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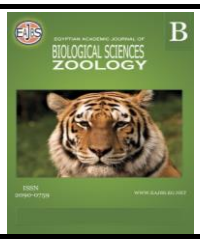

Chromosomal Aberrations Due to Acrylamide Exposure and The Protective Role of L-arginine in Bone Marrow Cells of Male Albino Rats.

Sabha E. Elballat; Ghada A. El Fakahani; and Samir A. Nassar
Zoology Department, Faculty of Science, Zagazig University, Egypt
E.Mail.: alighada621@gmail.com

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ABSTRACT

Acrylamide (Acr) is a human carcinogen which generated in foodstuffs rich with carbohydrates during overheating. It has been recorded to induce carcinogenic and genotoxic effects in experimental animals. So, the present work aimed to evaluate the genotoxic effect of Acr and the possible protective role of L-arginine (amino acid) against Acr genotoxicity using the chromosomal aberration assay in male albino rats (*Rattus norvegicus*). In the current investigation, 20 male albino rats were equally divided into four main groups (n = 5); **Group1 (control):** Animals were received the ordinary water and diet. **Group2 (L- arginine):** Animals were given L- arginine at a dose of 200mg/kg/day for a month by oral gavage. **Group3 (acrylamide):** Animals were given Acr at a dose of 50mg/kg/day for a month by oral gavage. **Group4 (Acrylymide+ L-arginine)**: Animals were given Arc (50mg/kg/day) together with L-arginine (200mg/kg/day) for a month by oral gavage. The results of the present work concluded that Acr is a genotoxic agent, it induced a significant increase in the frequency of total chromosomal aberrations (numerical and structural). L-arginine provides a protective potential against genotoxicity induced by Acr and this was supported by a significant reduction in the frequency of chromosomal aberrations although, the value remained higher and significant as compared with control group.

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INTRODUCTION

Acrylamide (Acr) is a very important industrial chemical compound that is mainly used in the manufacturing of copolymers and polymers. The polymeric form of Acr is used in the oil industry and construction, in the paper industry, textiles, and plastics, in cosmetics and in the treatment of wastewater (Friedman, 2003). it has been recorded that Acr is produced during formation of food under high temperature (above 120ºC) such as baking, roasting, cooking frying or toasting of foods with high carbohydrate content (crisps, potato chips, bread, and coffee), where it is formed by the interaction between the asparagine (amino acid) and the sugars especially, fructose and glucose due to Maillard reaction (Stadler *et al*., 2002; Mottram *et al.*, 2002; Claus *et al*., 2008 and Zamani *et al.*, 2017). The Scientific Committee on Toxicity, Ecotoxicity and the Environment recorded in 2001 that, Acr toxic properties include genotoxicity and neurotoxicity in both germ and somatic cells, reproductive toxicity and carcinogenicity (Keramat *et al.*, 2011). Acrylamide reaches ppm concentrations in potato and French fries, breakfast cereals, baked foods, bread crust, and coffee. Acrylamide exposure from foods is a worry, as it induces cancer in different tissues of rodents like

mammary adenomas, scrotal mesotheliomas, thyroid tumors, it is also a neurotoxicant and mutagenic in human and experimental animals (Bolt, 2003).

L-Arginine is a main natural amino acid that is present in food such as wheat flour, nuts, and seeds. It participates in many metabolic pathways in human body. It acts as an original precursor for the synthesis of not only proteins but also of polyamines, urea, glutamate, proline, agmatine, and creatine (Morris,2006). Moreover, L-arginine is the only precursor in the biosynthesis of nitric oxide (NO), which plays an essential role in various physiological processes in the body including vasorelaxation, neurotransmission, immunity, and cytotoxicity. Nitric oxide is able to decrease oxidative stress by hunt superoxide radicals and stoppage free radical chain reaction in lipid membrane thus reducing the inflammatory factors (Appleton 2002). The endogenous l-arginine is mainly synthesised in the kidneys, where it created from citrulline, which usually released by small intestine (Dhanakoti *et al.*, 1990). Also, the liver is able to synthesize large amounts of L-arginine, however; these amounts are totally reutilised in the cycle of urea so, the liver participates with little amounts or not participates completely to plasma arginine flux (Watford,1991).

According to many experimental and human studies, it was found that the exogenous L-arginine has many useful pharmacological effects when is taken in larger doses than normal dietary consumption. These effects including the decrease of the risk of cardiovascular diseases and immune response improvement (Gad, 2010).

