RESEARCH PAPER | Medical Science | Volume : 4 | Issue : 12 | Dec 2014 | ISSN - 2249-555X

Toxic Effect of Acetone on Experimental Male Wistar Rats

KEYWORDS: Histopathological alterations, Toxic Effect, Acetone, Wistar Rats

Entissar S. Al-Suhaibani
Associate professor of genetics.
King Saud University, Riyadh, KSA.
Riyadh 11342

Nermin A. El-Morshedi
Assistant professor of Histology, cell biology and genetics. Bilqas central hospital, Bilqas, Dakahlia, Egypt.

ABSTRACT *Acetone (dimethyl ketone) and 2-propanone (CH3COCH3) is an organic chemical compound which belongs to ketones. Acetone is produced normally in human body, but its excessive levels has toxic hazard effects. Acetone is used in many fields, but excessively as nail polish remover. Present study results proved acetone inhalation bad effects (with different concentration levels on experimental male Wistar rats), as neuro-behavior disorders, lack of red blood cells, biochemical imbalance in glucose and insulin levels, urinary acetone increasing level and histopathological alterations in some target tissues. We aimed to provide a greater awareness to consumers of acetone against its usage without attention as they may are exposed directly or indirectly to acetone inhalation.*

INTRODUCTION

2-propanone or dimethyl ketone (CH3COCH3) has a commercial name with acetone (Budavari et al., 2002) and is used as a chemical intermediate and a solvent in chemical and pharmaceutical applications (ATSDR, 2004). Acetone is produced endogenously or exogenously (by manufacturing way), completely miscible with water and highly volatile organic compound (WHO, 1998). It broadly studied as a metabolic intermediate that is naturally forms in humans and rodents under normal metabolic conditions, but highly forms under fasting conditions, high-fat ingestion, low-carbohydrate diets and uncontrolled diabetes, so toxicokinetics of acetone has been studied (Gentry et al., 2002).

Overall, available data indicate that humans and rodents readily absorb acetone by inhalation, ingestion, and dermal exposure (Ernstgard et al., 1999) and there is a similarity between toxicokinetic data on human subjects and rodents for its lipophilic character which allows for acetone diffusion into tissues, then distributes throughout the body (Clewell et al., 2001). The metabolism pathway occurs either by hepatic pathway (at low acetone concentrations) or extrahepatic pathway and appeared in excretion (at high acetone concentrations) as both lead to glucose (Isha et al., 2011).

At low concentrations pathway, acetone is appeared in methylglyoxal pathway. On the other hand, at high concentrations pathway, acetone propanediol pathway is involved in gluconeogenesis. Acetone metabolic and excretion appears to be dose-related (Kosugi et al., 1996a). In this respect, exposure to acetone low levels leads to small losses through expiration and vice versa. Acetone appears in the urine when exposure concentrations exceed approximately 15 ppm (Ankrah and Appiah-Opong, 1999). The purpose of this study is to provide public health officials, physicians, toxicologists and other interested individuals or groups with an overall perspective of acetone toxicology inhalation on long run, That will be via presenting background and justification of acetone hazards and dose-response about the risk of acetone inhalation.

MATERIALS AND METHODS

Materials: Animals and experimental design: experiment was carried out on 75 male Wistar rats (aged 75:90 days) with initial body weight 250:300 g. Rats were housed in clean and ventilated cages with constant controlled climate (Faculty of Pharmacy, King Saud University, KSA). All groups, received filtered tap water *ad libitum* and standard rodents chow diet (19.80% protein, 39.25% carbohydrate, 4.41% fat, 13.25% fibre, and 2.76 kcal/g of metabolizable energy).

Research Design: GROUP1 (control group, n=8) : Control rats, without acetone induction. **GROUP2 (n=8):** Rats inhaled 5,000 ppm acetone for 7 hours/daily for 7days. **GROUP3 (n=8):** Rats inhaled 7,000 ppm acetone for 7 hours/daily for 7days. **GROUP4 (n=8):** Rats inhaled 10,000 ppm acetone for 7 hours/daily for 7days.

Methods: Neurobehavioral testing "water maze test" (Faculty of Sciences, King Saud University, KSA)**:** Morris water maze is large round tub opaque water (made white with powdered milk) (1 m x 50 cm, 60 cm in deep) and two small hidden platforms (10 cm in diameter) located at 1-2 cm under water's surface. Rat was placed on a start platform and swim around till found the other platform to stand on. The period of individual rat to find hidden platform (by seconds) was measured daily (Morris et al., 1984).

Biochemical studies (Faculty of Sciences, King Saud University, KSA)**:** Animals were anaesthetized (0.1 ml I.P. of 1% sodium barbiturate) for biochemical measurements [serum glucose level (Goldberg et al., 1994), insulin levels (Larsen et al., 2002), urinary acetone level (Scholl and Iba, 1997) and blood count of RBCs (Isha et al., 2011)]. Blood samples were collected by intravenous (I.V.) of rats tails using heparinizied capillary tubes and stored in EDTA-coated tubes (NTP., 2005). Measurements were occurred at same day of blood samples collecting and repeated daily. Food was withdrawn 10 h before blood collection.

