Egyptian Journal of Occupational Medicine, 2025 49 (3) : 53 - 69

THE USE OF CYTOKERATIN 18 AS A BIOMARKER FOR EARLY DETECTION OF TOXICANT -ASSOCIATED STEATOHEPATITIS AMONG WORKERS IN PAINT INDUSTRY.

BY

El-Shafy WS and Helmy NM

Department of Occupational and Environmental Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

Corresponding Author: *El-Shafy WS.* ***E-mail:*** *wessam_sabry@kasralainy.edu.eg*

DOI: *10.21608/ejom.2025.390726.1374*

Submit date: *2025-06-01* ***Revise date:*** *2025-06-26* ***Accept date:*** *2025-06-28*

Authors' contributions: *Both authors contributed equally in this work.*

Abstract

Introduction: Volatile organic compounds (VOCs) are used as solvents in the paint industry. Industrial exposure to VOCs, have been associated with toxicant-associated steatohepatitis (TASH) due to necrosis of liver cells. Cytokeratin 18 (CK18) is an intermediate filament protein highly expressed by the liver. Recently (CK18) M65 and M30 are used as alternative noninvasive biological markers for detection of liver injury due to chemical exposures. **Aim of Work:** To evaluate the use of Cytokeratin 18 (CK18 M65 and CK18M30) for early detection of Toxicant-Associated Steatohepatitis (TASH) among workers exposed to volatile organic compounds in the paint industry. **Materials and Methods:** This cross section comparative study included 46 exposed workers and 46 nonexposed office workers as control. History, clinical examination, AST, ALT, GGT, CK18 M65, and CK18 M30 were examined for both groups. Environmental study was done. **Results:** All environmental samples revealed high levels of VOCs and poor Indoor Air Quality (IAQ). AST, ALT, GGT were significantly higher among exposed workers but AST and ALT were still within normal range. CK18 M65 was significantly higher among the exposed group compared to non exposed (599.2 ±193.9, 240 ± 51.8, respectively), while CK18 M30 showed no significant difference (165.39 ± 34.57, 156.33 ± 16.1, respectively), between both groups. CK18 M30/CK18 M65 was significantly lower among the exposed group compared to none exposed (26.01± 3.75, 62.95± 5.54, respectively). CK18 M65 correlated positively with duration of exposure, ALT and GGT among exposed workers. **Conclusion:** Cytokeratin18 can be used as biomarkers for early detection of TASH among paint workers. **Recommendations:** Toxicant Associated-Steotohepatitis should be considered among non obese, non alcoholic workers exposed to volatile organic compounds in the paint industry.

Keywords: Cytokeratin 18 (CK18), Volatile organic compounds (VOCs), Indoor Air Quality (IAQ) and Paint industry.

Introduction

Exposure to industrial and environmental chemicals is a known cause of liver toxicity in humans. Among these conditions is toxicant-associated steatohepatitis (TASH), which is a subtype of non-alcoholic steatohepatitis (NASH) linked to chemical exposure, particularly in industrial settings (Anna and Juliane, 2018- WHO, 2024).

Toxicant-associated steatohepatitis (TASH) represents an advanced form of toxicant-associated fatty liver disease (TAFLD), and progression in some cases lead to hepatic fibrosis (Cave et al., 2010 and Wahlang et al., 2013). TASH develops in individuals exposed to industrial chemicals while lacking conventional risk factors like excessive alcohol intake or obesity (Banrida et al., 2013).

TASH can develop even with normal levels of liver enzymes. This suggests that TASH prevalence may be underestimated, and that early diagnosis of TASH represents a clinical challenge, because conventional liver function tests (e.g., ALT, AST) lack specificity, (Veeral et al., 2017), and liver biopsy, is invasive and costly (Feldstein et al., 2009).

Cytokeratin 18 (CK18), which is a cytoskeletal protein present in hepatocytes and epithelial cells, is released into the extracellular space during cell death and can be detected in the serum (Miwa et al., 2024). Two measurable forms exist: total CK18 (CK18 M65), reflecting total necrotic cell death (uncontrolled cell death due to injury or disease and leading to inflammation) and the caspase 3-cleaved fragment (CK18 M30), specifically indicating apoptotic cell death (programmed, controlled cell death without inflammation) (Sabrina et al., 2023).

