Histological changes in liver structure following a therapeutic and overdose administration of paracetamol in female mice.

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Keywords: Paracetamol, liver, histology, mice.

ABSTRACT

The effects of administration of two formulations of paractamol, (pandol formulation) **PI** and (calpol formulation) **PII** were studied on the female mice liver, using routine histological technique. The histological examination of the liver obtained from the animals received daily therapeutic dose of PI and PII drugs for one month showed vascular congestion and small focal areas of inflammatory cells associated with central vein and portal vein. In addition, enlarged hepatocytes, and some normal hepatocytes were observed to contain abundant microvesicles.

On the other hand, the overdose administration caused intensive histological alterations in the liver. These changes included congested blood sinusoid, congested central vein and branch of portal vein. In addition, nuclear changes, necrotic cells were dispersed throughout the parenchyma, mild microvesicles and macrovesicles were also observed in hepatocytes.

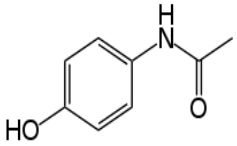
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INTRODUCTION

Paracetamol (Acetaminophen) was established in 1946, as the major constituent of phenacetin a white crystalline substance used to reduce body temperature and relieve pain. It became available in the UK in 1956 and was included in the British pharmacopoeia in 1963, **(Ucheya and Igweh 2006)**. The main concern with Paracetamol is death resulting from hepatic toxicity (toxicity liver) and nephrontoxicity (kidney toxicity) following overdose, either accidental or deliberate. The aim of this study is to examine the histological changes which may occur in the liver in association with prolonged administration of therapeutic dose as well as overdose treatment of two formulations of paracetamol drug in adult female Mus musculus.

Chemical structure:

Paracetamol or acetaminophen , chemically named N-acetyl-aminophenol, is a widely used over the-counter analgesic (pain reliever) and antipyretic (fever reducer**) (Moller *et al.*, 2005).** Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and a nitrogen atom of an amide group in the *para* (1,4) pattern. (Bales *et al.*, 1985)**.**



Paracetamol is used for the relief of pains associated with many organs of the body and also is approved for reducing fever in people of all ages (**Dewall *et al.*, 2010**). The therapeutic dose of paracetamol is defined

on the basis of (mg) paracetamol per (kg) bodyweight. It is generally accepted that the therapeutic range for both analgesic and antipyretic activity is a plasma paracetamol level of 10–15 mg/L which equates to a dose of 10-15 mg/kg. **(Nahata *et al.*, 1984**).

Mechanism of Action:

Paracetamol has recognised analgesic and antipyretic activities, and weak anti-inflammatory activity. The antipyretic activity of paracetamol, and possibly the analgesic action, is ascribed to a central inhibition of prostaglandin synthesis in neurons and brain endothelial cells. **(Aronoff *et al.*, 2006 and Remy *et al.*, 2006)**

Metabolism and Excretion:

Paracetamol is metabolized primarily in the liver, the major route of paracetamol metabolism is via sulphation and glucuronidation. Around 5-10% of paracetamol is oxidised by cytochrome P (CYP) enzymes (the expression and activity of which varies with age and between individuals) to form N-acetyl-p-benzoquinoneimine (NAPQI), a toxic by-product (Zaher ***et al.*,1998)**.

Normally NAPQI is detoxified by conjugation with glutathione in both adults and children. If the concentration of NAPQI exceeds glutathione levels (eg, after paracetamol overdose), NAPQI binds to hepatocytes causing severe liver damage **(Jackson*et al.*, 1984).**

Side effects of paracetamol:

Paracetamol can produce harmful effect on different body organs after administration. **McKee and Gass (2011)** found that administration of paracetamol induced histological changes in rats including epithelial hyperplasia and hyperkeratosis of the nonglandular mucosa of stomach. The submucosa was usually expanded by edema and occasionally infiltrated with of neutrophils, eosinophils and macrophages.