Histopathological investigations (Faculty of Sciences, King Saud University, KSA)**:** At 7th day end, animals were anaesthetized (0.1 ml I.P. of 1% sodium barbiturate), then, immediately, liver, lung and kidney of 5 animals from each group were dissected. Histopathological investigations occurred as samples (2-3 cm^3) were fixed in 10% forma-

Volume : 4 | Issue : 12 | Dec 2014 | ISSN - 2249-555X

lin neutral buffered for 24 hours, washed, dehydrated, cleared, embedded in paraffin and processed into 5 µm sections for light microscopic examinations by routine hematoxylin and eosin stain (Hx & E) (Luiz, and Jose, 2010).

RESULTS

Neurobehavioral testing "water maze test": There was a delaying in rats consumed time to reach final platform in 2nd , 3rd and 4th group that have been inhaled 5000 (ppm), 7000 (ppm) and 10000 (ppm) of acetone/daily for 7 days respectively, when compared to control group. (Table 1).

Table (1): Mean time in seconds which rats consumed to reach final platform. Values expressed as means ± standard deviation. (*)= Significant; P ≤ 0.05 and (**) =High significant; P < 0.01.

	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Group (1)	19±3.1	18±2.85	18±2.57	18±2.22	17±2.42	19±271	18±285
Group (2)	23±3.28*	26±3.71*	30±4.28*	34±4.85**	38±5.42**	42±6.12**	45±6.42**
Group (3)	24±3.42*	28±4.12*	32±4.57*	38±5.42**	43±6.14**	47±6.71**	51±7.28**
Group (4)	27±3.85*	30±4.28*	33±4.71*	43±6.14**	48±6.85**	52±7.42**	57±8.14**

Biochemical studies: In treated groups, there were an increasing in serum glucose concentration levels, accompanied by insulin concentration levels decreasing (Tables 2 and 3), urinary acetone concentration levels increasing (Table 4). All of these results were proportionally associated to inhaled acetone concentration levels, but RBCs count decreasing as it reverse proportionally associated to inhaled acetone concentration levels (Table 5).

Table 2: Mean of serum glucose levels (mg/dL). Values expressed as means ± standard deviation. (*)= Significant; P ≤ 0.05 and (**) =High significant; P < 0.01.

	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Group (1)	70±10.8	71±10.85	72±10.71	71±17.71	70±10.71	71±10.85	72±11.15
Group (2)	78±11.14*	80±11.42*	82±11.71*	88±12.57**	90±12.85**	93±13.28**	96±13.71**
Group (3)	79±11.28*	82±11.71*	85±12.14*	90±12.85**	93±13.28**	95±13.57**	99±14.14**
Group (4)	80±11.42*	84±11.89*	87±12.4*	94±13.42**	97±13.85**	99±14.14**	109±15.57**

Table 3: Mean of serum insulin levels (mg/dL). Values expressed as means ± standard deviation. (*)= Significant; P ≤ 0.05; (**) =High significant; P < 0.01.

	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Group (1)	0.3±0.074	0.31±0.075	0.3±0.074	0.31±0.077	0.32±0.075	0.3±0.074	0.31±0.075
Group (2)	0.47±0.075*	0.45±0.078*	0.42±0.082*	0.37±0.087**	0.34±0.092**	0.31±0.098**	0.28±0.094**
Group (3)	0.43±0.071*	0.43±0.08*	0.4±0.083*	0.36±0.091**	0.33±0.095**	0.3±0.101**	0.27±0.108**
Group (4)	0.42±0.076*	0.41±0.082*	0.38±0.089*	0.31±0.095**	0.31±0.098**	0.28±0.101**	0.25±0.11**

Table (4): Mean of concentration levels of urinary acetone (mg/L). Values expressed as means ± standard deviation. (*)= Significant; P ≤ 0.05 and (**) =High significant; P < 0.01.

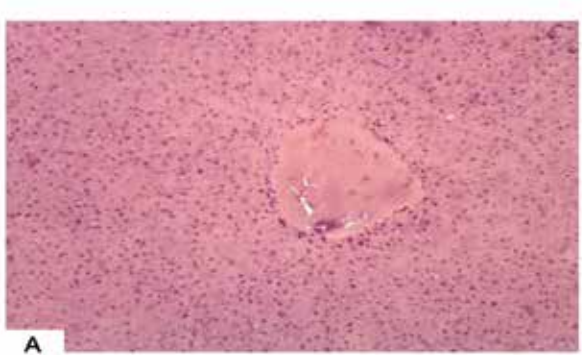
	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Group (1)	0.22±0.0314	0.22±0.0314	0.21±0.031	0.21±0.031	0.23±0.075	0.22±0.0314	0.21±0.031
Group (2)	0.71±0.104*	0.78±0.111*	0.85±0.121*	1.4±0.2**	1.8±0.257**	2.3±0.328**	2.7±0.385**
Group (3)	0.89±0.127*	0.95±0.135*	1.1±0.157*	1.6±0.228**	2.1±0.228**	2.8±0.371**	3.3±0.442**
Group (4)	0.92±0.131*	1.3±0.185*	1.4±0.2*	1.8±0.257**	2.3±0.328**	2.9±0.414**	3.4±0.485**