Clinically, elevated CK18 M30 is of limited value for diagnosing NASH (Huai et al., 2023) .Whereas CK18 M65 is gaining recognition as a potential biomarker for TASH particularly in cases with normal ALT, AST, and CK18 M30 levels (Feldstein et al., 2009)

Volatile organic compounds (VOCs) are colorless, flammable liquids that are commonly utilized as industrial solvents such as toluene, benzene, and xylene, as well as byproducts derived from petroleum (Banrida et al., 2024).

Workers in industries such as painting, printing, rubber manufacturing, plastic manufacturing, and petrochemi-

cals are regularly exposed to mixtures of hepatotoxic volatile organic compounds (VOCs) (Jones and Brischke, 2017). Prolonged workplace exposure to VOCs has been associated with toxic steatohepatitis and liver cancer in industrial workers (Banrida et al., 2024).

High-level workplace exposures to VOCs may lead to liver cell injury. However, further investigation is needed to assess the potential risks of chronic low-level environmental exposures (Wahlang et al., 2013). Also, the confounding factors (e.g., alcohol use, and smoking) may influence liver injury biomarkers (Wei et al., 2023)

Aim of Work

To evaluate the use of Cytokeratin 18 (CK18 M65 and CK18 M30) for early detection of

Toxicant-Associated Steatohepatitis (TASH) among workers exposed to volatile organic compounds in the paint industry.

Materials and Methods

Study design: This was a cross-sectional comparative study.

Place and duration of the study: The study was conducted in a paint factory in El Obour city, Cairo, Egypt ; from March to May 2025.

Study sample: The study included 92 participants who were divided into exposed and non exposed groups. The exposed group included 46 workers who are working in a paint factory and exposed to volatile organic compounds (VOCs) such as xylene, toluene, and acetone which are used as solvents in the paint manufacturing processes. The mean duration of exposure was 18.6 7.4 years. The non-exposed (control) group included 46 office workers who aren't exposed to any solvents in administrative and security sections in the same factory.

Sample size: Based on published literature from Matt et al., 2011; calculated sample size for current study was 92 (46 exposed and 46 non exposed) by using Easy Med Stat sample size calculator for analytical study with alpha error of 5.0% (type1 risk), beta error of 20% (type 2 risk) and power (1-β power) of 80% with drop-out rate estimated at 10%.

Inclusion criteria: All studied participants were males to avoid sex influence on measured CK18 levels as reported by Lingling et al., 2020. Exposed group: workers who are ex-

posed to VOCs for more than one year. Non exposed group: employees from administrative and security sections in the same paint factory with no history of exposure to any type of volatile organic compounds (VOCs).**Exclusion criteria:** Participants with other types of exposures from other jobs, or with a history of any liver diseases, alcohol consumption, diabetes, autoimmune diseases, metabolic diseases and/or obese participants with BMI ≥ 30.

Study methods:

Both groups were subjected to:

1. A specially designed questionnaire including the following**:** Socio demographic characteristics: age, special habits such as smoking or alcohol abuse. Medical and occupational histories to clarify occupational exposure, duration of work, and use of personal protective equipment. Past and family histories were taken.

2. Full clinical examination

3. Laboratory investigations:

A blood sample of 10 ml was taken from each subject. Samples were allowed to clot and stored in aliquot at –20°C for later use**.** The following tests were done for all samples:

a. Total Cytokeratin 18 (Ck18 M65) and Cytokeratin 18 Caspase 3- cleaved fragment (CK18 M30): The concentrations of Cytokeratin 18 (CK18) were quantified using **PEVIVA M65 and M30 ELISA kits** (TECO medical AG, Sissach, Switzerland). Absorbance readings were obtained using a Filter Max F3 Multi-Mode Microplate Reader, with data analysis performed through SoftMax Pro software (v7.0.3).

b. Liver enzymes (ALT, AST, and GGT): Measurement is done through fully automated analyzers that operate on photometric principles.

