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GENOTOXICITY OF BISPYRIBAC SODIUM IN ALBINO RATS

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ABSTRACT

Genotoxicity of pesticides constitute great concern that affect population health, commercial formulation of such pesticides may increase the genotoxicity of certain pesticides, the genotoxic effect of bispyribac sodium had been studied in albino rats given orally ***65.88, 32.94 and 16.47 mg/kg of bispyribac sodium*** *twice per week for 3 months and the results indicated that significant increase in chromosomal aberration (break, fragment, gap, ring and chromosomal association) in respect to control which was dose dependent also significant increase in DNA quantity, also there was significant increase in micronuclei level in respect to control and decrease in mitotic activity in bone marrow cell where the mitotic index had decreased drastically in response to control value and these results confirm that bispyribac sodium may have genotoxic effect affect in albino rats.*

Key words: *genotoxicity, Micronuclei, mitotic index, clastogenic, DNA quantity.*

INTRODUCTION

Pesticides considered as reactive compounds forming covalent bonds with cellular macromolecules, including DNA and so cancer induction and other chronic diseases through occupational exposure micronuclei (MN) and chromosomal aberrations (CAs) considered early signals of development of neoplasm **(Prasad et al.,2009).**

Micronuclei are round small cytoplasmic bodies contain DNA that formed during the cell division by the loss of single chromatid fragment or whole chromosome. CAs used in detection of clastogenic activity, on the other hand MN assay used in detection of clastogenic effects and mitotic apparatus damage **(Hagmar et al.,1998).**

Herbicides considered as group of pesticides, used extensively in agriculture, the means of their application assurance presence of such chemicals in environment with potential genetic risk in human **(Sivikova and Dianovsky, 1999).**

Bispyribac sodium (sodium 2, 6-bis [(4, 6-dimethoxy-2-pyrimidinyl) oxy] benzoate) considered as a pyrimidinyl thiobenzoate herbicide **(Reimche et al., 2015).**

Bispyribac sodium showed no significant increase in micronuclei in bone marrow polychromatic erythrocytes under genotoxicity micronucleus assay study carried out in mice at

dose level at 5000 mg/kg **(California Environmental Protection Agency, 2001).**

Bispyribac sodium cytotoxicity wasn't high but aberration frequencies and percent of cells with aberrations were increased at dose level 4000µg/ ml but also such value wasn't statistically significant in chromosomal aberration study in Chinese hamster cells **(California Environmental Protection Agency, 2001).** Mutagenicity- Rec-Assay with *Bacillus subtilis* showed positive results with inhibition of the DNA repair deficient strain (M45) **(Health Canada Pest Management Regulatory Agency, 2008).**

Exposure to different concentration of bispyribac sodium on the Chinese hamster ovary cells with and without metabolic activation at dose 4990 ug/ml caused complete cytotoxicity to the culture, when applying the chromosomal aberration assay at dose level ranged from 500 to 5000 ug/ml no significant increase in cells with chromosomal aberration observed **(Hemalatha Murli, 1990).**

Bispyribac sodium showed no significant increase in micronuclei level in mice dosed 1250, 2500, and 5000 mg/kg orally in micronuclei assay **(Hemalatha Murli, 1991).**

The aim of this study was to evaluate the genotoxic effect of bispyribac sodium herbicide in female albino rats after exposed to bispyribac sodium containing different dose level 1/40, 1/80 and 1/160 of the LD_{50} **equivalent to 65.88, 32.94 and 16.47 mg/kg** bw_t respectively orally twice per week for 3 months and chromosomal aberration, micronuclei had been evaluated in addition to mitotic index and DNA quantity also estimated.

MATERIAL AND METHODS

a) Material:-

1) Chemicals:

Colchicine $C_{22}H_{25}NO_6$

Commercial formalin 40%, Ethyl alcohol 99 %, Methyl alcohol 95% Glacial Acetic Acid CH_3COOH, Tri-chloro Acetic acid, Diphenyl amine, Sodium dibasic phosphate, Thiopental sodium, Giemsa stock solution, Sulfuric acid.