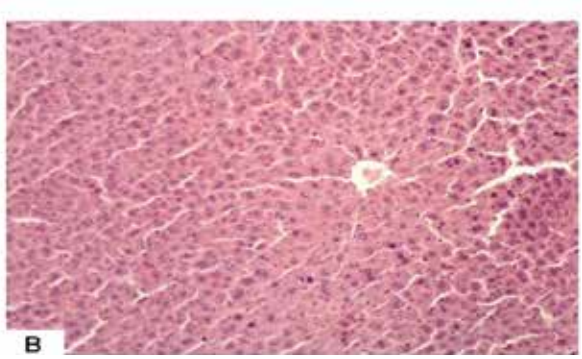
Table (5): Mean RBCs count level (x10^{12} cell/L). Values expressed as means ± standard deviation. (*)= Significant; P ≤ 0.05 and (**) =High significant; P < 0.01.

	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Group (1)	$10.5x10^{12}$ ±1.52	$10.6x10^{12}$ ±1.55	$10.6x10^{12}$ ±1.55	$10.5x10^{12}$ ± 1.52	$10.5x10^{12}$ ± 1.52	$10.6x10^{12}$ ±1.55	$10.5x10^{12}$ ±1.52
Group (2)	$10 x10^{12}$* ±1.42	$9.5x10^{12}$* ±1.35	$8.8 x10^{12}$* ±1.25	$8x10^{12}$** ±1.14	$7.7x10^{12}$** ± 1.1	$7x10^{12}$** ±1.07	$6.4x10^{12}$** ±0.91
Group (3)	$9.7x10^{12}$* ±1.38	$9x10^{12}$* ±1.28	$8.3x10^{12}$* ±1.18	$7.8x10^{12}$** ±1.11	$7.1x10^{12}$** ±1.014	$6.4x10^{12}$** ±0.91	$8x10^{12}$**±0 .85
Group (4)	$9.5x10^{12}$* ±1.32	$8.5x10^{12}$* ±1.21	$8.1x10^{12}$* ±1.15	$7.5x10^{12}$** ±1.07	$6.8x10^{12}$** ±0.97	$6.2x10^{12}$** ±0.88	$5.7x10^{12}$** ±0.8