4. Environmental sampling:

Air sampling for TVOCs was carried out inside the actual working areas by a specialized company for workplace environmental monitoring using QRAE Plus, multi gas monitoring system, S: M01C002068.

Environmental air sampling for total volatile organic compounds (TVOCs) was done in the studied factory. Also the indoor Air Quality (IAQ) was evaluated according to the level of TVOCs. This was consistent with (Tony, 2022) who mentioned that since many chemicals in paint production processes fall into the group of VOCs, it is not possible to measure each one separately.

Measurements were taken in seven selected exposure areas (colour mixing room, colour blending machine room, raw material laboratory, cylinder grinding machines' area , grinding machines area, doughs laboratory, and stamping machine's area). Measurement devices were placed as near as possible to the breathing zone of workers but were not affecting their workspace at a height of approximately 1.2 - 1.5 meters from the ground (head level).

Consent

A written consent was obtained from each participant. Strict confidentiality was followed.

Ethical Approval

The Research Ethics Committee of the Faculty of Medicine, Cairo University approved the study protocol (N-38-2025).

Data Management

Pre-coded data was collected and statistically analyzed using the statistical package of social science software program, (SPSS) version 21.Data was summarized using mean and standard deviation for quantitative variables. Independent Samples t test was done for comparison of quantitative variables between the two studied groups. Pearson Correlation coefficient (Pearson's r) test was done to find relations between quantitative variables. P value less than 0.05 was considered statistically significant and less than 0.001 was considered highly statistically significant.

Results

Table (1) Environmental measurements of TVOCs# in the selected areas of paint production process environment and Indoor Air Quality Standards.

Selected Work areas	Area 1 Color mixing room	Area 2 Color blending machine	Area 3 Raw materials labora-tory	Area 4 Cylinder Grinding machines	Area 5 Grinding machines	Area 6 Doughs laboratory	Area 7 Stamping machine
Environmental measurements TVOCs# (ppm)	58	41	39	36	46	36	52
Standards for IAQ ##according to TVOCs level		TVOCs level (ppm)			IAQ level		
	WHO[a]	> 0.61			Outside classes Greatly increased		
		0.20 - 0.61			Level 4 significantly increased		
		0.10 - 0.20			(Level 3 slightly increased(harmless		
		0 - 0.05			Level 1 target value		
	GFEA[b]	2.2 - 5.5			Unhealthy		
		0.66 - 2.2			Poor		
		0.22 - 0.66			Moderate		
		0.065 - 0.22			Good		
		0 - 0.065			excellent		
	RESET[c]	< 0.25			Acceptable		
		< 0.2			High performance		
	LEED[d]	< 0.25			Green building standard LEED		

#:TVOCs: total volatile organic compounds ##:IAQ:i Indoor Air Quality

[a]:World Health Organization, commission for clean air of the Austrian Academy of Sciences(KRL).Vienna(2014). [b]German Federal Environmental Agency.DOI:10.1007/s00103-007-0290-y. [c]RESET Air Standard for commercial Interiors v2.0, 2018. [d]Leadership in Energy and Environmental Design .

Table (1) showed that all environmental measurements of TVOCs in different areas in the factory were high and associated with poor indoor air quality according to the recommended standards of the mentioned organization and guidelines. The highest concentration was in the area1 (color mixing room, 58 ppm) and the lowest concentration was in the areas 4 and 6 (Cylinder Grinding machines and doughnuts laboratory, 36 ppm each).

Table (2): Socio demographic characteristics of the studied groups.

Variables	Exposed (No= 46)	Non exposed (No = 46)	t	P-value
Age (years)	46.17 ± 5.30	44.60± 6.7	1.35	>0.05
BMI[a] (kg/m^2)	27.2±2.4	26.2 ± 3.9	1.33	>0.05
Smoking index	16.08 ± 2.33	15.93 ± 2.10	0.33	>0.05

[a]:BMI: Body Mass Index.

Table (2) showed that there was no statistically significant difference between the exposed and non exposed groups as regard to age, BMI, and smoking index.

