato maturity by controlling planting time, harvest time, and input management.

Avoiding cold temperatures during harvest, transport, delivery, and storage of potatoes.

Using alternative coloration methods to discourage over-baking.

Data Acquisition

Google Scholar, Web of Science, PubMed, Scopus and SID databases were searched with a time limit of since 2010 and without language restrictions. Both in vivo and in vitro studies were equally evaluated. The included data, abstracts, titles, and full texts were reviewed by two independent researchers to determine the relevance for inclusion in the study. The search terms used were Acrylamide, Infertility, Reproduction, Male.

Table 1. The effect of acrylamide on male infertility

1	Author's name	Scope of study	Research model	Result
2	Saleh Alkarim (40)	Effects of low dose ACR on the rat reproductive organ’s structure, fertility, and gene integrity	Rats	A decreased number of seminiferous tubules containing mature sperm and degenerative changes in the sperm germ cell layers were observed. Additionally, some sperm in the epididymal cauda displayed head deformities.
3	Nesreen Rajeh (41)	Characterization of ACR mediated testicular toxicity in	Rats	AA-induced a significant reduction in body weight, an increase in the testis-to-body weight ratio, and a substantial reduction in sperm count. Abnormal sperm

		rat: light and electron microscopic study		shapes were detected, along with tail intersegmentation in mature sperm. Various abnormal histopathological lesions, including apoptosis in the rat testis, were observed, as well as failure in sperm release and phagocytosis of some sperm cells.
4	David A. Skerrett-Byrne (42)	Transcriptomic analysis of the seminal vesicle response to the reproductive toxicant ACR	Mice	The response may have implications for fertility, fetal development, and the health of later offspring.
5	C. Martínez- odríguez (43)	Evaluation of ram semen quality using polyacrylamide gel instead of cervical mucus in the sperm penetration test	Mice	Significant correlations were observed between the number of spermatozoa and several sperm quality parameters, with positive associations to progressive motility and velocity, and negative associations to damaged acrosomes and apoptotic cells.
6	Yuxin Ma (44)	Toxicological effects of ACR on the reproductive system of weaning male rats	Rats	The reproductive organ indexes of weaning male rats decreased, with serum levels of follicle-stimulating hormone and testosterone increasing, while luteinizing hormone levels decreased. Additionally, abnormal sperm were observed.
7	Fahime Khan (45)	Evaluation Of In Vitro Fertilization Potential and Sperm Parameters In ACR Treated Mice	Mice	ACR causes toxicity in the reproductive system, leading to a significant decrease in fertilization rates and a notable increase in the number of arrested embryos. Sperm count, motility, and viability are reduced, and there is an increase in the number of sperm exhibiting DNA damage.
8	Noorah Saleh Al-Sowayan (46)	Effects of ACR and children snack food on sex hormones nucleic acid and chromosomes of mature male Wister rats	Mice	The administration of ACR induced a significant decrease in sperm cell motility percentage and sperm concentration. Additionally, there was a notable increase in the percentage of sperm abnormalities. ACR treatment resulted in a significant reduction in serum testosterone levels, alongside a marked decrease in DNA and RNA content. Furthermore, histological analysis revealed atrophy of the seminiferous tubules and diffuse testicular degeneration, characterized by a single layer of vacuolated spermatocytes.
9	Rajeh, Nisreen Abdullah (47)	Antioxidant effect of Ferula hermonis Boiss on ACR induced testicular toxicity in male rats	Rats	There was a significant reduction in both sperm count and serum testosterone levels.
10	Mazen, Nehad F (48)	Role of coenzyme Q10 in testicular damage induced by ACR in weaned albino rats a histological and immunohistochemical study	Rats	ACR has the potential to adversely affect male reproductive capacity, as evidenced by a reduction in the number of PCNA immunoreactive spermatogonia and spermatocytes. There was also an increase in the number of iNOS immunoreactive cells. Furthermore, male rats exhibited variable degrees of testicular affection.
11	Junqiang Zhang (25)	Exposure to ACR inhibits testosterone production in mice testes and Leydig cells by activating ERK1/2 phosphorylation	Rats	In the medium/high-dose ACR group, there was a decrease in the number of epididymal sperm, testicular Leydig cells, serum testosterone levels, and the expression of testicular steroidogenic genes and enzymes, including cytochrome P450 family 11 subfamily A member 1 (CYP11A1) and cytochrome P450 family 17 subfamily A member 1 (CYP17A1). Additionally, a significant decrease in sperm reserves within the epididymis was observed, along with a reduction in mature sperm and damage to testicular structure.
12	Soichiro Hagio, Naho Tsuji (49)	Effect of sampling time on somatic and germ cell mutations induced by ACR in gpt delta mice	Mice	ACR induces male reproductive toxicity and the induction of mutations, resulting in testis weight loss. Additionally, spermatogonial stem cells exhibit less sensitivity to the mutagenicity.
13	Yu, Xingxing Xie (50)	Gestational exposure to ACR inhibits mouse placental development in vivo	Rats	There were decreased numbers and motility of sperm, along with increased testosterone concentration and sperm head abnormalities, which resulted in reduced mating frequency and fertility rates in males.
14	Ji-Guang Gao (50)	Pubertal exposure to ACR disrupts spermatogenesis by interfering with meiotic progression in male mice	Mice	The testis-to-body index and epididymis weights were significantly reduced, resulting in a decline in the testes index, sperm quality, and an increase in the induction of germ cell apoptosis in the testes. Additionally, exposure to ACR was observed to have adverse effects on H2AX