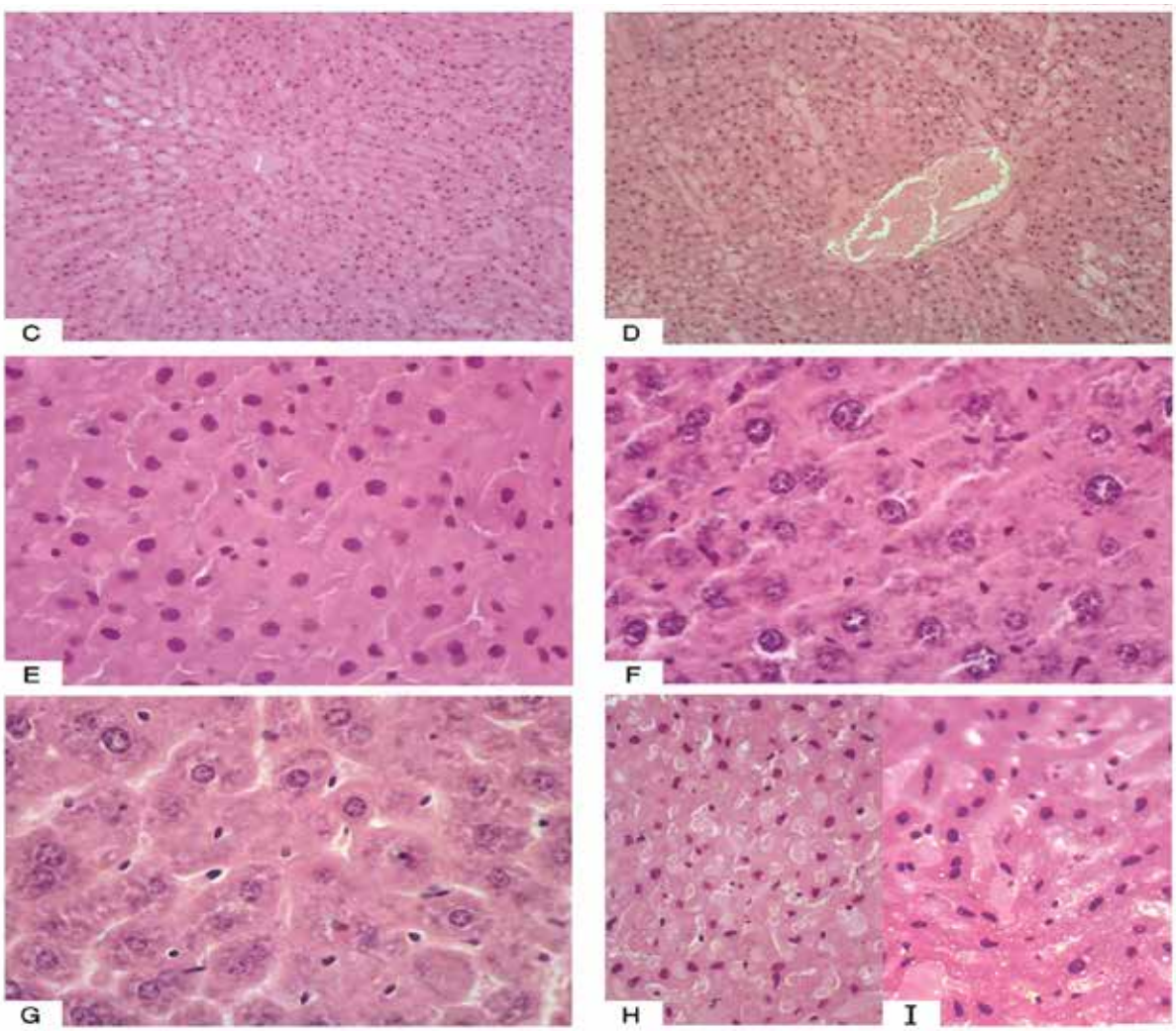
Histopathological studies: Liver: normal structure of liver appeared in the control group with sheets of connective tissue which divided the liver into small hexagonal units (lobules) with a central vein. Polygonal parenchymal cells of liver (hepatocytes) nuclei were distinctly round, with one or two prominent nucleoli (Figures 1A&E). Treated groups livers (Figures 1B,C&D) showed hepatic narcosis, hepatocytes swilling, macrovacuolation and centrilobular hypertrophy. Figures 1F,G,H&I showed necrotic nucleus, degeneration accompanied by apoptotic bodies. These alterations were in different degrees according to inhaled acetone concentration levels, as light effects appeared at level 5,000 ppm of acetone/daily for 7 days, moderate effects appeared at level 7,000 ppm of acetone/daily for 7 days, and sever effects appeared at level 10,000 ppm of acetone/daily for 7 days.

Figure 1: Histopathological findings of subjects livers (transitional section) by Hx&E stain. Normal histological findings were seen in control group: [A(X100)&E(X250)]. Treated groups subjects livers showed histopathological alterations after inhalation of 5,000 ppm of acetone/daily for 7 days [B(X100)&F(X250)], 7,000 ppm of acetone/daily for 7 days [C(X100)&G(X250)] and 10,000 ppm of acetone/daily for 7 days [D(X100),H&I(X250)].

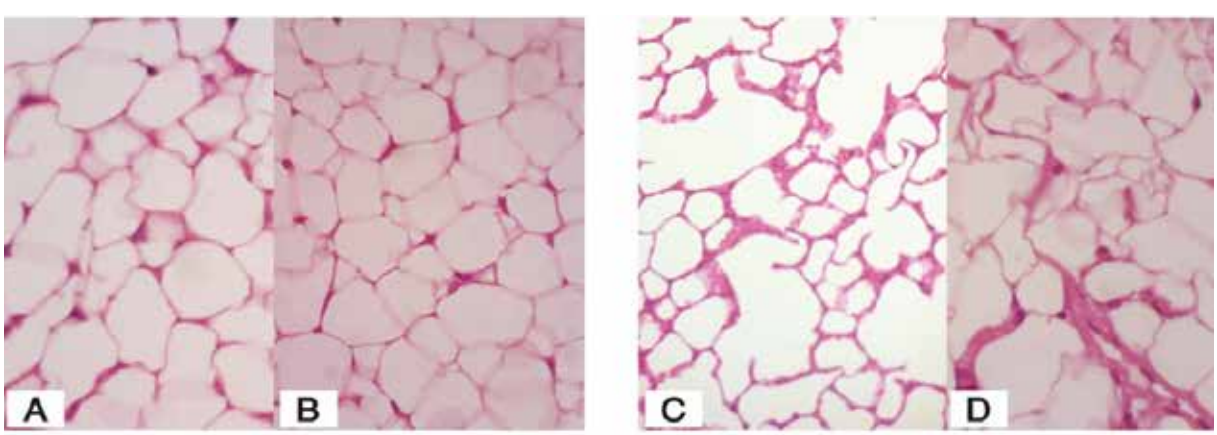




Volume : 4 | Issue : 12 | Dec 2014 | ISSN - 2249-555X



Lung: In control group, lung normal structure appeared with fine lace which was composed of thin-walled alveoli which a single layer of squamous epithelium and thin layer of connective tissue in-between with numerous capillaries (Figures 2A&B). Treated groups rats lungs showed, interstitial fibrosis, alveolar spaces dilatation with rupture in some inter alveolar septa. These histopathological alterations appeared lightly after inhalation of 5,000 ppm of acetone/daily for 7 days (Figures 2C&D), moderately after inhalation of 7,000 ppm of acetone/daily for 7 days (Figures 2E&F), and severely after inhalation of 10,000 ppm of acetone/daily for 7 days (Figure 2G). Also, after inhalation of 10,000 ppm of acetone/daily for 7 days there were congested blood vessels in the alveolar septa, marked dilatation with rupture and pink transudation fluid in some alveolar spaces (edema). (Figure 2G).