Paracetamol can also affect the kidney structure after long term treatment. Paracetamol induced mild vascular and inflammatory changes with signs of congestion, tubular necrosis and glomrular atrophy (**Lim *et al.*, 2010 and Ucheya and Igwah 2006).** In addition, **Lorz *et al.* (2003**) found that paracetamol caused acute and chronic renal failure. They also reported that paracetamol induced cell death with features of apoptosis in murine proximal tubular epithelial cells. **Lim *et al.* (2010)** observed mild vascular congestion and inflammatory changes such as myocyte coagulation in mice treated with paracetamol. Paracetamol overdose-induced liver damage is one of the most wide spread drug-induced side effects. Although the exact mechanism of paracetamol toxicity remains largely unknown, it appears to involve two pathways: direct hepatotoxicity and adverse immune reactions. This impairment of liver functions can culminate in cell death, leading to variety of pathological conditions including acute hepatitis **(Somanawat *et al*., 2013).**

Materials and methods

Ten albino mice were obtained from animal shop in Benghazi city. They were bred in the Department of Zoology, Faculty of Science, University of Benghazi, until they became 70 animals. Thirty-five female albino mice weighing 22-26 g were used in this experiment. Mice were maintained in plastic cages and housed for 15 days prior initiation of experiment. Animals were fed a standard commercial pellets and tap water was provided *ad libitum*, the sawdust bedding of cages was changed every other day to keep the animals dry and clean throughout the period of the experiment.

Experimental Design

This study was designed to investigate the effect of paracetamol on the structure of the liver. Two kinds of paractamol were used in this work**.** These were: Paracetamol(calpol suspension) was referred to as **PI** and Paracetamol (Panadol suspension) was referred to as **PII.**

The thirty-five female albino mice were divided into the following groups:

Group 1: (Control group) Animals received normal saline: This group included five animals ,which received normal saline solution orally.

Group 2: Animals received therapeutic dose of paracetamol drugs :

The dose was adjusted for mice according to the formula of **Paget** and **Barnas (1964)** and **Tvrzicka *et al*. (1995)** and was found to be

5mg/kg/day (which is equal to the recommended dose). The drug was administered orally, using the original gastric tube with a syringe needle head **(Baker *et al*.,1980)**. Animals in this group were given a daily therapeutic dose of PI & PII drugs. This group included (10) animals,which were subdivided into two subgroups, subgroup A for PI and subgroup B for PII, with five animals in each.

1- **Subgroup A (1 month of treatment):** The animals received daily therapeutic dose of PI drug for 1 month .
2- **Subgroup B (1 month of treatment):** The animals received daily therapeutic dose of PII drug for 1 month .

Group 3 : (Animals received overdose of PI & PII drugs for one week): This group included (10) animals, which were subdivided into two subgroups, subgroup A for PI and subgroup B for PII, with five animals in each.

Group 4 : (Recovery group) after three weeks of recovery :

This group included (10) animals, which were subdivided into two subgroups, subgroup A for PI and subgroup B for PII, with five animals in each. The animals of this group were treated exactly as in group 2, then the drugs intake were stopped and the animals were left for recovery for three weeks.

Histological Examination:

Animals of all the above groups were sacrificed following mild diethyl ether anesthesia and the liver tissue was excised (from each animal rapidly) and immediately fixed in 10% neutral phosphate- buffer formalin and processed for paraffin method **(Preece, 1972)**.

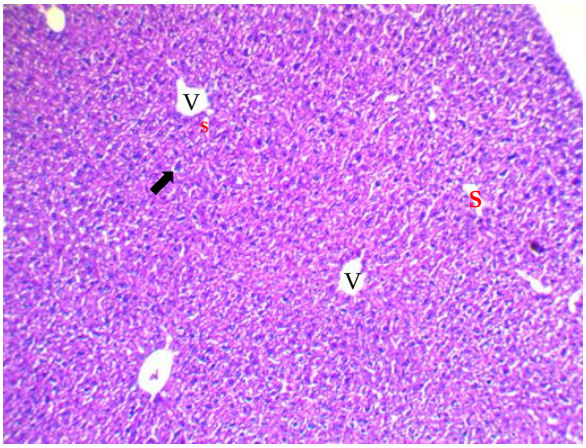
The specimens were processed according to **Culling *et al*. (1985)**, i.e., dehydrated with ascending grades of ethyl alcohol (70% up to100%), cleared with xylene, infiltrated with molten soft paraffin and blocked with molten hard paraffin. Each specimen was sectioned into serial section of 7µm in thickness, using rotary microtome. The sections were flattened by floating, using water bath at 40^0C, then, mounted on clean slides, and left to dry on hot plate for 1 hour at 40^0C to ensure sections adherence.

The tissues were stained using the hematoxline and eosin (H&E) stains. The sections were examined under a Carl Zeiss research microscope with a digital camera attached. Photomicrographs of the liver sections were taken at various magnifications.

Results

Control group:

Light microscope examination of liver sections of control showed liver lobules consisted of anastomosing cord of hepatocytes radiating from central vein. The hepatocytes were acidophilic and contained central pale stained nuclei and some binucleated. The hepatocyte cords were separated blood sinusoid **(fig. 1)**.