- Diphenylamine reagent: **(Karp, 2013).**
- Diphenylamine 1.0 gm
- Sulphuric acid 2.75 cc
- Glacial acetic acid 100ml

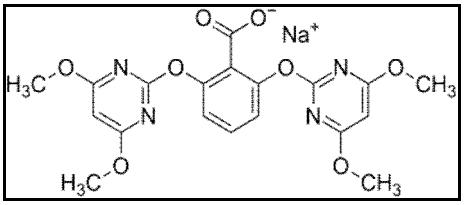
2) Tested Pesticide:-

Nominee SL 2% (Bispyribac sodium):

Bispyribac sodium (sodium 2, 6-bis [(4, 6-dimethoxy-2-pyrimidinyl) oxy] benzoate) considered as a pyrimidinyl thiobenzoate herbicide, First was developed by Japan Kumiai Chemical and belongs to the group pyrimidinyl oxybenzoic acid, The oral LD_{50} in rats was measured to be 4111 mg/kg body weight in male while 2635 mg/kg body weight in female while tissue distribution in male larger than female due to superiority in excretion in female besides repeated administration not affect absorption nor metabolism and excretion (Gawarammana et al., 2010).

Nominee SL 2% (Bispyribac sodium), was kindly obtained from Kafr El Zyat pesticides and chemical company, Egypt

Structural formula:-



b) Methods:-

Experimental animals and grouping:-

Female albino rats were obtained from Experimental Unit, Faculty of Pharmacy, Mansoura University; weighted from 95 to 115 gm. Animals were housed in plastic cages contain wood shaving as a bedding. Animals accommodated for 2 weeks before starting the experiment and maintained on a balanced ration, feed and water ad libitium throughout the experiment. Rats were divided into four groups each one contains eight rats weighted 115±5 gm ; First three groups intubated with bispyribac sodium orally at dose level 1/40, 1/80 and 1/160 of the LD_{50} and fourth group intubated with distilled water as control. Animals were weighted twice per week during the experimental study.

1- Chromosomal aberration detection:

Chromosomal aberration were carried out according to **(Al-Joubori et al., 2014),** Rats intraperitoneally injected with colchicine (0.5 mg/kg body weight) 3hours before sacrificing, femur were removed immediately and bone marrow received in centrifuge tube by injection of 5 ml KCl (0.57%) hypotonic solution then incubated for 20 minutes at 37ºC followed by centrifugation for 2 minutes at 2000 rpm.and Supernatant discarded and 5ml of cold fixative solution (methanol and glacial acetic acid with ratio 3:1) added to precipitate and left at room temperature for 5 minutes followed by centrifugation for 2 minutes at 2000 rpm and such technique repeated twice, then from the 75 cm by using Pasteur pipette suspension dropped on a clean, moisten and cold slide followed by air drying and staining with giemsa stain solution 5% and at least investigation of one thousand metaphase cells per each group examined for chromosomal aberration.

2-DNA preparation, extraction and determination:

DNA was determined by the diphenylamine Procedure calorimetrically according to **(Karp, 2013),** after the animals sacrificed the liver removed, washed with saline solution and weighting one gm of liver tissue was homogenized with 4 ml cold distilled water, then 2ml of liver homogenate suspended in 5ml of 10% solution of trichloroacetic acid then centrifugation at 3000 rpm for 2 minutes followed by discarding the supernatant and repeating the same technique, Followed by resuspending the pellet in 10 ml ethyl alcohol 95% followed by centrifugation at 3000 rpm and discarding the supernatant to obtain the purified pellet and such technique repeated with the same way, purified pellet resuspended again in 5ml of trichloroacetic acid TCA 5% and put in boiling water bath at 90°C for 15 minutes then centrifuged and two ml of supernatant put in centrifuge tube with 4 ml of diphenylamine reagent (1g of diphenylamine + 100 ml of the glacial acetic acid + 2.57 ml conc. sulphuric acid), tubes were put in boiling water bath for 10 minutes then cooled quickly and observe the change in color, Finally solution then transferred to cuvette and measured with spectrophotometer at 600 nm weave length.

3- Mitotic index detection:

Mitotic index detected according to **(Sehgal et al., 2006),** Where approximately 3000 cells for each group analyzed for the mitotic index (MI), calculated as the number of divided cells at metaphase per total number cells according to following formula:-

MI%= number of the divided cells X 100 / total number of the calculated cells.

4- Micronuclei detection:

Micronuclei assay detected according to **(Gebel et al., 1997)**, Bone marrow cells from the femur flushed by 5 ml saline solution by using syringe in a centrifuge tube and centrifuged at 4 °C for 15 min, supernatant discarded, and the pellet was resuspended in 100 µl then one drop applied to a glass slide followed by air drying then fixed in methanol solution 95% for 2 minutes and stained with giemsa stain 5% stock solution, At least 1000 examined for each group and number of micronuclei detected from the total number of cells. The chi-square test used to determine the significance and the total chi-square.