Volume : 4 | Issue : 12 | Dec 2014 | ISSN - 2249-555X

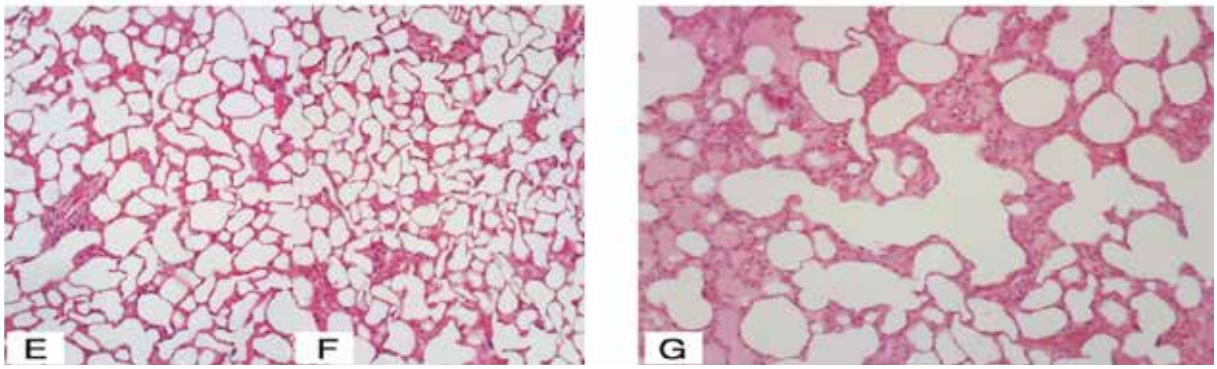
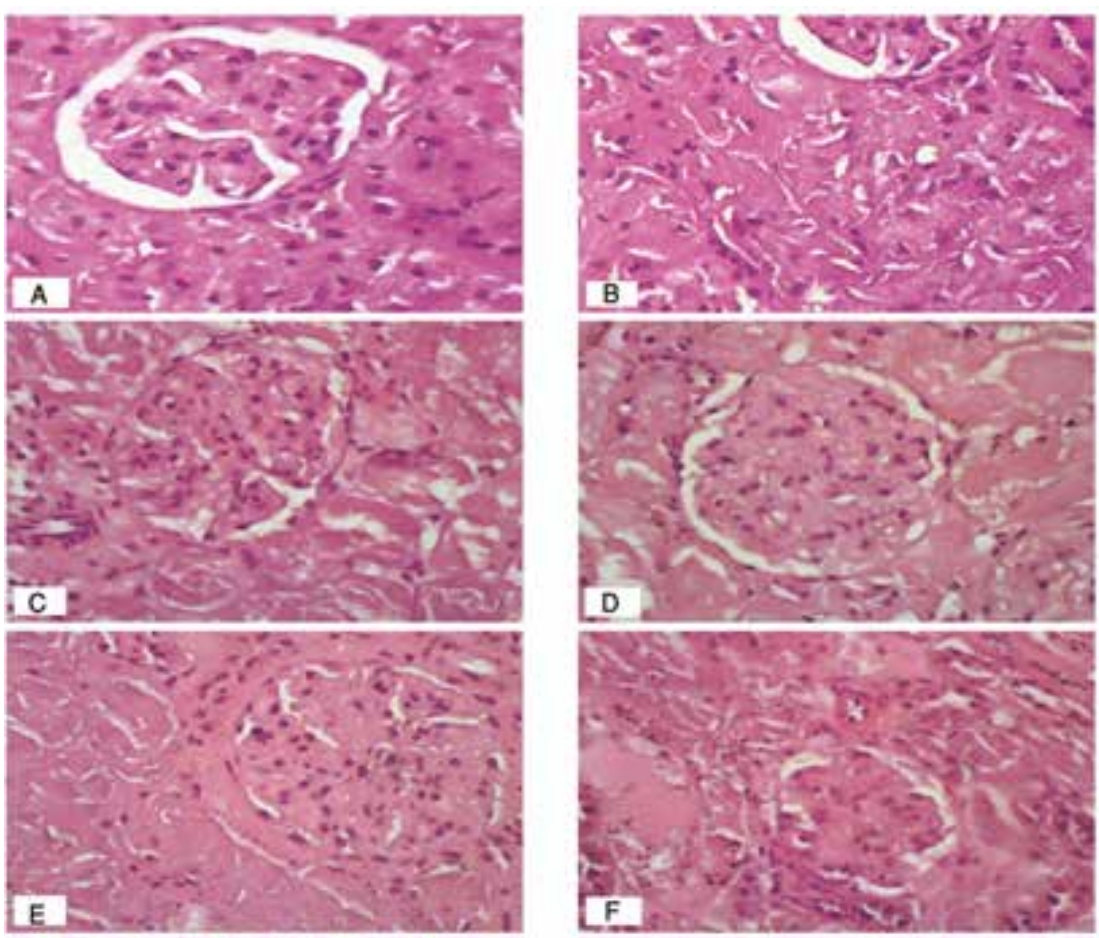