Currently, L-arginine classified among the most common ingredients in food supplements, which are used globally by about one hundred million people (Davidson and Geohas, 2003).Due to the broad exposure of Acr in both environment and food, the aim of the present work was to evaluate Acr genotoxic effect in addition to, the possible protective role of L-arginine against its toxicity using chromosomal aberration assay in bone marrow cells of male albino rats.

MATERIALS AND METHODS

Animals:

In present study, twenty male albino rats (*Rattus norvegicus*) aged about 10-11 weeks and weight 150 ±10g were used. Rats were purchased from the animal house, Faculty of Veterinary Medicine, Zagazig University, Egypt. Animals were given pasteurize milk, bread, and filtered tap water. They were housed in hygienic plastic cages in a clean well-ventilated room.

Chemicals:

Acrylamide is a white crystalline, odorless, solid at room temperature. Its molecular formula is C3H5NO. It was purchased from Sigma-Aldrich Chemical Company (St Louis, MO, USA). Animals were given Acr at a dose of 50mg/kg/day for a month according to (Tyl and Friedman, 2003).

L-arginine was purchased from research-lab fine chem industries (Mumbai, India). Animals were given L-arginine at a dose of 200mg/kg/day for a month according to (Monica, *et al.* ,2011)

Experimental Design:

Twenty rats were equally divided into four main groups (n = 5); **Group1 (control)**: received the ordinary water and diet. **Group2 (L- arginine)**: Animals were given a dose of L-arginine (200mg/kg/day for a month) dissolved completely in filtered tap water for oral gavage. **Group3 (acrylamide):** Animals were given a dose of Acr (50mg/kg/day for a month) dissolved completely in filtered tap water for gavage orally. **Group4(Acrylymide+ L-arginine)**: Animals were given the same acrylamide dose (50mg/kg/day) together with L-arginine (200 mg/kg/day) for a month; dissolved completely in filtered tap water for gavage

orally. The doses of Acr and /or L-arginine were freshly prepared just before use. L-arginine was given to the animals of group 2 & group 4 one week before starting the application of Acr.

Chromosomal Aberration Assay:

At the end of the experiment, metaphase chromosomes were extracted from the bone marrow cells of animals, according to Preston *et al.* (1987).

Statistical Analysis:

The results were analyzed by SPSS software (version 14). Data were expressed as mean ± S.E. Comparison of mean values of studied variables among different groups was done using ANOVA test. P≤0.05 was considered to be significant (Levesque, 2007)

RESULTS

The control animals recorded a frequency of chromosomal aberrations within normal values. Acr administration (50mg/kg/day for a month) to albino rats induced a highly significant increase in the frequency of total chromosomal aberrations which reached (123.2±2.82) compared with (17.4±1.02) in the control group (Table 1, Fig.1).

Table 1: The frequency of chromosomal aberrations in bone marrow cells of male rats treated by acrylamide and/ or L-arginine.

Groups	No. of rats	No. of scored cells 50/rat	Chromosomal aberrations					
			Numerical aberrations		Structural aberrations		Total aberrations	
			sum	Mean± S.E	sum	Mean± S.E	sum	Mean± S.E
Control	5	250	57	11.4±0.92 c	30	6.0±0.54 c	87	17.4±1.02 c
L-arginine	5	250	64	12.6±0.50 c	20	4.2±0.37 c	84	16.8±0.80 c
Acrylamide	5	250	229	45.8±1.88 a	387	77.4±1.36 a	616	123.2±2.85 a
Acrylamide + L-arginine	5	250	133	26.6±0.40 b	137	27.4±0.67 b	270	54±0.63 b

Means within the same column in each category carrying different litters are significant at (p≤0.05) using Duncan's multiple range test, where the highest mean value has a symbol (a) and decreasing in value were assigned alphabetically. Similar letters are non-significant on the statistical level.