Table (3): Liver enzymes of the studied groups.

Items	Exposed (No = 46)	Non-Exposed (No = 46)	r	P-value
AST[a] (U/L)	18.60± 3.83	16.58 ± 4.32	2.14	**< 0.05**[*]
ALT[b] (U/L)	24.86 ± 2.64	18.36 ± 3.58	9.89	**< 0.001**[**]
GGT[c] (U/L)	45.46 ± 5.32	16.32 ± 4.45	28.45	**< 0.001**[**]

[a]:AST: Aspartate aminotransferase, [b]:ALT: Alanine aminotransaminase, [c]: GGT: Gamma-glutamyl transferase [*]: Statistically significant [**]:Highly statistically significant

Table (3) showed that there was a statistically significant difference ($p < 0.05$) among the studied groups as regards the serum level of AST and highly statistically significant difference ($p < 0.001$) regarding the serum level of ALT; although both were within the normal range (0-40 IU/L). Moreover, the serum level of GGT revealed a highly statistically significant difference $P < 0.001$ between both groups.

Table (4) Serum CK18 M65, CK18 M30, and CKM65/CKM30 levels of the studied groups.

Items	Exposed group No =46 Mean ± SD	Non exposed group No =46 Mean ± SD	t	P-value
CK18 M65 (U/l)[a]	599.2 ±193.9	240 ±51.8	12.1	**<0.001****
CK18 M30 (U/l)[b]	165.39± 34.57	156.33 ± 16.1	1.61	>0.05
CK18 M30/CK18 M65[c]	26.01± 3.75	62.95± 5.54	37.39	**<0.001****

[a]:CK18 M65: total Cytokeratin 18, [b]:CK18 M30: Caspase3-cleaved fragment . [c]:CK M65/CK M30: total Cytokeratin 18/Caspase3-cleaved fragment ratio. *: Statistically significant. **:Highly statistically significant

Table (4) showed that the serum level of Cytokeratin 18 M65 was highly statistically significant among the exposed group compared to non exposed $p < 0.001$. No statistically significant difference $P > 0.05$ was found as regards serum level of cytokeratin18 M30 between the studied groups. Moreover, CK18 M30/CK18 M65 ratio was highly statistically significantly lower ($p < 0.001$) among the exposed group compared to the non exposed.

Table (5): Correlation between serum levels of total Cytokeratin 18(CK18 M65) with liver enzymes and duration of exposure to TVOCs.

Parameters	CK18 M65	
	r	P
AST[a] (U/L)	0.22	>0.05
ALT[b] (U/L)	0.50	**<0.001****
GGT[c] (U/L)	0.60	**<0.001****
Duration of exposure to TVOCs[d] (yrs)	0.32	**<0.05***

[a]:AST:Aspartate aminotransferase, [b]:ALT:,Alanine aminotransaminase, [c]:GGT:gamma-glutamyl-transferase, [d]:TVOCs: Total volatile organic compounds *:Statistically significant **:Highly statistically significant

Table (5) showed a highly statistically significant positive correlations between the serum level of Cytokeratin 18 M65 with ALT, and GGT; $P < 0.001$ and statistically significant positive correlation between Cytokeratin 18 M65 and duration of exposure to TVOCs; $P < 0.05$ among the exposed group. In contrast, the correlation between Cytokeratin 18 M65 and AST was statistically non significant; $P > 0.05$.

Discussion

Volatile organic compounds (VOCs) are used as solvents in a wide range of industrial and chemical applications (Cruz and Bowen, 2021). Steatohepatitis is a common liver cell pathological finding due to environmental or industrial toxicants (Toxicant associated steatohepatitis, TASH) (Swati et al., 2015).

The current study aimed at evaluating the use of Cytokeratin 18 (CK18) M65and M30 as biomarkers for early detection of toxicant- associated steatohepatitis due to exposure to total volatile organic compounds (TVOCs). This helped for early detection of chemically induced liver cell injury mainly toxicant-associated steatohepatitis (TASH) among exposed workers in the paint industry.

