Oxidative Stress and Histopathological Markers in Offspring and Dams Rats Exposed to Leufenuron during Lactation Period

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Abstract: Different toxicants can be transferred to a nursing mother's breast milk. Infants Exposure to chemicals through breast milk and related markers in breast-fed infants are needed for conducting true assessment of infant exposure and transfer of chemicals in milk (milk transfer). So, this study was carried out to assess the effect of lufenuron at a *sub*lethal dose *via* drinking water on the vital organs (brain and liver) of offspring from dams treated with this growth regulator during lactation period by determination biochemical markers of oxidative stress and pathological findings in both mothers and offspring. The results of this study confirmed the transfer of leufenuron in milk to offspring by imbalance of oxidative stress markers (GST, SOD, CAT, GSH and MDA) of dams and offspring and the pathological changes in both liver and brain of offspring and dams.

Keywords: leufenuron- lactation- oxidative stress- histopathological injurey.

1: Introduction:

It has been pointed out that, different classes of xenobiotics such as, pesticides and heavy metals can be accumulated in human milk (**Mead, 2008**). Infants Exposure to chemicals through breast milk and related markers in breast-fed infants are needed for conducting true assessment of infant exposure and transfer of chemicals in milk (milk transfer) (**Salama, 2017**). The physico-chemical properties of chemical xenobiotics such as lipophilicity, ionization, molecular weight and maternal physiology determine the transfer of xenobiotic from nursing dam to suckling pups (**Clewell and Gearhart, 2002**).

Xenobiotics have been illustrated its relation with the production of reactive oxygen species leading to development of many pathological conditions such as, neurodegenerative diseases and chronic diseases **(Agrawal and Sharma, 2014)**. Also, they concluded that, free radicals have the power to destroy cell membrane, causing lipid peroxidation and reduce the antioxidant capacity the cell through depletion of reducing power of the cell

Lufenuron is a benzoylurea insecticide that interferes with chitin synthesis in larvae of insects. Lufenuron is used in veterinary remedy in dogs and cats for preventing the maturation of flea larvae into adult fleas. Also, lufenuron is used in crop protection against Lepidoptera insect in soybeans and maize. Lufenuron inhibit metamorphosis stages *via* contact and ingestion. Lipid peroxidation was significantly increased in liver of mice treated with lufenuron at a dose level of 0.152 mg/ Kg. While, the antioxidant enzymes (catalase, superoxide dismutase and reduced glutathione) were significantly decreased (**Deivanayagam *et. al.*, 2010).**

Nursing women may be exposed to different pollutants during lactation period *via* food or water intake. From this view, this study was carried out to assess the effect of lufenuron at a dose (9.18 mg/kg≈/1/40 LD_{50}) *via* drinking water on the vital organs (brain and liver) of offspring from dams treated with this growth regulator during lactation period by determination bio-chemical markers of oxidative stress and pathological findings in both mothers and offspring.

2. Materials and Methods:

2.1. Chemicals:

Lufenuron (5%EC) Kafer-EL-Zyat pesticides company, Egypt (KZ pesticides, company, Egypt).was obtained from Mammalian Toxicology Dept., Central Agricultural Pesticides Lab., Agriculture Research Center, Dokki, Giza, Egypt.

2.2. Animals and Treatment:

Twenty female albino rats and ten males, weighting 140-160g were obtained from the Animal Breeding House of the Central of Agricultural Pesticides Laboratory (CAPL), Dokki, Giza, Egypt. Rats were maintained separately dependent on sex in controlled conditions of 12-hour light/dark cycle and 24±2˚C air temperature, 60% relative humidity. Animals were acclimatized for two weeks period and fed on a standard pellet diet and tap water *ad libitum*. Females were mated with male in a ratio of 2 female:1 male and the vaginal smear daily inspected using light microscope to detect the sperm. Presence of sperm in vaginal smear or vaginal plug was considered as Zero day of pregnancy. The pregnant females were assigned and distributed randomly into two groups (n=10), control group and lufenuron group. The pregnant females were weighted every three days for follow-up the pregnancy. The day of parturition (PND-0) was considered zero day of lactation and the pups were adjusted to 6 pups/litter and maintained with it for 21-days (lactation period).