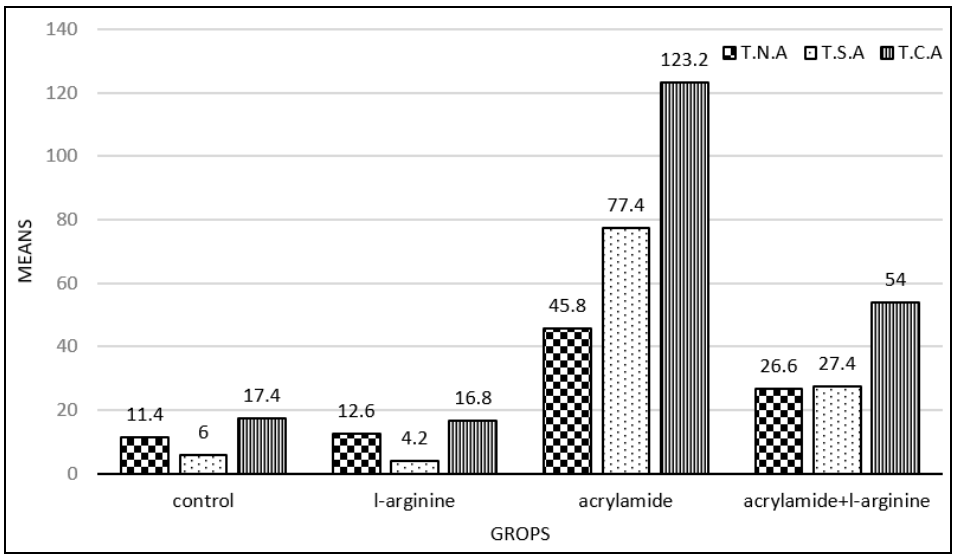

Fig. 1. Comparison between the means of total chromosomal aberrations (numerical and structural) in bone marrow cells of male albino rats after in experimental groups

The total chromosomal aberrations included both structural and numerical aberrations. Total structural aberrations recorded a highly significant increase and reached (77.4±1.36) versus (6.0±0.54) among control group. The most abundant structural aberrations were; acentric fragment (27.2±1.15) , deletion (19.2±1.88) , break (17.4±1.43) , ring (6±0.89) and exchange figures(5.4±0.6) compared with acentric fragment (2±0.31), deletion (1.8±0.3) , break (0.6±0.4) , ring (0.4±0.24) and exchange figures (0.2±0.20) in control group respectively (Table 2, Fig2).

Also, the total numerical aberrations were significantly increased (45.8±1.88) compared with the control group (11.4±0.92). Aneuploidy (hypodiploid) was the most common aberration with frequency reached (45.6±1.91) compared with (8.4±0.74) in control group (Table2, Fig 2).

The application of L-arginine only resulted in a non-significant change in the frequency of both total structural and numerical aberrations as compared to that of control animals (Table1, Fig.1).

The treatment of animals with L-arginine together with Acr decreased the frequency of total chromosomal aberrations and attenuated significantly to (54±0.63) compared with (123.2±2.85) in acrylamide exposed animals but the value was still significant as compared to control ones (17.4±1.02). herein L-arginine significantly reduced total structural (27.4±0.67) and total numerical (26.6±0.40) aberrations compared with acrylamide only (77.4±1.36 and 45.8±1.88 respectively), although the values remained at significant increase as compared with control ones (Table1, Fig.1). Collectively, all forms of structural and numerical aberrations were significantly decreased as compared to that in Acr exposed animals. Moreover; ring and exchange figures were decreased and giving non- significant values. Other forms (deletion, break, acentric fragment, and hypodiploid) were decreased but still higher and significant at the statistical level as compared to control ones.

Table 2: The frequencies of structural and numerical chromosomal aberrations in bone marrow cells of rats administered acrylamide and/ or l-arginine

Groups	NO. Of Rats	NO. of scored cells	Chromosomal aberrations								
			Numerical aberrations			Structural aberrations					
			Aneuploidy		Polyploidy	Dicentric	Break	Deletion	Ring	Exchange figures	Acentric fragment
			Hyperdiploid	Hypodiploid							
Control	5	250	3±0.31^{b}	8.4±0.74^{c}	0±0.00^{a}	1±0.44^{a}	0.6±0.4^{c}	1.8±0.3^{c}	0.4±0.24^{b}	0.2±0.20^{b}	2±0.31^{c}
L-arginine	5	250	0±0.00^{b}	12.6±0.5^{b}	0±0.00^{a}	0.6±0.24^{a}	0.2±0.2^{c}	1.2±0.37^{c}	0.6±0.4^{b}	0.2±0.20^{b}	1.2±0.37^{c}
Acrylamide	5	250	0±0.00^{b}	45.6±1.91^{a}	0.2±0.2^{a}	2±0.83^{a}	17.4±1.43^{a}	19.2±1.88^{a}	6±0.89^{a}	5.4±0.6^{a}	27.2±1.15^{a}
Acry+ l-arginine	5	250	0±0.00^{b}	25.8±0.66^{b}	0.8±0.48^{a}	0.4±0.24^{a}	3.6±0.50^{b}	9.6±0.50^{b}	1.8±0.37^{b}	0.8±0.48^{b}	11.20±0.73^{b}

Means within the same column in each category carrying different litters are significant at ($p \leq 0.05$) using Duncan's multiple range test, where the highest mean value has a symbol(a) and decreasing in value were assigned alphabetically. Similar letters are non-significant on the statistical level.