Figure 2: Histopathological findings of subjects lungs (transitional section) by Hx&E stain. Normal histological appearance was seen in control group: [A&B(X250)]. Treated groups rats lungs showed histopathological alterations after inhalation of 5,000 ppm of acetone/daily for 7 days [C&D(X250)], 7,000 ppm of acetone/daily for 7 days [E&F(X100)] and 10,000 ppm of acetone/daily for 7 days [G(X250)].

Kidney: In control group, kidney showed Bowman's capsule which was composed of structure-less basement membrane surrounding each glomerulus (with noticed podocytes) and urinary space appearance, as well as proximal and distal convoluted tubules. Upon capsules inner surface was a continuous layer of flat, epithelial cells, which are continued over glomerulus itself (Figure 3A). Treated groups showed proximal and distal convoluted tubules with destructive lining epithelial cells and congested blood vessels (Figure 3B,C,D). There were appearance of hyaline droplets and proteinaceous casts (Figure 3D,E,F). Cellular infiltrations appeared as fibroses, vacuolation and degenerative alterations between glomeruli and convoluted tubules epithelia cells (Figure 3G,H,I), this appeared severely after inhalation of 10,000 ppm of acetone/daily for 7 days (Figure 3J,K). Sever tubular atrophy, marked tubular diameter reduction and pronounced redundancy of tubular basement membrane with mesanglial cells were observed (Figure 3G,H,I). There were mass cellular edema with completed obliterated of Bowman's capsule with of pyknotic nuclei (Figure 3E,K). All of these histopathological alterations appeared lightly after inhalation of 5,000 ppm of acetone/daily for 7 days, moderately after inhalation of 7,000 ppm of acetone/daily for 7 days, and severely after inhalation of 10,000 ppm of acetone/daily for 7 days.