RESULTS

1. Chromosomal aberration:-

Chromosomal aberration were dose dependent with significant increase in all doses 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) specially higher doses represented by structural abnormalities as chromosomal break, fragments, gap, association and a centromeric chromosomes beside numerical abnormalities as polyploidy and hypoploidy where the results illustrated in figure (1) and table (1).

2. DNA concentration:-

Two doses of Bispyribac sodium (1/40 and 1/80 of LD_{50}) showed significance increase in quantity of DNA after 3 months of administration compared to control group as illustrated in table (2) and fig (2).

3. Mitotic index:-

The result according to chi square analysis showed that significant difference in mitotic index between treated and control groups were there is a dose dependent significant decrease in mitotic index in rats exposed to (1/40,1/80 and 1/160 of the LD_{50}) of bispyribac sodium equivalent to (**65.88, 32.94 and 16.47 mg/kg**) in comparison with the control group .

4. Micronuclei assay:-

The result according to chi square analysis showed that significant difference in micronuclei count between all treated and control groups while there was no significance change between control and group 1/160 of LD_{50} but there was a highly significant increase in micronuclei in groups 1/80 and 1/40 of the LD_{50} and control group and results illustrated by table (5), (6) and fig. (3).

Table (1) Chromosomal aberration in bone marrow of rats administered orally 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) of bispyribac sodium twice per week for 3 months (mean± SE):-

Group	Dose (mg/kg BW)	Toal	Break	Fragment	gap	Ring	Chromosomal association	Acentromeric chromosome	Hypoploidy	Polyploidy
Control	**D.W.**	2.75 ± 0.36^{d}	1.125 ± 0.22^{c}	1.25 ± 0.25^{b}	$0.38\pm0.0.18^{c}$	0^{b}	0^{c}	0^{c}	0^{b}	0^{c}
1/160	**16.47**	9.12 ± 0.63^{c}	2 ± 0.26^{b}	2.13 ± 0.44^{a}	1.38 ± 0.18^{b}	1.38 ± 0.18^{a}	0.63 ± 0.18^{b}	0.5 ± 0.18^{b}	0.75 ± 0.16^{a}	0.38 ± 0.18^{c}
1/80	**32.94**	13.75 ± 0.52^{b}	3 ± 0.32^{a}	2.5 ± 0.18^{a}	3 ± 0.32^{a}	1.88 ± 0.22^{a}	0.88 ± 0.13^{ab}	0.88 ± 0.13^{a}	0.75 ± 0.16^{a}	1 ± 0.18^{b}
1/40	**65.88**	16.62 ± 0.73^{a}	3.75 ± 0.25^{a}	2.87 ± 0.22^{a}	3.5 ± 0.18^{a}	1.5 ± 0.18^{a}	1.25 ± 0.25^{a}	1.13 ± 0.13^{a}	1.125 ± 0.13^{a}	1.75 ± 0.25^{a}

Means in the same column having the same superscribts not significantly different ($p\leq0.05$)

