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ARABIC SUMMARY

List of Abbreviations

ANOVA	:	Analysis of variance
BPA	:	Bisphenol – A
GP_R	:	Glutathione reductase
GP_x	:	Glutathione peroxidase
GSH	:	Reduced glutathione
GSSG	:	Oxidized glutathione
HPLC	:	High performance liquid chromatography
IU	:	International unit (s)
M	:	Mole (s), (Molarity)
mmol/L	:	Millimole per litre
ng/ml	:	Nonogram per milliliter
nm	:	Nanometer
nmol/gm	:	Nanomole per gram
PCB	:	Polychlorinated biphenyl
Pg/ml	:	Pigogram per milliliter
r.p.m.	:	Revolution per minute
SE	:	Standard Error
SHBG	:	Sex hormone binding globulin
TCDD	:	Tetrachloro-dibenzo-p-dioxin .
TCDF	:	Tetrachloro- dibenzo-furans .
TE	:	Toxic Equivalent Factor
TG	:	Total glutathione
TQ	:	Toxic Equivalency
μmol/gm	:	Micromole/gram
γ-HCH	:	Gamma-hexachlorocyclohexane
30/30	:	30 days pregnancy / 30 days of treatment started at zero day of pregnancy
30/45± 3	:	30 days pregnancy / 45±3 days of treatment started 15±3 days before mating
Fult term pregnancy / 63± 3	:	Pregnancy from zero day till labor / 63 - 3 days of treatment, started at zero day of pregnancy till labor

Summary

In the past, the primary focus of researches regarding the effect of man-made chemicals has been on their capacity to act as mutagen or to induce gross abnormalities after administering such chemicals to laboratory animal's indices, which were typically much higher than those found in food, water or air without regarding the real endocrine disruptive effects of these chemicals.

Recently, a number of man-made chemicals that have the ability to mimic endogenous hormones and disrupt the endocrine system had been discovered after a long time from their release in the environment. Therefore, this work was conducted to investigate the biochemical and cytotoxic effect of two of these xenobiotics: γ -HCH (γ -hexachlorocyclohexane) and Bisphenol-A.

The effect of oral administration of γ -HCH (1mg/kg b.w/day) and Bisphenol-A (10 μ g/kg.b.w) in male and pregnant female guinea, pigs were studied by verifying the following parameters:-

- 1) - Determination of blood glucose, pyruvate and lactate Concentrations.
- 2) - Determination of cortisol and follicular stimulating hormone (FSH) in both sexes, testosterone in male and estrogen in Female guinea pigs.
- 3) - Determination of malonaldehyde (MDA) in hepatic tissues.
- 4) - Determination of the activities of both glutathione peroxidase

and glutathione reductase beside the determination of total reductase and oxidizing glutathione in hepatic tissues of guinea Pigs.

5)-Studying the chromosomal abnormalities in both parents and offspring.

Male guinea pigs were subjected to the treatment with either γ -HCH or Bisphenol-A for 7, 14, 21 and 28 days, while pregnant female guinea pigs were subjected to the same treatment for 30, 45 ± 3 and 63 ± 3 days as females treated for 30 and 63 ± 3 days has been received their treatment from the onset of pregnancy till the 30th day and 63 ± 3 days of pregnancy (full term pregnancy) respectively. Meanwhile, those female treated for 45 ± 3 days, has been received their treatment at 15 ± 3 days before the zero day of pregnancy and proceeded until the 30th day.

All animals were injected intramuscularly with colchicines (0.5%) in a dose of 0.25ml/100kg. b. w. at 90 minutes before scarification to obtain cells at the metaphase stage of mitotic division needed for the study of chromosomal abnormalities.

After collection and preparation of samples (serum, plasma, liver and femurs from adult animals and intestine from offspring), the specified biochemical parameters were examined where blood, glucose, pyruvate and lactate concentrations as well as malonaldehyde and glutathione status and glutathione concerned enzymes in hepatic tissues were determined

spectrophotometrically. Cortisol concentration was determined using high performance liquid chromatography while follicle stimulating hormone, testosterone and estrogen were determined using ELISA diagnostic kits. Chromosomal abnormalities were studied by examining the metaphases cells under microscope and photographing the cells that showed chromosomal abnormalities.

The present study showed that there was a great correlation among carbohydrate metabolism, hormonal changes, hepatic lipid per oxidation, glutathione status and glutathione concerned enzymes as well as chromosomal abnormalities. The results indicated that the longer period of treatment, the stronger the distribution of these biomolecules.