Volume : 4 | Issue : 12 | Dec 2014 | ISSN - 2249-555X

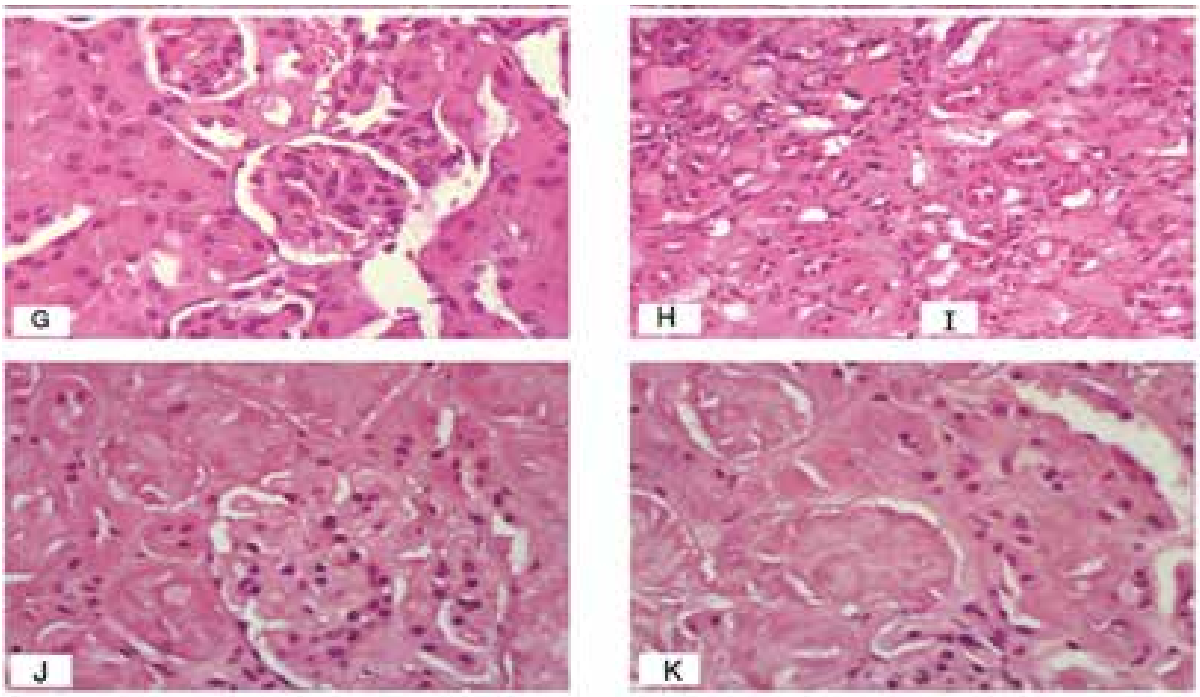


Figure 3: Histopathological findings of rat kidney (transitional section) by Hx&E stain. Normal histological findings were seen in control group: [A(X250)]. Male Wistar rats kidney histopathological appearance after inhalation of 5,000 ppm of acetone/daily for 7 days [B(X250) & G(X250)], 7,000 ppm of acetone/daily for 7 days [C(X250), E(X250), H(X250) & J(X250)] and 10,000 ppm of acetone/daily for 7 days [D(X250), I(X250), F(X250) & K(X250)].

DISCUSSION

The average annual production of acetone is expected to rise at a global rate. Major end of acetone usage can be divided into two separate categories included: i) a chemical feedstock, ii) a formulating solvent for commercial products, therefore, acetone has many favorable properties that make it useful (Andersson and MacGregor, 1994). Acetone is broadly distributed throughout the body, particularly in organs with high water content. Under starvation conditions, high-fat and low-carbohydrate diets, or uncontrolled diabetes, fat is metabolized to form aceto-acetate, which is converted to acetone (Argiles, 1999). Overall, available data indicated that humans and rodents readily absorb acetone by inhalation, ingestion and dermal exposure (Wigaeus et al., 2002).

A positive linear correlation has been shown between acetone concentration levels in the breathing zone (Bruckner and Peterson, 2004), blood and alveolar/urine concentrations (Wang et al., 2001). Collectively, acetone has a rapid absorption via respiratory, gastrointestinal tracts and broad distribution throughout the body into organs with high water content (Christoph et al., 2007). During inspiration, acetone passes through epithelial cells in nasal cavity and dissolves into bloodstream where it is transported, and can cause respiratory tract histopathological alterations (Dahl et al., 1999).

The hepatic route involves acetone conversation to acetol, then acetol in turn converts to methylglyoxal which is converted either directly to glucose or indirectly to D-lactate, which is converted to glucose (Kosugi et al., 1996). Methylglyoxal has been shown to have potentially effects at levels higher than normal in the body, including: genotoxicity (Wieland, 1998) and apoptosis induction (Mast et al., 2005). Methylglyoxal has also been shown to affect glucose tolerance indicating potential concerns for individuals with diabetes (Ankrah and Appiah-Opong, 1999). Acetone exposure to humans can result in diabetes like symptoms, e.g., hyperglycemia and glycosuria (Wigaeus et al., 2002). As discussed by NTP. (2001), hyperglycemia and glycosuria are commonly seen in cases of acetone poisoning.

Dietz et al. (2001) showed hematological effects in the form of reduced erythrocyte counts. Both species (human and rodents) eliminate acetone from the body efficiently (Wang et al., 2001). Other endpoints were noted that acetone including significant changes in hematology level in males albino rats as the changes in red blood cells count parameter was consistent with mild anemia, a depressed regenerative response, an inhibition of visual vigilance, motor imbalance and decreasing in memory scanning and avoidance behavior (Dick et al.,1999). Acetone was evaluated for effects on a delayed match-to-sample task in male juvenile baboons (Geller et al., 2000a); decreased duration of immobility in a behavioral despair swimming test in mice (DeCeaurriz et al., 2001) and in coordination in a "match to sample" behavioral test in rats (Geller et al., 2000b).

Carcinogenicity assessment provides information on carcinogenic hazard potential of acetone in qualitative and quantitative estimates of risk of its inhalation exposure. The information includes a weight-of-evidence judgment of likelihood that acetone is a human carcinogen and the conditions under which its carcinogenic effects may be expressed (Scholl and Iba, 1997). Dose-related of acetone increases incidence and severity of centrilobular hepatocellular hypertrophy and nephropathy symptoms as tubular degeneration and hyaline droplet accumulation (NTP, 2005).

CONCLUSIONS AND RECOMMENDATIONS

An examination of all available information on acetone bio-

Volume : 4 | Issue : 12 | Dec 2014 | ISSN - 2249-555X

logical activity indicated that acetone vapors were mildly toxic after both direct contact or systemic absorption. Primary effects of acute high-level exposure appeared as central nervous system depression. Present data indicated that acetone appeared to pose a neurotoxic, tissue alterations, or generally health hazard at reported concentration levels which are found in higher levels than the recommended ones which should be in environment or for consumed. We recommended for women consumer who are always in contact with acetone inhalation to take precautions.