Environmental study revealed that there were high exposure levels of TVOCs with poor IAQ according to the recommended standards by world health organization (WHO) and others in all selected areas of the work environment (Table1). Also, the highest exposure level (58 ppm) was detected in color mixing room (area 1).This was in accordance with Safiye et al., 2023 who measured VOCs in different sectors in paint factories and found high exposure level (92489.91± 0.65 ug/mg^3 or 92.49ppm) in the paint production areas.

The two studied groups were matched as regards their age, body mass index (BMI) as all participants were non obese, (BMI < 30) (Table 2) which exclude the association between obesity and aggravation of nonalcoholic fatty liver disease (NAFL) (Jayavardhan et al., 2023).

In addition, the two groups were matched as regards to smoking index which neutralise the effect of smoking as a source of residential exposure to VOCs (Gresner et al., 2021) and also, neutralise its hepatotoxic effect between the two groups as mentioned by Jung et al., 2019 that smoking has been proposed to contribute to early liver disease onset and advanced liver fibrosis (Table 2).

There was a statistical significant difference as regards aspartate aminotransferase (AST) and alanine aminotransaminase (ALT) between the groups (Table 3) but both enzymes are within the normal range. This was consistent with cave et al., 2011 who found that workers exposed to VOC as vinyl chloride had been associated with Toxicant

Associated Steatohepatitis (TASH) with normal both liver enzymes. In contrast, Perez et al., 2006 who studied a group of petrochemical workers in Argentina exposed to VOCs and found that 14 out of 27 workers had fatty liver associated with elevated liver enzymes. This controversy may be due to the type of VOCs to which the workers were exposed and/or the duration of exposure to VOCs.

There was a statistical significant difference between the studied groups as regards serum level of GGT which was higher among the exposed group (Table 3) which was in harmony with Lui et al., 2009 who demonstrated an increase of serum level of GGT associated with exposure to a mixture of VOCs. This finding may be explained by first; the ability of VOCs to cause oxidative stress and inflammatory response (Qianyong et al., 2024) and GGT is considered a marker of oxidative stress (Ebenezer et al., 2020).

This oxidative stress leads to liver cell injury mainly necrosis due to high exposure level of VOCs (Table 1). This explanation was in accordance with Saito et al., 2006 who reported that high exposure to oxidative stress leads to necrotic cell death.

Second; Hideki et al., 2020 noticed that elevated GGT is associated with high risk of liver injury in nonalcoholic fatty liver disease (NAFLD) in the absence of metabolic diseases. The elevation of serum GGT level associated with the high exposure to VOCs and exclusion of alcohol intake and metabolic diseases (as diabetes) in the exposed group went with the presence of chemically associated liver injury namely toxicant associated steatohepatitis (TASH). Moreover, this finding is agreed with Weber et al., 2022 who reported elevated GGT associated with drug hepatotoxic exposure.

Based on Lee et al., 2020 who reported that CK18 has been suggested as a unique biomarker of nonalcoholic steatohepatitis (NASH) and TASH in the presence of chemical exposure. There was a statistical significant difference in the serum level of Cytokeratin 18 M65 (CK18 M65, total Cytokeratin 18) between the two studied groups but there was no statistical significant difference of the serum level of Cytokeratin 18 M30 (CK18 M30, Cytokeratin 18 Caspase 3-cleaved fragment) between them (Table 4).

In the current study the level of CK18 M65 was statistically significant-

ly high (P < 0.001) among the exposed group and the level of CK18 M30 was within normal in both groups with no statistical significant difference(Table 4). These findings were consistent with Cave et al., 2011 who found high level of CK18 M65 (>300) with normal level of CK18 M30 (< 200 U/l) in the suspected TASH group and normal level of CK18 M65 and CK18 M30 in the non exposed group.

There was a high CK18 M65 levels among the exposed group (Table 4) accompanied with normal CK18 M30 level, normal range of liver enzymes (Table 3), negative history to alcohol intake, and negative history of metabolic diseases especially diabetes mellitus; all these findings were strongly indicated the presence of TASH among the exposed group due to exposure to high level of TVOCs (chemical exposure).