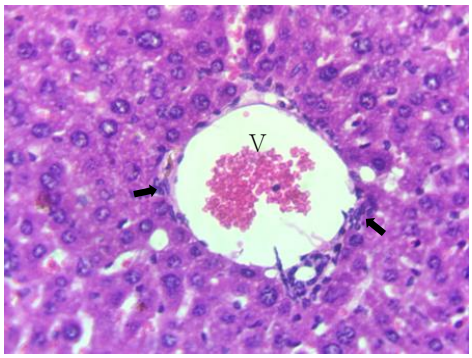


(Fig. 1) : Photomicrograph of liver tissue taken from control group showing anastomosing cords of hepatocytes radiating from central vein (**V**), separated blood sinusoids (**S**) and hepatocytes contains central pale stained nuclei (**arrow**). (H & E stain, X 100)

Group 2 (treated group):

Sub group A: Animals received therapeutic dose of (PI) drug.

Histological assessment of the liver of the animals in (PI) treatment group showed significant abnormal alteration in the histological profile when compared with that of animals in control group. Some of the histological deviations include; vascular congestion and small focal areas of inflammatory cells associated with central vein. In addition, this group showed some hepatocytes contained abundant of microvesicles **(fig. 2a,b).**

a 

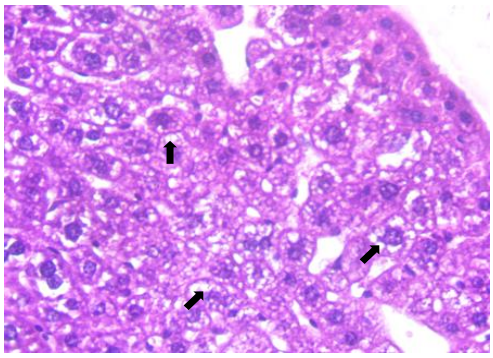
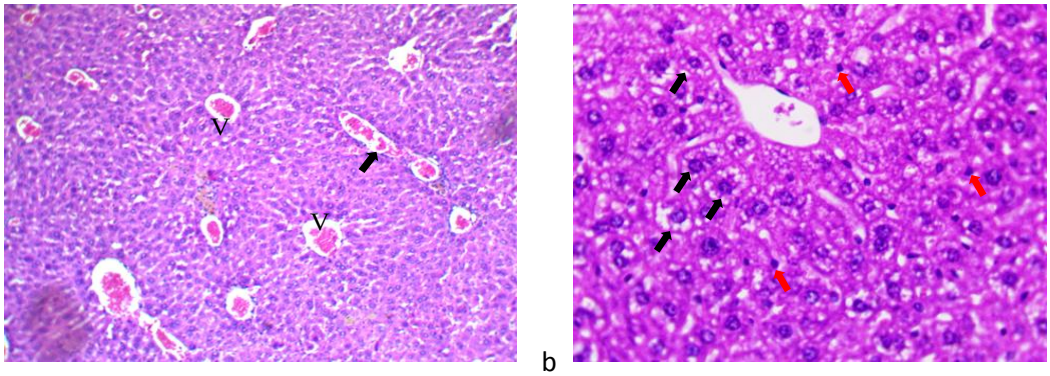
b 

Fig 2: Photomicrograph of liver section after administration of PI (0.5ml / kg / day), **(a)** showing small focal area of inflammatory cells(arrows) associated with congested central vein(v). **(b)** showing microvesicles (**arrows**) which are multiple small

vacuoles present within hepatocytes gives the cytoplasm a foamy appearance. (H & E stain, (a)X 100 (b)X400).

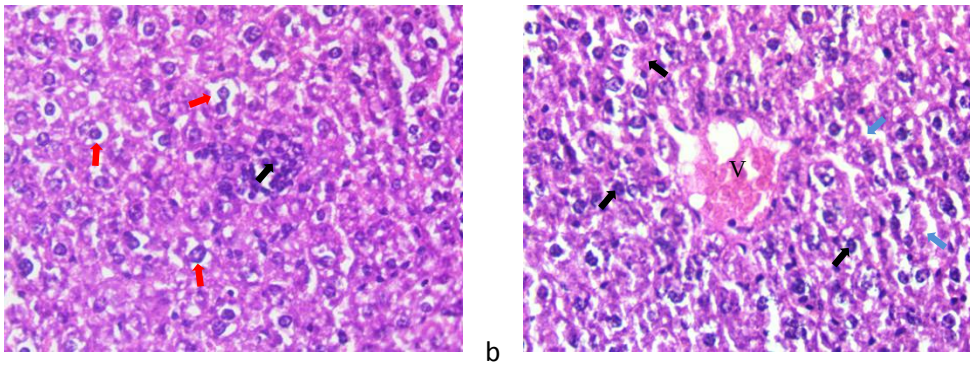
Sub group B: Animals received therapeutic dose of (PII) drug. Section of this subgroup showed extensive congested portal vein and central vein. Many small focal areas of inflammatory cells were also observed some associated with central vein and portal vein **(fig.3).**