2.3. Blood and Organs Sampling:

After weaning, blood samples were collected from dams and pups under ether anesthesia from retro orbital plexus vein into non- heparinized Eppendorf and left for

2-hours in refrigerator after that, the samples were centrifuged at 3500 rpm (600g) to separate serum. The animals were humane killed, the liver and brain of both dams and pups were dissected and a portion of these organs were kept in 10% formalin for pathological findings. The other portion of pups organs were homogenized in phosphate buffer 50mM, pH 7.4 containing 1.15% potassium chloride and centrifuged at 10,000 rpm. The serum of dams and supernatant of pups organs were collected in a clean Eppendorf and kept in a deep freezer (-20˚C) for assaying the biochemical markers of oxidative stress.

2.4. Biochemical Markers of Oxidative Stress:

2.4.1. Determination of Glutathione-S-Transferase (GST) Activity:

The activity of glutathione-S-trans-ferases (GST) was determined at 340 nm in the reaction medium contained phosphate buffer (0.1 M, pH 6.5), GSH (1.0 mM), 1-chloro 2, 4-dinitrobenzoic acid (1.0 mM) and a sample (**Habig *et. al.,* 1974**).GST activity expressed as U/ml.

2.4.2. Determination of Superoxide Dismutase (SOD) Activity:

Superoxide dismutase activity (SOD) was determined by the method based on the percentage inhibition of pyrogallol *auto*-oxidation by sample at 420 nm in the reaction mixture contained Tris buffer (0.1 M, pH 8.5), pyrogallol (20 mM), and 20 µl of sample (**Marklund and Marklund, 1974**).the activity of SOD expressed as U/ml.

2.4.3. Determination of Catalase (CAT) Activity:

Catalase (CAT) activity was measured by the method of **Aebi (1984)**. The reaction started by adding H_2O_2 (30 mM) to an appropriate volume of homogenate in 50 mM sodium phosphate buffer with pH 7. Then, the absorbance was read at a wavelength of 240 nm within 3-min. The CAT activity was expressed as U/ml.

2.4.4. Determination of Reduced Glutathione (GSH) level:

Reduced glutathione content (GSH) estimation of supernatant was performed by the method of **Beutler, *et. al.,* (1963)**. Determination of GSH is based on the reaction of DTNB [5, 50-dithiobis-(2-nitrobenzoic acid)] with GSH yielding a yellow colored chromophore with a maximum absorbance at 412 nm. The amount of GSH present in the selected tissue was calculated as nmol/ml.

2.4.5. Determination of lipid peroxidation (MDA) level:

The malondialdhyde (MDA) content as a lipid peroxidation end product of the homogenates was determined according to the method of **Ohkawa *et al.,* (1979).** The reaction mixture, containing 8.1% sodium (SDS) dodecyl sulfate, 20% acetic acid (pH 3.3) and 0.8% thiobarbituric acid, was placed in a boiling water bath for 60-min. After cooling, an *n*-butanol and pyridine mixture (15:1, v/v) was added and then shaken vigorously and centrifuged at 3000 rpm for 10-min. The absorbance of the supernatant was measured spectrophoto-metrically at 532 nm at room temperature. MDA level was expressed as nmol/ml.

2.5. Histopathological Assessment:

Liver and brain tissues of dams and pups collected for histopathological examination and fixed in 10% buffered formalin overnight, then embedded with paraffin. All paraffin-embedded tissue was sectioned at 4µm, deparaffinized in xylene, dehydrated by ethyl alcohol in a decreasing concen-trations (100%, 95%&70%), and stained with haematoxylin and eosin stain. These specimens were examined under bright-field optical microscopy using a light microscope and 40×magnification powers. Corres-ponding digital images were captured for later analysis **(Banchroft *et al.,* 1996).**

2.6. Statistical Analysis:

Analysis of data was performed by using SPSS (Version 15) and the results are expressed as M±S.E. Statistical differences were determined by *t*- test for comparison.

3.Results

The effect of lufenuron exposure during lactation period on offspring liver anti-oxidant enzymes activity is tabulated in Table (1). The results revealed a drastic increase in GST activity ($p<0.001$) in pup's liver after lactation period whose, mothers exposed to lufenuron (9.18 mg/kg≈1/40 LD_{50}) through drinking water. The adverse trend, catalase ($p<0.001$), superoxide dismutase ($p<0.01$) activities and GSH level ($p<0.01$) decline was noticed in offspring's liver of lufenuron treated group at a concentration (9.18 mg/kg≈1/40 LD_{50}) through mothers milk. Furthermore, offspring's liver MDA were increased significantly ($p<0.01$) after tratment during lactation period.