Based on the observation that hepatic malonaldehyde concentration (MDA), which is the major end product of lipid peroxidation was always significantly increased when compared with control, it was concluded that γ -HCH and Bisphenol-A could induce oxidative stress which could be confirmed by the decreased concentration of reduced glutathione in one hand and the increased concentration of oxidized in the other hand, a case which resulted in the reduction of GSH/GSSG ratio.

These findings were also accompanied with elevated blood glucose, lactate concentrations, and lowered pyruvate concentration. These results could be attributed to the destruction of the cell membrane as a result increased lipid per oxidation that made cell membrane as a result of increased lipid per oxidation that make cells insensitive to insulin , leading to increased rate of lipolysis as another source of energy ,or γ -HCH and Bisphenol-A might antagonize the insulin effects against the effects of glucagons , epinephrine or norepinephrine , although there was no any other researches that could support this suggestion expect the proposition of some authors which concluded that a single chemical may have multiple hormonal effects.

The decreased levels of the antioxidant enzymes activities (glutathione peroxidase and glutathione reductase) might referred to the exhaustion of these enzymes in response to the continuous oxidative stress that offered on the animals specially after 28 days treatment with either γ -HCH and Bisphenol-A in male guinea pigs and after 63 ± 3 days in the full term pregnant females.

The hormonal profile showed that corisol resisted a significant increase in all treated male and female groups as a result of direct effect of γ -HCH and Bisphenol-A.

It was also found that (FSH) concentration was significantly decreased while testosterone concentration was unchanged in male guinea pigs that had been treated with γ -HCH where this observation was directly referred to the ability of γ -HCH to induce inhibition in hormone production that specified in the inhibition of (FSH) production from the anterior pituitary without affecting LH release (that is responsible for testosterone production). Meanwhile, in case of male guinea pigs that had been treated with Bisphenol-A, it was found testosterone concentration was decreased (as the result of the known estrogenic effect of Bisphenol-A) and accompanied by increased (FSH) concentration that could be attributed to the positive feed back mechanism of the low testosterone level on hypothalamus and anterior pituitary to produce more FSH and LH.

The effect of oral administration of either γ -HCH or Bisphenol-on pregnant female guinea pigs could be studied also from the hormonal profile that showed that cortisol concentration showed a high significant increase in females that had been treated for 45 ± 3 and 63 ± 3 days. This finding could be explained on the bases that γ -HCH or Bisphenol-A had the ability to increase cAMP that is responsible for the release of cortisol.

Estrogen concentration as a result of treatment with γ - HCH showed only a significant decrease in the full term pregnant group indicating that γ - HCH might act as androgenic or antiestrogenic in females , while estrogen

concentration in case of Bisphenol - A treatment showed increased values (although not a statistically significant levels) , meanwhile all groups showed a least significant difference between each other in the increasing way .

FSH concentration in all treated groups with either γ - HCH and Bisphenol - A showed non significant difference in comparison with their respective control pregnant groups and this might be as a result of the normally low level of FSH during pregnancy that can't be differentiated from the control, pregnant group values .

From the cytogenetic toxicity point of view it was found that γ - HCH and Bisphenol - A treatments could participate in some types of chromosomal abnormalities that gave an indication that not only the parents will be in danger , but also their offsprings .

Therefore our recommendation was focused on the strengthening of environmental health education at the community level and the coordination between agriculture , health , industry , commerce , education sectors and consumers to improve both environmental and personal health .

Conclusion and Recommendations

It was concluded from the present study that environmental hormone like substances such as γ -HCH and Bisphenol-A could threat human and animal health through many mechanisms that need more researches and international cooperation's to investigate many of the masked dangerous effects and mode of actions of these hormonally active pollutants .

The recommended procedures to study and avoid the dangerous effects of the environmental hormone like substances could be as follows:-

- 1) Sensitive methodologies should be developed and optimized to screen greater number of pollutants against their mode of actions and effects in relation to the endocrine system.
- 2) The preparation of national guidelines with more attention to organic chemicals and wastes of all origins where the recycling of industrial effluents as well as hygienic disposal and treatment of agricultural and sewage wastes could minimize the risk of bioaccumulation of dangerous chemical in the environment and in the animal and human body .
- 3) Encouraging clean technologies and pollution prevention programs.

- 4) Taking into consideration the integrated international management systems of hazardous substances and wastes, as the global problems need global solutions.
- 5) Active participation in all the related-international conventions and negotiations.
- 6) Strengthening of environmental health education at the community level .
- 7) Finally , coordination between agriculture , health , industry , commerce , education sectors and consumers is very important to achieve environmental , animal and human health safety and to insure awareness of hazardous and risk associated with hazardous substances and wastes specially those of hormonal activities .