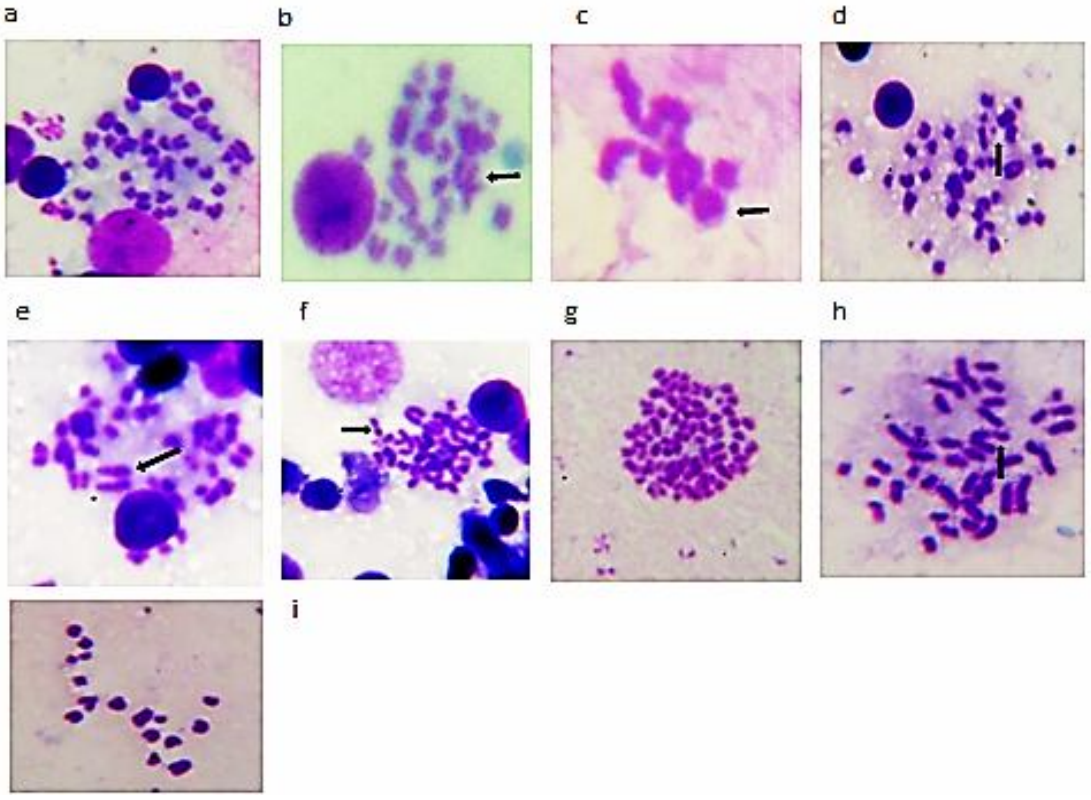


Fig (1) Bone marrow cell of rats in metaphase spread showing **a)** normal chromosomes in metaphase **b)** chromosomal association **c)** Ring **d)** fragment **e)**Acentromeric Chromosome **f)** gap **g)** polyploidy **h)** break **i)** hypoploidy at dose level 1/ 40 of LD_{50} (**65.88** mg/kg B.W.) of bispyribac sodium administered orally twice per week for 3 months.

Table (2): showing DNA concentration in liver tissue of rats orally administered Bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) twice per week for 3 months.

Bispyribac	Dose (Mg/Kg BW)	DNA quantity absorbance rate
Control	D.W.	0.134 ± 0.004^{c}
1/160 of LD_{50}	16.47	0.158 ± 0.018^{bc}
1/80 of LD_{50}	32.94	0.188 ± 0.012^{ab}
1/40 of LD_{50}	65.88	0.206 ± 0.017^{a}

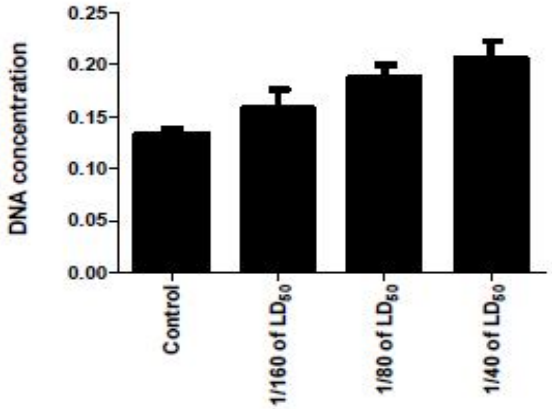


Fig (2) DNA in liver tissue of rats orally administered Bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) twice per week for 3 months.

Table (3): show Mitotic index and Total Chi-square in rats' bone marrow orally administered Bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) twice per week for 3 months.

Group	Dose mg/kg B.W.	Total no.of counted cells	No of divided cells	No. of non-divided cells	M.I.
control	**D.W.**	3000	127	2873	4.23
1/160	**16.47**	3000	103	2897	3.43
1/80	**32.94**	3000	95	2905	3.16
1/40	**65.88**	3000	83	2917	2.76
Total chi-square = 10.51*			Degree of freedom= 3		Probability= 0.015

* value means that there was significant difference between the control and the treated groups at the dose level of ($p< 0.05$).

Table (4): show chi square analysis between groups in rats orally administered Bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) twice per week for 3 months.

Group	**Control**	**G1/160**	**G1/80**	**G1/40**
Control				
G1/160	2.39*			
G1/80	4.49*	0.26		
G1/40	9.12*	2.00	0.70	

* value means that there was significant difference between the control and the treated groups at the dose level of ($p< 0.05$).

Table (5): Show Micronuclei assay in rats' bone marrow and Total chi square orally administered Bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) twice per week for 3 months.

Group	**Total No. of examined cells**	**No. of micronuclei**	**No. of normal cells**
Control	2000	198	1802
Group 1/160	2000	231	1769
Group 1/80	2000	278	1722
Group 1/40	2000	309	1691
Total chi-square= 32.77*	Degree of freedom= 3	probability= 000	

*value means that there was significant difference between the control and the treated groups at the dose level of ($p< 0.05$).