This is partially consistent with Clair et al., 2018 who used serum CK18 as a biomarker of liver cell injury among workers exposed to polychlorinated biphenyl (PCBs) and found that mean CK18 M65 was significantly higher in TASH than the control group and its level was more than (>300 U/l.) .In contrast to the current study he found a statistically significant difference between the TASH and control group with regards to CK18 M30 but its level was still lower than (<200 U/l) which also went with TASH. This difference may be due that the studied groups were matched as regards age, sex, race, BMI, special habits (as drinking alcohol) and medical history(as diabetes) in contrast to Clair et al., 2018 who had unmatched groups.

CK18 precise insight into liver cell death mechanism (either necrosis or apoptosis) as reported by lee et al., 2020, Banrida et al., 2021 that the presence of CK18 M65 is indicative of necrotic cell death in contrast, cleavage of CK18 into Caspase-cleaved M30:CK18 M30 fragments due to activation of cell death pathways is indicative of apoptotic cell death. The pattern of serum CK18 M65 and CK18 M30 (high level of Ck18 M65 which indicated neurotic liver cell injury and normal level of CK18 M30 which excluded apoptotic liver cell injury) together with normal liver enzymes (Table 3) in the current study suggested the necrotic liver cell injury which also went with TASH (Table 4). These findings agreed with Cave et al., 2010 who described TASH among non obese workers highly exposed to VOCs (vinyl chloride) when

liver enzymes were normal CK18 M65, but CK18 M30, was elevated with normal serum transaminases and categorized TASH as a necrotic liver disease. Also, this was in harmony with Swati et al., 2015 who reported that necrosis is the primary cause of death in TASH due to hepatotoxic exposure with normal liver transaminases (AST, ALT).

In addition, CK M30/CK M65 ratio could help in distinguishing between TASH from NASH depending on the difference of liver cell mechanism (either necrosis or apoptosis). The - study revealed a statistically significant lower CK M30/CK M65 among the exposed group. This finding supported the above high CK18 M65 with predominantly necrotic cell death demonstrated in the current study(Table 4) and was in accordance with Cave et al., 2011 who found statistically significantly lower CK M30/CK M65 in the suspected TASH group than the healthy group among chemically exposed workers (elastomer/ polymer workers).

There was a statistically significant positive correlation between CK18 M65 and ALT among the studied group (Table 5). This finding agreed with Simran et al., 2024 who reported that ALT is the specific liver enzyme which reflects liver cell necrosis and steatosis. Also, it was in harmony with the previously detected CK18 M65 which also reflected the necrotic cell death among the exposed group and explained by suspected liver cell necrosis and TASH due to exposure to VOCs.

Additionally, the study demonstrated a statistically non significant positive correlation between CK18 M65 and AST (Table 5) which may be explained as AST is less specific than ALT in necrotic liver cell injury (Dauris, 2025).These findings were consistent with (Benash et al., 2020) who found the same correlations in their previous study.

Moreover, the study revealed the presence of statistically significant positive correlation between serum level of CK18 M65 and serum levels of GGT (Table 5). Although this correlation was not done in the previous studies, it supported the above previous findings which revealed that both (CK18 M65 and GGT) were high and mainly related to necrotic liver cell injury as reported by Weber et al., 2022 on a group of individuals who had hepatotoxicity with a predominant GGT elevation.

Serum level of CK18 M65 as a biomarker of necrotic liver cell injury

correlated positively with the duration of exposure to TVOCs (Table 5) .This finding was in accordance with Heeley-Hill et al., 2021 who reported that occupational exposure to VOCs is associated with severe risk.

Conclusion

Significantly high serum levels of CK18 M65 with normal serum levels of CK18 M30 and liver transaminases (ALT, AST) and high levels of GGT were detected among the exposed workers. The pattern of the measured serum CK18 M65 and M30 reflected the necrotic liver cell injury associated with TASH among the exposed group. Serum level of CK18 M65 correlated positively with serum level of ALT, serum level of GGT, and duration of exposure to VOCs.