				phosphorylation expansion patterns, chromosome synapsis, and the number of crossovers.
15	Aimee L. Katen (21)	Chronic ACR exposure in male mice induces DNA damage to spermatozoa; Potential for amelioration by resveratrol	Mice	The DNA damage induced in germ cells indicates that sensitivity to ACR exposure extends to mature spermatozoa, which exhibited significantly elevated levels of DNA damage.
16	Natalie A. Trigg (51)	ACR modulates the mouse epididymal proteome to drive alterations in the sperm small non-coding RNA profile and dysregulate embryo development	Mice	Paternal exposure to environmental stressors induces notable alterations in the profile of small non-coding RNA (sncRNA) in sperm.
17	Aimee Lee Katen (52)	Epididymal CYP2E1 plays a critical role in ACR-induced DNA damage in spermatozoa and paternally mediated embryonic resorptions	Mice	ACR induces dominant lethal mutations and contributes to reproductive toxicity associated with acute exposure to ACR in the epididymis.
18	Zhuoqun Wang (53)	ACR disturbs genomic imprinting during spermatogenesis	Rats	(ACR) can cause chromosomal damage in somatic cells and induce mutagenesis.
19	J X Zhang (54)	Enhanced fat consumption potentiates ACR-induced oxidative stress in epididymis and epididymal sperm and effect spermatogenesis in mice	Mice	The quality of spermatozoa is significantly reduced, accompanied by decreased activity of glutathione peroxidase (GPx) in the cauda epididymides. This has an adverse effect on spermatogenesis.
20	Natalie A Trigg (51)	ACR modulates the mouse epididymal proteome to drive alterations in the sperm small non-coding RNA profile and dysregulate embryo development	Mice	Paternal exposure to environmental stressors results in distinct alterations to the sperm small non-coding RNA (sncRNA) profile.
21	Belinda J Nixon (30)	Chronic exposure to ACR induces DNA damage in male germ cells of mice	Mice	Acute exposure to ACR in males can result in decreased fertility and dominant lethality. ACR treatment did not significantly affect mouse or testis weight, and no gross morphological changes were observed in the testes. However, there was a significant dose-dependent increase in DNA damage in male germ cells.
22	Fernanda Ivanski (14)	Prepubertal ACR exposure causes dose-response decreases in spermatic production and functionality with modulation of genes involved in the spermatogenesis in rats	Rats	ACR exposure affects male adult reproductive physiology. It did not impact the age at puberty, the weight of reproductive organs, or serum hormonal levels. However, ACR reduces spermatogenesis, induces morphological and functional defects in sperm, and alters the transcript expression of sexual hormone receptors.
23	Belinda J Nixon (55)	Mouse spermatocytes express CYP2E1 and respond to ACR exposure	Mice	DNA damage is associated with impaired spermatogenesis and adverse effects on reproductive health, resulting in high levels of DNA damage in spermatocytes.
24	ojdeh Hosseinpoor Kashani M.Sc (56)	The effect of ACR on sperm oxidative stress, total antioxidant levels, tyrosine phosphorylation, and carboxymethyl-lysine expression: A laboratory study	Mice	The motility and viability of spermatozoa were significantly decreased following exposure to ACR.
25	Erkekoglu and Baydar (57)	Risk assessment, formation, and mitigation of dietary ACR : Current status and future prospects	Mice	ACR has been shown to have toxic effects on both neurological and reproductive systems.
26	Pourentezari (58)	Vitamin C attenuates detrimental effects of diabetes mellitus on sperm parameters, chromatin quality and rate of apoptosis in mice Iranian	Mice	Sperm count decreased, and motility was reduced.
27	Zhao (59)	Blueberry anthocyanins extract inhibits ACR -induced diverse toxicity in mice by preventing	Mice	Sperm count and motility were reduced, accompanied by a decrease in the rate of abnormal sperm.