Table (6): show chi square analysis between groups of the Micronuclei assay in rats' bone marrow orally administered Bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg B.W. (1/40, 1/80 and 1/160 of the LD_{50} respectively) twice per week for 3 months.

	Control	**G1/160**	**G1/80**	**G1/40**
Control				
G1/160	2.67			
G1/80	14.88**	4.76*		
G1/40	27.32**	12.69**	1.80	

* value means that there was significant difference between the control and the treated groups at the dose level of ($p< 0.05$).

** Value means that there was a highly significant difference between the control and the treated groups at the dose level of ($p< 0.001$).

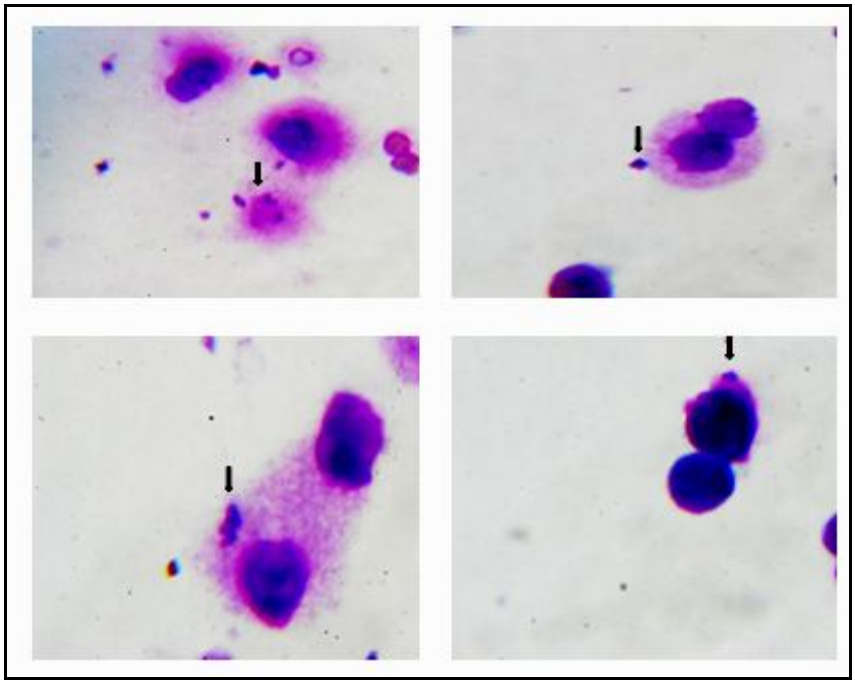


Fig (3) showed micronuclei in rats bone marrow cells exposed to bispyribac sodium at dose level 65.88, 32.94 and 16.47 mg/kg orally twice per week for 3 months.

DISCUSSION

Chromosomal aberration were dose dependent with significant increase in all doses (1/160 ,1/80 and 1/40 of the LD_{50}) specially higher doses represented by structural abnormalities as chromosomal break , fragments, gap , association and a centromeric chromosomes beside numerical abnormalities as polyploidy and hypoploidy which disagree with **Hemalatha Murli, (1990)** who studied the genotoxic effect of technical bispyribac sodium on the Chinese hamster ovary cells with and without metabolic activation at different concentration reach to 4990 ug/ml when applying the chromosomal aberration assay at dose level ranged from 500 to 5000 ug/ml no significant increase in cells with chromosomal aberration observed ; on the other hand **California Environmental Protection Agency, (2001)** stated that on a cytogenetic chromosomal aberration study in Chinese hamster ovary cells cytotoxicity wasn't high but aberration frequencies and percent of cells with aberrations were increased at dose level 4000µg/ ml but also such value wasn't statistically significant ; also **Health Canada Pest Management Regulatory Agency, (2008)** reported that Mutagenicity- Rec-Assay with *Bacillus subtilis* show positive results with inhibition of the DNA repair deficient strain (M45).