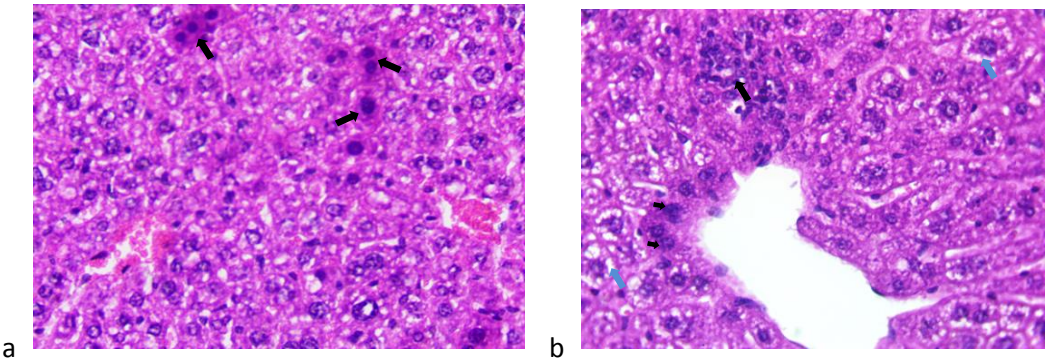
(Fig.3a,b): Photomicrograph of liver section after administration of PII(0.5ml / kg / day), **(a)**. showing extensive congested branches of portal vein (**arrow**), congested central vein (**V**) associated with cellular infiltration. (**b)**. showing hepatocytes with microvesicles (**arrows**) and another hepatocytes with pyknotic nuclei (**red arrows**). (H & E stain, a X 100, b X400).

Sub groups C & D: Animals treated with overdose PI and PII. Histological examination of specimens obtained from PI and PII overdose groups displayed more serious lesions in liver tissues in comparison with control group and subgroup A and B (animals received therapeutic dose). In **PI overdose** drug showed remarkable changes especially in the hepatocytes. Hepatocytes were highly appeared highly hydropic cells and focal area of inflammatory cells were also observed. Some specimens showed nuclear changes and congested central vein and branch portal

vein **(fig. 4 a, b).** In PII overdose drug showed necrotic cells dispersed throughout the parenchyma with pyknotic nuclei, mild microvesicles and focal area of inflammatory cells were also observed **(fig.5 a, b).**



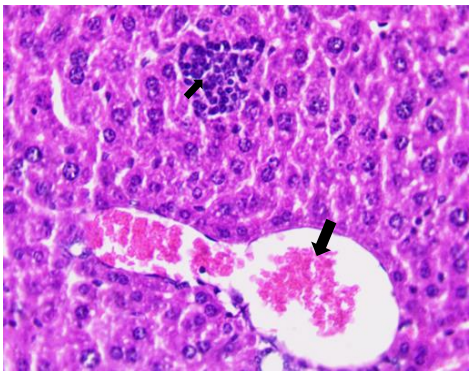
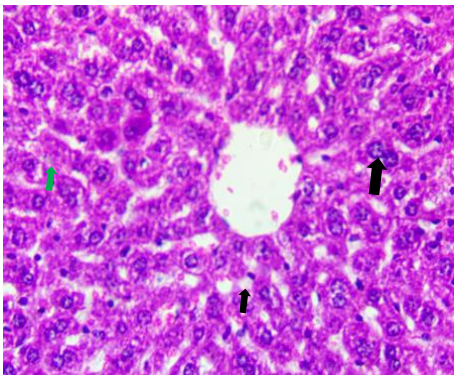
(Fig. 4a,b): Photomicrograph of liver tissue after overdose of PI drug intake, **(a)** showing small focal area of inflammatory cells (**black arrow**) and hepatocyte with hydropic degeneration (**red arrows**). **(b)** showing nuclear changes (different shapes and sizes) (**arrows**) and congested central vein (**V**) surrounded by dilated sinusoids (**blue arrows**). (H & E stain, X 400).