Table (1): Effect of Lufenuron on GST, SOD & CAT, Activities & GSH and MDA Levels in offspring's Liver:

Parameters / Treatment	GST (U/ml)	SOD (U/ml)	CAT (U/ml)	GSH (nmol/ml)	MDA (nmol/ml)
Control	**15.17** ±0.38	**10.13** ±0.17	**12.1** ±0.63	**157.40** ±5.83	**20.81** ±0.24
Lufenuron	**23.68***** ±0.90	**9.32**** ±0.08	**6.35***** ± 0.21	**125.17**** ±6.89	**25.21***** ±0.44

*** Significant at 0.05 ** Significant at 0.01 *** Significant at 0.001.**

Results of oxidative stress in brain of offspring whose mothers were exposed to lufenuron at a concentration of (9.18 mg/kg≈1/40 LD_{50}) in drinking water are shown in Table (2). There was *non*-significant difference in GST activity. The activities of SOD and CAT were significantly decreased in brain of offspring

whose mothers exposed to lufenuron at a concentration of (9.18 mg/kg≈1/40 LD_{50}) in drinking water. The offspring's brain of lufenuron group has shown a sharp decline ($p<0.01$) in glutathione content. While, MDA in offspring; brain was significantly increased ($p<0.05$).

Table (2): Effect of Lufenuron on GST, SOD & CAT Activities & GSH and MDA Levels in offspring's Brain:

Parameters / Treatment	GST (U/ml)	SOD (U/ml)	CAT (U/ml)	GSH (nmol/ml)	MDA (nmol/ml)
Control	**1.86** ±0.076	**13.81** ±0.09	**5.25** ±0.50	**89.43** ±2.07	**7.82** ±0.58
Lufenuron	**2.03** ±0.09	**13.55*** ±0.07	**3.49*** ±0.31	**75.04**** ± 3.47	**9.32*** ±0.34

*** Significant at 0.05** **** Significant at 0.01.**

The effect of lufenuron exposure during lactation period on biomarkers of oxidative stress in dam serum is shown in Table (3). The results indicated that, GST, CAT ($p<0.01$) and SOD ($p<0.05$) activities were greatly diminished in serum of leufenuron- exposed female dams. Also, reduced glutathione ($p<0.001$) was significantly declined in dams serum while, MDA ($p<0.001$) was significantly increased in dams exposed to leufenuron at (9.18 mg/kg≈1/40 LD_{50}) of lethal dose through drinking water.

Table (3): Effect of Lufenuron on GST, SOD & CAT Activities & GSH and MDA Levels in Dam's Serum:

Parameters / Treatment	GST (U/ml)	SOD (U/ml)	CAT (U/ml)	GSH (nmol/ml)	MDA (nmol/ml)
Control	**1.31** ±0.04	**10.33** ±0.32	**6.59** ±0.19	**106.7** ±2.63	14.49 0.51
Lufenuron	**1.16**** ±0.03	**8.78*** ±0.5	**4.01***** ±0.095	**90.2***** ±1.70	34.38*** ±1.87

*** Significant at 0.05** **** Significant at 0.01** ***** Significant at 0.001**

3.1.Histopathological Examination of Dam and offspring's Liver:

Microscopically, dam's liver of rats from control group revealed that the hepatocytes (long arrows) are large and polyhedral in shape with spherical nuclei (short arrows); each has chromatin and a prominent nucleolus. The hepatocytes are arranged radially forming hepatic plates. On the other hand, dam's liver-treated group revealed cytoplasmic vacuolization of hepatocytes, necrosis of sporadic hepatocytes (Fig. 2), focal hepatic necrosis associated with hemorrhage (Fig.3) and fibroplasia in the portal area around the bile duct (Fig.4). However, liver of control offspring revealed the normal histological structure of hepatic lobule (Fig.5). Meanwhile, examined sections from treated offspring showed cytoplasmic vacuolization of hepatocytes (Fig.6), steatosis of hepatocytes and cholangitis (Fig.7).

3.2.Histopathological Examination of Dam and offspring's Brain:

Microscopically, dam's brain (cerebral cortex) of control group revealed no histopathological changes (Fig. 8). Meanwhile, brain of treated dame's rats revealed necrosis of neurons and neuronophagia (Fig. 9) and focal hemorrhage (Fig. 10). However, offspring's brain of control revealed no histopathological changes (Fig. 11). Some examined sections from treated pup have revealed no histopathological changes. Whereas, other sections from this group showed necrosis of some neurons (Fig. 12) and focal gliosis (Fig. 13).