Two doses of Bispyribac sodium (1/40 and1/80 of LD50) equivalent to **65.88 and 32.94 mg/kg** showed significance increase in quantity of DNA after 3 months of administration compared to control group where active protein synthesis and Cellular enlargement are reliant on DNA and RNA content but Pesticides cause deoxyribonucleic acid damage and structural chromosomal

abnormalities as stated by **Vrhovae and Zeljezic, (2000)** so Pesticides may directly attack DNA producing primary lesions as breaks, DNA protein crosslink and eventually loss of cell structure also proliferation with a total control loss of cellular mechanism may occur leads to increase quantity of DNA synthesis and mutagenicity **Gowri et al., (2013)** such results agree with **Kishiyama and Gee (1991)** who assayed where dimethoate at concentrations of of 7.63, 22.9, 76.33, 229, and 763.33 ug/ml induce increasement of unscheduled DNA synthesis in hepatocytes of male rats in vitro that indicate precarcinogenic effect where according to **Serafini, (2010)** Bispyribac Na causes some toxicity in the liver and bile duct with microscopic and macroscopic changes in dogs , mice and rats and cause liver granulation and intrahepatic bile duct hyperplasia of female rats at dose level 100 mg/kg/day and such hyperplasia and granulation may promote carcinogenicity and uncontrolled DNA synthesis and damage .

There was significant difference in mitotic index between treated and control groups were there is a dose dependent significant decrease in mitotic index in rats exposed to (1/160 ,1/80 and 1/40 of the LD50) of bispyribac sodium equivalent to (**65.88 , 32.94 and 16.47 mg/kg**) in comparison with the control group ;according to **(Serafini, 2010)** bispyribac sodium act by inhibiting the enzyme acetolactate synthase (ALS) that is essential in the biosynthesis of branched chain amino acids as valine ,leucine and isoleucine , that subsequently interferes with cell division causing cessation of plant growth, as a result leads to necrosis, chlorosis, and death of sensitive plants and also accoding to **(Gawarammana et al.,2010)** where acetoacetate synthase inhibited by bispyribac may inhibit branched chain amino acids bio synthesis as leucine in human and animals so it may decrease the mitotic activity of cells .

There was significant difference in micronuclei count between all treated and control groups while there was no significance change between control and group 1/160 of LD_{50} but there was a highly significant increase in micronuclei in groups 1/80 and 1/40 of the LD50 and control group, micronuclei considered as cytoplasmic extra nuclear bodies formed of chromatin when whole or chromosomal fragment not incorporated during mitosis in daughter nuclei so used as indication of genotoxicity **(Kassie et al., 2001);** such results disagree with **California Environmental Protection Agency, (2001)** which reported that micronucleus assay study carried out in mice at dose level at 5000 mg/kg and animals were euthanized 24,48 and 72 hrs after dosing followed by extraction of bone marrow and micronuclei were assessed in slides in1000 polychromatic erythrocytes founded that no significant increase in micronuclei in bone marrow polychromatic erythrocytes under such condition ; also disagree with **(Hemeleche Murli ,1991)** who found that the ability of technical bispyribac sodium to induce micronuclei in vivo in the bone marrow polychromatic erythrocytes of mice at dose level 1250, 2500, and 5000 mg/kg orally and euthanized 24 hours after dosing there was no significant increase in micronuclei level under such condition.

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الملخص العربي

السميه الوراثيه للبيسبيريباك صوديوم في الفئران البيضاء

فتحي رضوان على سليم و محمود محمد الألفي الحفناوى ومحمد سمير عبد الستار أبومسلم

قسم الطب الشرعي والسموم - كليه الطب البيطري- جامعه المنصوره

السميه الوراثيه للمبيدات تشكل مصدر قلق كبير لأنها تؤثر على صحه المجتمع. تمت دراسه التأثير السمي الوراثي للبيسبيريباك صوديوم " نوميني" في الفئران البيضاء عن طريق تجريع الفئران عن طريق الفم ٥٦,٨٨ ، ٣٢,٩٤ و ١٦,٤٧ مجم / كجم من وزن الجسم مرتين في الأسبوع ولمده ثلاثه أشهر ووجد زياده معنويه في التشوهات الكروموسوميه مقانه بالمجموعه الظابطه وقد كانت معتمده على الجرعه. وكذلك كان هناك زياده معنويه في كميه الديوكسي ريبونيوكليك اسيد والتى تعد كإشاره لما قبل حدوث السرطان وكذلك زياده معنويه في النويات الصغرى مقارنه بالمجموعه الضابطه والتى تعتبر كإشاره لتكسير المحتوى الجيني وكان هناك ايضا خلل في النشاط الإنقسامي والذي وجد أنه يقل في خلايا نخاع العظام حيث أن مؤشر الإنقساميه نقص بحده مقارنه بالمجموعه الضابطه وهذه النتائج تؤكدعلى السميه العامه وكذلك السميه الوراثيه للبيسبيريباك صوديوم