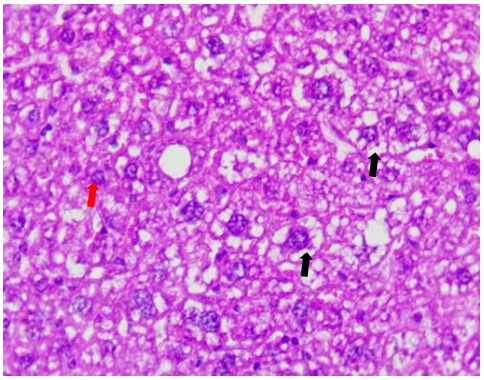
(Fig. 5 a, b): Photomicrograph of liver section after overdose of PII administration, **(a)** showing necrotic cells were dispersed throughout of parenchyma (arrows) with pyknotic nuclei. **(b)** showing focal area of inflammatory cells (arrows), necrotic hepatocytes with pyknotic nuclei (small arrows) and another hepatocytes with microvesicles (blue arrows). (H & E stain, X 400).

<u>Group 4:</u> After 3 weeks of recovery:

The histological profile of the liver section of animal in the recovery group revealed preserved structure of hepatic tissue except of the presence of slightly congested central veins and small focal area of inflammatory cells, **(fig. 6 a , b**) While cytoplasmic and nuclear changes still persist **(fig.7).**

a  b 

(Fig.6 a, b): Photomicrograph of liver tissue after three weeks of recovery from PI intake **(a),** showing small area of inflammatory cells within parenchymal tissue (**arrows**) and mild congestion of central vein (**thick arrow**). **(b),** PII intake showing little hydropic degeneration of hepatocytes (**arrows**), some are binuclaeted (**thick arrow**) and mild congested blood sinusoid (**green arrow**). (H & E stain, X 400).



(Fig.7) : Photomicrograph of liver tissue after three weeks of recovery from PII intake, showing hepatocytes with microvesicles (**black arrows**), as well as normal hepatocytes (**red arrows**), (H & E stain, X 400).

DISCUSSION:

The liver was chosen in this study to reveal the effect of administration of paracetamol as it is a good indicator of chronic effect of toxic substance and it is the first organ to be exposed to xenobiotics due to its role in metabolism.

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents . Certain medicinal agents when take in overdoses and sometime even when introduced within therapeutic ranges , may injure the liver. More than 900 drugs have been implicated in causing injury **(Friedman *et al.*, 2003)**. Injury maybe a direct toxic effect or Immunological reaction to either the drug or its active metabolite formed by bioactivation (it was reported that for 62% of withdrawn drugs it is the metabolits that were toxic), **(Brind, 2007).**

In the present study , several histological changes were observed in the liver tissue including vascular congestion , inflammation , different

morphological changes in hepatocytes including hypertrophic hepatocytes, nuclear changes and microvesicles and macrovesicles changes.

These findings were in agreement with the results obtained by **(Yousef *et al.*, 2010 and Lozano *et al* ., 2012)**. **Williams *et al.*, (2010)** also reported similar observations in their studies on mice treated with paracetamol, where, they found that the treatment with paracetamol resulted in severe liver cell necrosis at 12 and 24 hour. This injury was accompanied by accumulation of inflammatory cell in the liver. In addition many investigators reported that the administration of paracetamol and other drugs such as aspirin and depakin lead to infiltration of inflammatory cells in experimental animals **(Lozano *et al.*, 2012 and Al-Nagaz, 2013)**.

The inflammation observed after paracetamol overdose may be characteristic for response sufficient to recruit neutrophil for the purpose of removing necrotic cell but is not severe enough to cause additional damage (**Judy *et al.*, 2000 and Radosavljević *et al.*, 2010**). Paracetamol induced hepatotoxicity has been reported to occur with hepatic congestion in human **(Lee, 2004**).

In the present study , areas of congested blood sinusoid appeared in treated group and increased to the highest levels at overdose treatment . These areas of congested blood sinusoid were prominent and associated with hepatocellular necrosis and may indicate hemorrhage necrosis . Similar observations were also reported by **(Mamta *et al.*, 2011 and**

Portmann *et al.*, 1975) in their studies on male mice chronically fed paracetamol.

Additional support to the present study results came from **(Ito *et al* ., 2003)** who showed that the erythrocytes infiltrated into the space of Disse and the area occupied these cells was markedly increased and reduced sinusoidal perfusion.