4.Discussion:

Different toxicants chemicals can be transferred to a nursing mother's breast milk from the body stores and/or from the blood and can therefore be exposed to chemicals that may pose a health hazard. There is a risk of adverse effect on the lactation process and the content of nutrients in the milk at high exposure levels of certain chemicals (**Salama, 2017**).

Newborns conjointly, really consume a lot of bigger amounts of milk fat further as, different foods than adults do on a weight basis and thus are exposed to considerably higher levels of exposure to bound venomous chemicals. These lifespan exposures will lead infants to the next risk of chronic venomous effects than exposure later in life (**Philip *et al.,* 2002).**

The organism- environmental disturbance as occurred in oxidative stress and organism's failure to adapt to its environmentally induced oxidative stress through ROS that, results in a high level of oxidative stress, cell death and fitness impairment (**Jones and Go, 2010**; and **Lismont *et al.,* 2015**).

Toxicity of many xenobiotics is often associated with reactive oxygen species (ROS) which Involved in many diseases ' pathophysiology **(Abdollahi *et al.,* 2004).** Pesticide exposure triggers oxidative stress and progresses to lipid peroxidation in animals and other organisms (**Melekoglu *et. al.,* 2000**). The antioxidant enzymes SOD and CAT are specific biomarkers of antioxidant defenses system which inactivate the oxidative stress induced by environmental contaminants. They constitute the primary antioxidant enzymes and first lines of defense against the free radicals in cell **(Chakroun *et. al.,* 2017).** The suppression of SOD and CAT antioxidants enzymes involved in oxidative stress removal occurred in superoxide deposition that encouraged lipid peroxidation and DNA modification, altered expression of genes and apoptosis (**Calviello *et. al,* 2006**). Phase II detoxification includes the GSTs, which defends cells from reactive electrophiles attack. It help facilitate glutathione conjugation with electrophilic species (such

as chemical carcinogenic substances and cytotoxic chemotherapeutic agents), which was the first step to remove toxic substances. (**Lai *et. al.*, 2005)**.

The tripeptide, GSH, is the primary cell-based antioxidants and redox controller that is essential in preventing cellular component oxidation. Cells spend more energy on maintaining high amounts of GSH, which then in effect helps to keep proteins in a low state. (**Forman *et. al.*, 2009**). GSH deficiency is an essential biomarker of oxidative damage due to its use of conjugation and/or its involvement as antioxidants in the neutralization of pesticide reactive oxygen species and the conservation of the intracellular redox equilibrium in animal cells. (**Lu, 1999**). These effects have been previously observed by other authors (**Maran *et. al.*, 2009**; **El-Shenawy, 2010; and El-Demerdash, 2011**). Moreover, GSH also participates in the detoxification of xenobiotics as a substrate for the enzyme GST. The fundamental requirement for the production of ROS is the degradation of intracellular sulfhydryl groups by insecticides. The significant decline in GSH level detected in this study could therefore lead to increased susceptibility to free radical damage (**Fetoui, *et. al.*, 2009**).

Pollutants, chemicals and inflammation in the body can probably Increases the production of ROS and/or reduce GSH content and probably cause a change in the balance of cellular redox level ultimately resulting in more oxidative damaged biomolecules. Changing the normal redox balance can alter the different enzymes activity and cell signaling pathways in tissues and can therefore be an important mechanism for exercising intoxication of different xenobiotics and mediating the pathogenesis of many diseases **(Mishra, and Srivastava, 2015).**

MDA adducts are clinically important as they can participate in secondary harmful effects (e.g. crosslinking) by facilitating intramolecular and intermolecular protein/DNA crosslinking that can cause modifications in cell biology properties and persist during aging and chronic diseases **(Cheng *et. al.*, 2011**). Tissue lipid peroxidation is a major consequence of the free radical-mediated injury and propagation because of high concentration of polyunsaturated fatty acids in cells (**Verma, *et. al.*, 2007)**