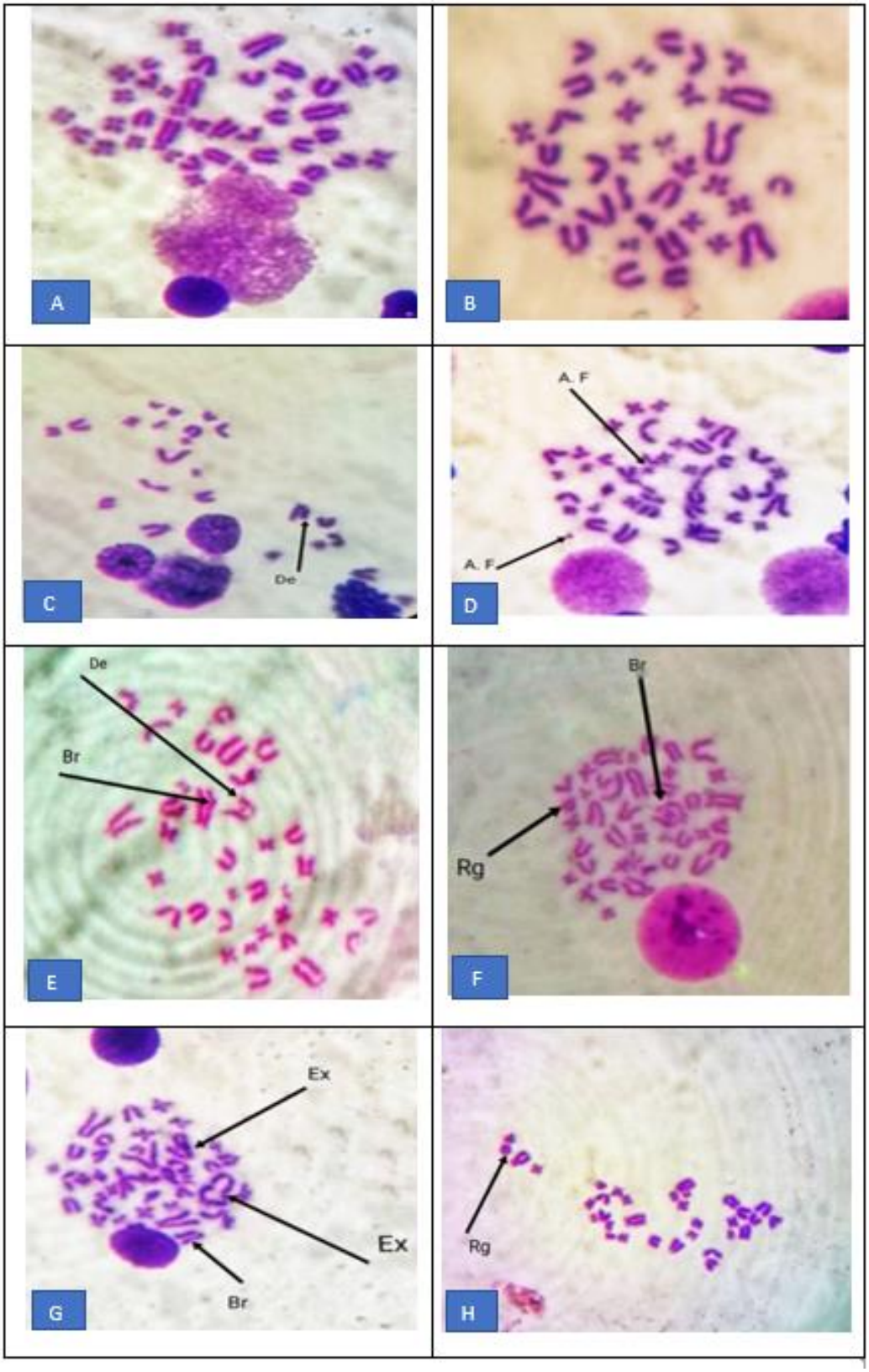

Fig. 2. Several metaphases from bone marrow cells of male albino rat after Acr administration showing**: (A)** A normal metaphase (n=42) , **(B)** Numerical chromosomal aberrations: Aneuploidy (Hypodiploid), **(C,D,E,F,G,H)** Structural chromosomal aberrations; mDe(Deletion),Br(Break), Rg(Ring), Ex(Exchange) and A.F.(Acentric Fragment).