		oxidative stress and cytochrome P450 2E1 activation		
28	Zeinab Omidi (60)	The effect of ACR on mitochondrial membrane potential and glutathione extraction in human spermatozoa: A laboratory study	Mice	. ACR compromises sperm membrane integrity under apoptotic and oxidative stress conditions, negatively affecting mitochondrial function and reducing the activity of antioxidative enzymes in sperm, such as glutathione.
29	Bansal Amrit aur (61)	Cheema Ranjna Sandhey Analysis of sperm and relationship between conventional sperm parameters and hypo-osmotic swelling test/ACR penetration assay - crossbred cattle bulls	Mice	A positive correlation was observed between the ACR penetration assay (APA) and all tested parameters, including membrane integrity, viability, and percent progressive motility.
30	Aimee L (23)	The genetic consequences of paternal ACR exposure and potential for amelioration	Mice	The fertility effects induced by ACR occur predominantly in males, with significantly increased levels of DNA damage observed. Additionally, Cyp2e1 is present within epididymal cells.
31	H. Zenick (62)	Reproductive toxicity associated with ACR treatment in male and female rats	Mice	These disruptions in mating performance interfered with the ejaculatory processes and the subsequent transport of sperm.
32	Mohamed Lebda (63)	Effects of Lipoic Acid on ACR Induced Testicular Damage	Rats	The administration of ACR resulted in a significant elevation in the levels of malondialdehyde in both the testicular and epididymal tissues. Additionally, ACR significantly reduced serum levels of total testosterone and progesterone, while increasing estradiol (E2) levels.
33	Nawal Awad Hasanin (64)	Histological and ultrastructure study of the testes of ACR exposed adult male albino rat and evaluation of the possible protective effect of Vitamin E intake	Rats	ACR is a hazardous and unavoidable gonadal toxin known for its harmful effects on the testis. Studies have revealed that AA induces testicular damage, characterized by decreased diameters of the seminiferous tubules and reduced epithelial height. Notably, these changes were maximally improved in the group treated with vitamin E. The antioxidant and anti-apoptotic effects of vitamin E helped mitigate the testicular damage induced by ACR .
35	Gouda, Sahar G (65)	Curcumin protects against testicular damage and genotoxicity induced by ACR in male albino mice	Mice	ACR resulted in atrophy and exfoliation of the germinal epithelium of the seminiferous tubules, accompanied by thickening of their basement membranes.
36	BO Yilmaz (66)	Evidence of ACR - and glycidamide-induced oxidative stress and apoptosis in Leydig and Sertoli cell	Mice	Oxidative stress likely plays a major role in ACR induced apoptosis of Leydig and Sertoli cells.
37	Yasemin Aydin (67)	ACR and its metabolite glycidamide can affect antioxidant defenses and steroidogenesis in Leydig and Sertoli cells	Mice	Infertility may result from the disruption of spermatogenesis, leading to decreased germ cell production and reduced sperm fertilization ability due to the toxic effects on the male reproductive system. These toxic effects cause inhibition of antioxidant and steroidogenic enzymes in Leydig and Sertoli cells, altering testicular function and thereby disrupting male reproduction.
38	Mirjalili A (68)	Glycyrrhiza glabra and vitamin C can reduce toxic effects of ACR on sperm parameters in rat	Rats	It can reduce the detrimental effects of ACR on sperm parameters
39	Sedat KAÇAR (69)	L-Cysteine Partially Protects Against ACR-Induced Testicular Toxicity	Rats	ACR exerts toxic effects on various organ systems. Following a 10-day intraperitoneal injection period, the animals were euthanized, and their body and testis weights were recorded.
40	Mohamed M. Ahmed (70)	Reproductive Injury in Male Rats from ACR Toxicity and Potential Protection by Earthworm Methanolic Extract	Rats	ACR has neurotoxic, genotoxic, and carcinogenic effects. The ACR monomer causes reproductive toxicity in males, resulting in diminished function by reducing sperm concentration and increasing the sperm deformity index. ACR-induced reproductive toxicity is characterized by increased sperm motility and viability, enhancement of sperm count, decreased oxidative stress, and normalization of the expression of p53 and Ki-67.

Conclusion

The exploration of ACR's effects on male infertility has shed light on its far-reaching impact on reproductive health. This compound, found in various foods and industrial products, has an influence on sperm parameters, testicular cells, and hormonal balance. The mechanisms behind these effects, including oxidative stress, DNA damage, and endocrine disruption, underscore the complexity of ACR's interaction with the male reproductive system.

To tackle this issue, a multi-faceted approach is needed. Making smart dietary choices, tweaking food preparation methods, and implementing regulatory measures are key steps to reduce ACR exposure. While more research is needed to fully grasp the long-term effects of chronic low-dose exposure in humans, the current findings highlight the importance of awareness and proactive measures to safeguard male reproductive health. By staying informed and taking practical steps, individuals can play a role in mitigating potential risks associated with ACR exposure.

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