Notable fatty change in portal area with necrosis implied that certain harmful byproducts could be transferred to the liver, resulting in these modifications. **(Nidhi Benjamin, *et. al.*, 2006)**. Marked congestion and hemorrhage were observed in tissues seemed to be a sort of inflammation induced by toxic agent such pesticides. Histamine liberated from damaged cells is an important factor in the vascular response that follows injury, causing increased blood flow into the capillary bed and vessels which induced vasodilation. The inflammation entails both residing and circulating inflammation cells movement and stimulation and cytokine production Triggered inflammatory cells and produced cytokines stimulate fibroblasts to divide, migrate, secrete and generate collagen. **(Nagao *et al.*, 2003).** Fatty liver or steatosis refers to the abnormal accumulation of lipid in hepatocytes, primarily as triglycerides, due to an imbalance between the uptake of *extra*hepatic triglycerides and the hepatic secretion of triglyceride-containing lipoproteins and fatty acid catabolism. Basically, lipid accumulation is related to disturbances in either the synthesis or the secretion of lipoproteins. Excess lipid can result from an oversupply of free fatty acids from adipose tissues or, more commonly, from impaired release of triglycerides from the liver into the plasma. Triglycerides are secreted from the liver as lipoproteins, such as very low density lipoprotein (**Ernest Hodgson, 2010).**

The results of this study are in agreement with **Deivanyagam, *et. al.*, (2014),** who reported an increase in lipid peroxidation and a decrease in antioxidant enzymes (SOD&CAT) in liver of mice exposed to *sub*lethal dose of leufenuron. The inhibition in antioxidant defense system may be related to the reduction in total thiol content or glutathione level (**Ramanathan, *et. al.*, 2002**).

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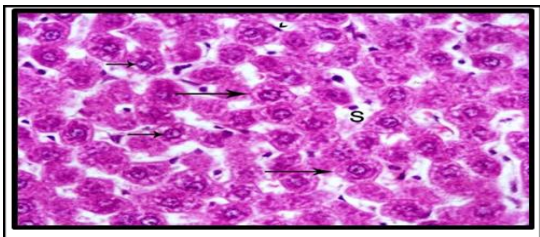

Fig.(1): Dam liver of control showing normal histological structure. (H&E-X400).

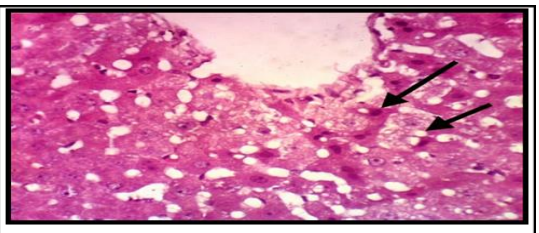

Fig. (2): Dam Liver of treated group showing cytoplasmic vacuolization of hepatocytes and necrosis of sporadic hepatocytes (H & E-X 400).

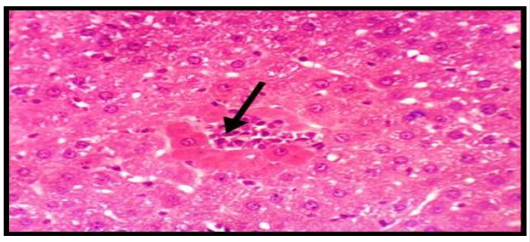

Fig.(3): Dam Liver of treated group showing focal hepatic necrosis associated with hemorrhage (H &-E X 400).

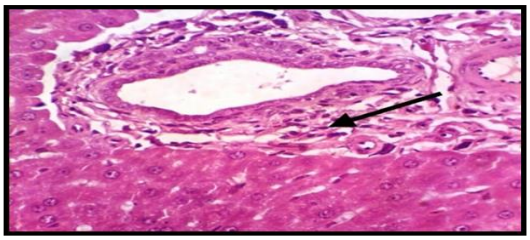

Fig. (4): Dam Liver of treated group showing fibroplasia in the portal triad around the bile duct (H & E-X 400).

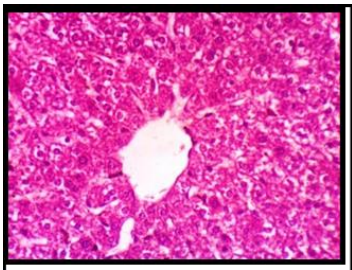

Fig. (5): Foeti liver of control group showing the normal histological structure of hepatic lobule (H & E X 400).

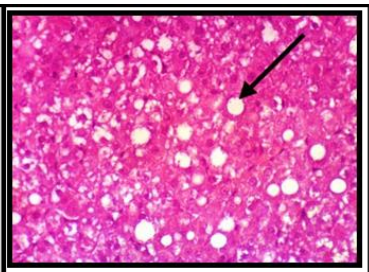

Fig. (6): Foeti Liver of treated group showing steatosis of hepatocytes (H & E X 400).