DISCUSSION

The use of L-arginine as antioxidant in Acr exposure studies was proved to be valuable. present work aimed to evaluate the genotoxicity of Acr (50mg/kg/day for a month) in addition to the possible improvement role of L-arginine (200mg/kg/day for a month) against Acr genotoxicity in the bone marrow cells of male albino rats, using the chromosomal aberration assay.

In the current investigation, Acr showed a genotoxic effect on bone marrow cells of male albino rats, this was evident by a significant increase in the frequency of total chromosomal aberrations (numerical and structural).

The present results extend and confirm those Alzahrani, (2011), Ismail, (2016) and Algarni, (2018) who reported that Acr has a strong genotoxic/clastogenic potential. It increased the frequencies of micronuclei and chromosomal aberrations (both structural and numerical) in bone marrow cells of mice in the dose-dependent manner. Also, Oliveira *et al*. (2009) who reported that Acr was able to induce chromosomal aberrations, in Chinese hamster V79 cells *in vitro* and *in vivo* in bone marrow cell of mice.

The genotoxicity of Acr may be attributed to its biotransformation to a highly reactive glycidamide which directly reacts with DNA molecule forming DNA-glycidamide adducts. Acrylamide and/or glycidamide able to induce in the formation of free radicals which cause oxidative stress on the cellular DNA leading to chromosomal aberrations (numerical and structural).

This explanation was confirmed by El-Mottaleb and Rashed, (2008**)** who concluded that Acr hydrolyzed into glycidamide, is the highest metabolite of Acr, considered to be the main cause of genotoxicity since glycidamide is more reactive toward proteins and DNA than acrylamide. In addition, Watzek *et al.*, (2013) said that, after dietary uptake, Acr is metabolically converted to the genotoxic glycidamide which reacts with positions of nucleophilic bases in DNA, producing N7-(2-carbamoyl-2-hydroxyethyl) guanine (N7-GA-Gua) adducts. Moreover, Adler *et al.* (2000) recorded that, acrylamide is mainly metabolized by the cytochrome P450 into glycidamide (epoxide) which was a strong DNA- reactive clastogen in mice spermatids.

Acrylamide strongly induced the formation of reactive oxygen species (ROS), affecting the redox chain in the cell. It is mainly oxidized to very reactive glycidamide., both Acr and its metabolite (glycidamide) able to react with nucleophiles group (like as –NH2, –SH or –OH) in cells (Zamani *et al.,* 2017). Chronic exposure of humans to dietary Acr produced oxidative stress. It induced in significant increase in GSH oxidation and ROS formation in human monocyte (Naruszewicz *et al.,* 2009).

The present results recorded that Acr is a genotoxic agent induces significant increase in the frequencies of chromosomal aberrations (acentric fragment, deletion, break, ring, exchange figures and hypodiploid) which closely related to cancer risk.

These results are in agreement with Casado *et al.* (2010) and Kalita *et al*. (2013) who confirmed that Acr and its metabolite glycidamide can form adducts with hemoglobin, DNA, and many vital groups of proteins as SH, inducing gene mutations and chromosomal aberrations, increasing malignant and benign neoplasms in rodents. Acrylamide induced marked DNA alterations in liver cells and lymphocytes, in addition to formation of micronuclei in bone marrow cells (Mucci *et al*. (2003); Hogervorst *et al.* (2007); Zhao *et al.* (2015) and Zhivagui *et al.***,** 2019).

The current study recorded non-significant changes in the frequency of both total structural and numerical aberrations hence, the total chromosomal aberrations in L-arginine group when compared with control group. In addition, we have also evaluated the ability of L-arginine to improve Acr -induced genotoxicity (chromosomal aberrations). Where, the animals that given Acr (50mg/kg/day) together with L-arginine (200mg/kg/day) for a month orally by gavage (i.e Acrylymide+ L-arginine group) showed a significant reduction in the frequency of total chromosomal aberrations compared with acrylamide-exposed animals. In this group, L-arginine significantly attenuated the percentage of total structural and numerical aberrations compared with acrylamide-exposed animals. Where all forms of aberrations significantly decreased compared with that scored in Acr. Moreover, ring and exchange figures decreased and became non- significant; other forms of aberrations (deletion, break, acentric fragment, and hypodiploid) also decreased but still higher and significant compared with control group.