Further support came from **(Al-Nagaz, 2013)** who obtained similar results in experimental mice treated with depakin drug. The present findings also suggest that the reduced sinusoid perfusion and increased inflammatory cells contributed to the development of paracetamol induced liver injury. Moreover the work has also shown that the light microscopic observations revealed several changes in hepatocytes, these changes included vacuolation of their cytoplasm (microvesicular& macrovesicular) and nuclear changes.

Microvesicular changes, which are also called fatty changes represent the intracytoplasmic accumulation of triglycerides (neutral fats). At the beginning, the hepatocytes shown small fat vacuoles (liposomos) around the nucleus (microvesicular fatty changes). In this stage, liver cells are filled with multiple fat droplets that do not displace the centrally located nucleus **(Reddy & Rao, 2006 and Goldman, 2003).** The size of the vacuoles increases, pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance (macrovesicular fatty change) (**Adams *et al.*, 2005)**. Similar observations were also reported by **(Al-Nagaz 2013)** in their studies on mice treated with depakin drug.

Another histopathological sign prevailed in this work was the hydropic degeneration. Hydropic changes usually occur when the cell is unable to maintain ionic and fluid homeostasis. It reflects an excessive accumulation of water in cells cytoplasm. This can happen when an injurious agents such as toxin causes disruption of the cell membrane resulting in increased permeability (**Wang *et al.*, 2007 and Abdelhalim and Jarrar, 2012).**

Additional support to the present results given by the study of **Matsumoto *et al. (*2006) and Gkretsi *et al.(* 2007)** who showed that the hydropic degeneration were found to be associated with number of drugs and alcohol.

Finally, regarding the recovery group, the discontinuation of the drug for three weeks resulted in an incomplete recovery.

In conclusion, it could be suggested that paracetamol induced liver tissue injury. These effects were more pronounced in the PII (calpol formulation) than in PI (panadol formulation).

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الملخص العربي

التغيرات النسيجية في تركيب الكبد المعرضة للجرعة المسموح بها والجرعة المفرطة لدواء الباراسيتمول في إناث الفئران البيضاء.

مبروكة عبدالخالق الرفادى و سعاد احمد الإنجليزي

قسم علم الحيوان- كلية العلوم – جامعة بنغازي

الكلمات المفتاحية: الباراسيتمول- الكبد –الأنسجة- الفئران

تم في هذا البحث دراسة تأثيرات استعمال صيغتين مختلفتين من دواء الباراسيتمول (صيغة الباندول) المشار إليه PI وصيغة (الكالبول المشار) إليه PII على نسيج كبد الفئران ومدى التغيرات النسيجية التي تحدث سواء بالجرعة المسموح بها أو بالجرعة المفرطة.

استعملت في هذه التقنية النسيجية الروتينية باستخدام شمع البراقين للحصول على مقاطع نسيجية وصباغتها بالهيماتوكسلين والايوسين وفحصها بالمجهر الضوئي.

وقد أظهرت فحوصات المجهر الضوئي للقطاعات المأخوذة من الحيوانات المعرضة يوميا للجرعة المسموح بها عدة تغيرات نسيجية في نسيج الكبد. كانت أهم هذه التغيرات احتقان وعائي مع وجود مناطق تحتوى على خلايا التهابية مرتبطة بالوريد الكبدي والوريد البابي، إضافة إلى ذلك تضخم في الخلايا الكبدية مع ظهور بعض الحويصلات الدهنية الصغيرة في بعض الخلايا الكبدية.

أما القطاعات النسيجية المأخوذة من الحيوانات المعرضة إلى الجرعة المفرطة فقد أظهرت هذه المقاطع أن هناك تغيرات كبيرة في النسيج الكبدي، تشمل هذه التغيرات احتقان في الجيوب الدموية الكبدية والأوردة المركزية وكذلك يمتد الاحتقان بين فروع الأوردة البابية. أما ما يخص NHالخلايا الكبدية فقد لوحظ تغيرات نووية ونخر للخلايا الكبدية إضافة إلى ظهور الحويصلات الدهنية الصغيرة والكبيرة في هذه الخلايا.

أما بالنسبة لمجموعة الاستشفاء فقد أوضحت نتائج هذه الدراسة أن التغيرات الخلوية والخلايا الالتهابية والاحتقان لاتزال موجودة في المقاطع النسيجية ولكن بمعدل اقل من المجموعات المعاملة.