REFERENCE

Anderson, D. and MacGregor, D. (1994). The effect of solvents upon the yield of revertants in the Salmonella/activation mutagenicity assay. Carcinogenesis., 1:363-366. | Ankrah, N. and Appiah-Opong, R. (1999). Toxicity of low levels of methylglyoxal: depletion of blood glutathione and adverse effect on glucose tolerance in mice. Toxicol. Lett., 109:61-67. | Argiles, J. (1999). Has acetone a role in the conversion of fat to carbohydrate in mammals. TIBS., 11:61-63. | ATSDR. (Agency for Toxic Substances and Disease Registry). (2004). Toxicological profile for acetone. U.S. Department of Health and Human Services, ATSDR, Atlanta, GA. | Budavari, S., Neil, M. and Smith, A. (2002). The Merck Index. Whitehouse Station, NJ: Merck & Co., Inc., p. 12. | Bruckner, J. and Peterson, R. (2004). Evaluation of toluene and acetone inhalant abuse. II. model development and toxicology. Toxicol. Appl. Pharmacol., 61:302-312. | Christoph, G., Keller, D. and Stadler, J. (2007). Subchronic inhalation of acetone vapor. J. Mol. Cell Bio., 24:124-128. | Clewell, H. Gentry, P. and Gearhart, J. (2001). Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acetone. Toxicol. Sci., 63:160-172. | Dahl, A., Snipes, M. and Gerde, P. (1999). Sites for uptake of inhaled vapors in beagle dogs. Toxicol. Appl. Pharmacol., 109:263-275. | Deceaurriz, J., Micillino, J., Bonnet, P. and Guenier, J. (2001). Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett., 9:137-143. | Dick, R., Setzer, J. and Taylor, B. (1999). Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. Br. J. Ind. Med., 46:111-121. | Dietz, D., Leininger, J. and Rauckman, E. (2001). Toxicity studies of acetone administered in the drinking water of rodents. Fund. Appl. Toxicol., 17:347-360. | Ernstgard, L., Gullstrand, E. and Johanson, G. (1999). Toxicokinetic interactions between orally ingested chlorzoxazone and inhaled acetone or toluene in male volunteers. Toxicol. Sci., 48:189-196. | Geller, I., Gause, E. and Kaplan, H. (2000a). Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. Pharmacol. Biochem. Behav., 11:401-406. | Geller, I., Hartman, R. and Randle, S. (2000b). Effects of acetone and toluene vapors on multiple schedule performance of rats. Pharmacol. Biochem. Behav., 11:395-399. | Gentry, P., Covington, T. and Andersen, M. (2002). Application of a physiologically based pharmacokinetic model for isopropanol in the derivation of a reference dose and reference concentration. Regul. Toxicol. Pharmacol., 36:51-68. | Goldberg, M., Johnson, H. and Pozzani, U. (1994). Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvent vapors on pole-climb performance in rats. Am. Ind. Hyg. Assoc. J., 25:369-375. | Isha, B., Ragini, S., Sheetal, M., Khushbu, P. and Umesh, G. (2011). Lead induced alterations in blood cell counts and hemoglobin during gestation and lactation in Swiss albino mice. J.of Cell and Mol. Bio., 9:69-74. | Kosugi, T., Yasugi, T. and Mizunuma, K. (1996). Curvi-linear relation between acetone in breathing zone air and acetone in urine among workers exposed to acetone vapor. Toxicol. Lett., 62:85-91. | Larsen, J., Lykkegaard, M. and Ladefoged, O. (2002). Infertility in rats induced by 2,4-hexanedione in combination with acetone. Pharmacol. Toxicol., 69:43-46. | Luiz, D. and Jose, C. (2010). Pasic histology and histological techniques. McGraw-Hill Publishing Co. 12th edition., Chapter 16:142-150. | Mast, T., Evanoff, J. and Rommereim, R. (2005). Inhalation developmental toxicity studies: teratology study of acetone in mice and rats. Int. Arch. Occup. Environ. Health., 50:112-119. | Morris, R. (1984). Developments of a water-maze procedure for studying spatial learning in the rat. J. neuroscien. Meth. 11:47–60. | NTP. (National Toxicology Program). (2001). Toxicity studies of acetone (CAS No. 67-64-1) in F344/N rats and B6C3F1 mice (drinking water studies). NTP. TOX., 3: 91-3122. | Scholl, H. and Iba, M. (1997). Pharmacokinetics of and CYP1A induction by pyridine and acetone in the rat: interactions and effects of route of exposure. Xenobiotica., 27:265-277. | Wang, G., Maranelli, G. and Perbellini, L. (2001). Blood acetone concentration in "normal people" and in exposed workers 16 h after the end of the shift. Int. Arch. Occup. Environ. Health., 65:285-289. | WHO. (World Health Organization). (1998). Environmental health criteria 207. acetone. WHO, Geneva. | Wieland, O. (1998). Ketogenesis and its regulation. Adv. Metab. Disorders., 3:1-47. | Wigaeus, E., Holm, S. and Åstrand, I. (2002). Exposure to acetone: uptake and elimination in man. Scand. J. Work Environ. Health., 7:84-94. |