The reduction in frequency of total chromosomal aberration in Acr+ L-arginine group might be a result of action of L-arginine as a natural donor of nitric oxide which acts as antioxidant inhibits the free radicals generated by Acr that consider the main inducer for chromosomal damage.

Our results support and confirm other previous studies Morris (2006) and Lin *et al*. (2006) who identified L-arginine as a semi-essential amino acid that is found in natural foods as seeds, wheat flour, and peanuts. It acts as a precursor for nitric oxide (NO) synthesis by NO synthase and many biologically important compounds that support cellular homeostasis. Nitric oxide was able to decrease oxidative stress by hunt superoxide radicals and stoppage free radical release in lipid membrane thus, reducing the inflammatory factors

Also, L-arginine has the ability to reduce the activity of xanthine oxidase in different tissues, such as skeletal muscle, heart, lung, and liver (Huang *et al.*, 2008). L-arginine has anti-atherogenic effect and decreases oxidative stress in experimental animals (Boger *et al.*, 1998). The carbonyl content in plasma proteins is reduced by L-arginine and thus reducing per-oxidation of protein that induced by oxidative stress. (Tripathi *et al.* ,2010).

Conclusion

According to the results of the present investigation, it is necessary to mention that, Acr is a genotoxic agent inducing a significant increase in the frequency of both numerical and structural chromosomal aberrations (total aberrations) in bone marrow cells of rats. However, L-arginine able to attenuate the genotoxicity of Acr by reducing the frequency of chromosomal aberrations although the value still higher and significant compared to control. It could be concluded that dietary intake of L- arginine together with applying some percussions like as heating time, temperature, moisture and pH can help to avoid or at least to reduce Acr production in food hence, its toxicity.

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ARABIC SUMMARY

زيادة نسبة التشوه الكروموسومى بواسطة الاكريلاميد والدور الوقائى المحتمل لـ إل-أرجينين في خلايا النخاع العظمى لدى ذكور الفئران البيضاء.

سمير عبد العظيم نصار؛ صابحه السيد البلاط؛ غادة على الفكهانى
قسم علم الحيوان-كلية العلوم- جامعه الزقازيق-جمهورية مصر العربيه

الأكريلاميد هو مادة مسرطنة للإنسان تتكون في المواد الغذائية الغنية بالكربوهيدرات أثناء الطهى باستخدام درجات الحراره العاليه وقد تم تسجيله كعامل مسبب للسميه الوراثية والسرطان في الحيوانات التجريبية. لذا ، يهدف هذا البحث إلى معرفة الاثار السميه الوراثيه للأكريلاميد بالاضافه الى الدور الوقائى المحتمل لـ إل-أرجينين داخل الجسم الحى باستخدام تجربة التشوه الكروموسومي في خلايا نخاع عظم الجرذ الأبيض .حيث ، أجريت هذه التجربه على عشرون جرذاً أبيضاً (ذكور- بالغة) قسمت هذه الجرذان عشوائيا الى أربع مجموعات رئيسية وهى : المجموعة الضابطة ، المجموعة المعالجه إل-أرجينين (٢٠٠مليجرام/كجم من وزن الجسم/يوم ،يوميا لمدة شهر، بالتزجيج الفموي) ، المجموعة المعالجه بالاكريلاميد(٥٠مليجرام/كجم من وزن الجسم/يوم ،يوميا لمدة شهر، بالتزجيج الفموي) واخيرا المجموعة المعالجه بالاكريلاميد مع إل-أرجينين باستخدام نفس الجرعات السابق ذكرها . خلصت نتائج العمل الحالى إلى أن الاكريلاميد هو عامل سام للجينات ، وقد تسبب في زيادة كبيرة في وتيرة الانحرافات الصبغية الكلية (العددية والهيكلية) كما ثبت ان إل-أرجينين قادر على تحسين السمية الوراثية التي يسببها الاكريلاميد وهذا كان مدعومًا بتخفيض كبير في تواتر الانحرافات الكروموسومية رغم أن القيمة ظلت مرتفعه ومؤثره مقارنة مع مجموعة التحكم.