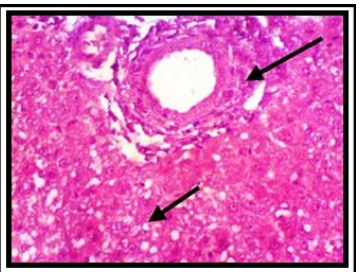

Fig. (7): Foeti liver of treated group showing steatosis of hepatocytes and cholangitis (H&E X 400).

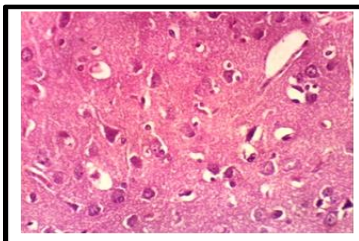

Fig.(8): Dam brain of control group showing no histopathological changes (H&E-X400).

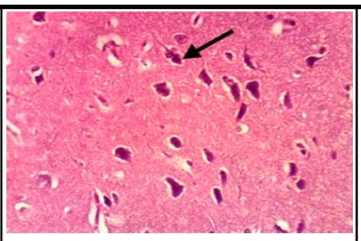

Fig.(9): Dam brain of rat treated group showing necrosis of neurons and neuronophagia (H&E-X400).

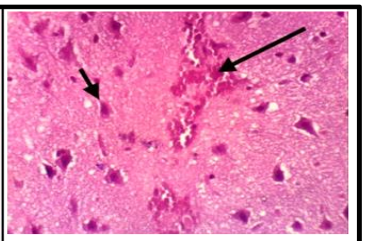

Fig. (10): Dam brain of treated dam group showing necrosis of neurons and focal haemorrhage (H&E-X400).

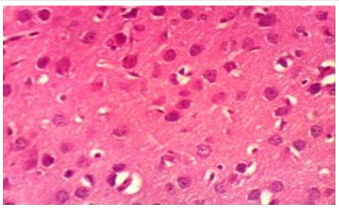

Fig.(11): Foeti Brain of rat from control group showing no histopathological. (H&E-X400).

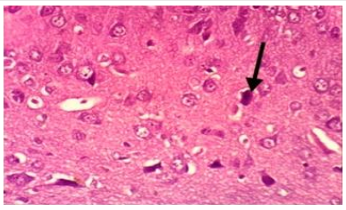

Fig.(12): Foeti Brain of treated group showing necrosis of some neurons (H&E-X400).

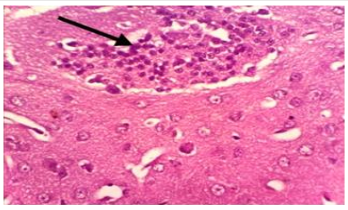

Fig.(13): Foeti Brain of treated group showing focal gliosis (H&E-X400).

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الإجهاد التأكسدي ,والتغيرات الهستوباثولوجية فى رضع وامهات الجرذان المعرضة لليوفينيورون خلال فترة الرضاعة

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قسم بحوث سمية المبيدات للثدييات ، المعمل المركزى للمبيدات ، مركز البحوث الزراعية ، الدقى ، الجيزة ، مصر

الملخص العربى:

يمكن للمواد السامة أن تنتقل الى الامهات المرضعة ولذلك فدراسة تعرض الاطفال للمواد الكيميائية من خلال حليب الثدي والعلامات ذات الصلة عند الرضع الذين يتم إرضاعهم من الثدي ضروري لإجراء تقييم حقيقي لتعرض الرضع ونقل المواد الكيميائية في الحليب (الانتقال خلال الحليب). لذلك ، أجريت هذه الدراسة لتقييم تأثير الليوفينيورون بالجرعة تحت المميتة فى مياه الشرب على الأعضاء الحيوية (المخ والكبد) للرضع المعرضة أمهاتهم لمنظم النمو خلال فترة الرضاعة عن طريق تحديد العلامات الكيميائية الحيوية للإجهاد التأكسدي والباثولوجي في كل من الأمهات والرضع وقد أكدت نتائج الدراسة هذه الدراسة انتقال اليوفينيورن خلال اللبن الى الرضع مما أدى الى اختلال علامات الإجهاد التأكسدي GST ، SOD ، CAT، ، GSH MDA فى كل من الامهات والرضع ومن التغيرات الباثولوجية فى كل منهما.