Toxicant Associated-Steotohepatitis (TASH) should be considered among non obese ,non alcoholic workers exposed to volatile organic compounds (VOCs) in the paint industry. Cytokeratin 18 M65 and M30 can be used as simple, noninvasive biomarkers for early detection of TASH associated with exposure to VOCs in the paint industry. Also, elevated serum level of GGT with normal liver transaminases and absence of obstructive cholestatic diseases among VOCs exposed workers should be considered as another indicator of the presence of necrotic liver cell injury, mainly TASH which needs further investigation.

Recommendations

Close follow up and future ultrasound and liver biopsy should be performed for workers with the same biochemical changes and highly suspicious of toxicant-associated steatohepatitis.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgment

The authors would like to express their deepest gratitude to all of the studied subjects who generously agreed to participate in this study.

References

1. Anna LL and Juliane IB (2018): Interaction of volatile organic compounds and underlying

liver disease: a new paradigm for risk. Biol Chem; 25; 399(11):1237–48. DOI: 10.1515/hsz-2017-0324.

2. Banrida W, Hong G, Shesh NR, Rachel JK, Craig JM, et al. (2024): Workplace exposure standards for airborne contaminants. Safe Work Australia. Available at: www.safeworkaustralia.gov.au.
3. Banrida W, Juliane IB, Heather BC, Heather J , Bellis-Jones K ,et al. (2013): Toxicant-associated steatohepatitis .Toxicol Pathol; 21;41(2):343-60. DOI: 10.1177/0192623312468517.
4. 4- Banrida W, Tyler C , Hong G, Tatiana K, Rachel J, et al. (2021): Associations Between Residential Exposure to Volatile Organic Compounds and Liver Injury Markers. Toxicol sci; 185 (1): 50–63. DOI: 10.1093/toxsci/kfab119.
5. Benash A, Anam R, Shireen J , and Abdul R (2020): Association of liver biomarkers and cytokeratin-18 in Nonalcoholic fatty liver disease patients. Pak J Med Sci; 36(3):387–90. DOI: 10.12669/pjms.36.3.1674.
6. Cave M, Falkner K, Ray M, Joshi-Barve S, Brock G, et al. (2010): Toxicant-Associated Steatohepatitis in Vinyl Chloride Workers. Hepatology; 51(2): 474-81. DOI:10.1002/hep.23321.
7. Cave M, Falkner K, Henry L, Costello B, Gregory B, et al. (2011): Serum cytokeratin 18 and cytokine elevations suggest a high prevalence of occupational liver disease in highly exposed elastomer/polymer workers. J Occup Environ Med; 53: 1128–33. DOI: 10.1097/JOM.0b013e31822cfd68.
8. Clair H, Pinkston C, Rai S, Pavuk M, Dutton ND, et al (2018): Liver Disease in a Residential Cohort With Elevated Polychlorinated Biphenyl Exposures. Toxicol Sci; 19; 164 (1):39–49. DOI: 10.1093/toxsci/kfy076.
9. Cruz SL, and Bowen SE (2021): The last two decades on preclinical and clinical research on inhalant effects. Neurotoxicol Teratol; 87:106999. DOI: 10.1016/j.ntt. 2021. 106999.
10. Dauris R (2025): How to approach elevated liver enzymes. Liver Fellow Network. American Association for the Study of Liver Diseases. Available at: https://www. aasld.org/liver-fellow-network/core-series/back-basics/how-approach-elevated-liver-enzymes
11. Ebenezer T, Vincent F, Ehimen A, Emir V, John W et al. (2020): Non-Alcoholic Fatty Liver Disease Modifies Serum Gamma-Glutamyl Transferase in Cigarette Smokers. Original Article; 12(8):472-82. DOI: https://doi.org/10.14740/jocmr3932.
12. Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN, et al. (2009): Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis. Hepatology; 50(4): 1072 – 8. DOI: 10.1002/hep.23050.
13. Gresner P, Krol M B, Swiercz R, and Gromadzinska J (2021): Blood plasma levels of biomarkers of liver status and lipid profile among nail technicians occupationally exposed to low-level mixture of volatile organic compounds. Int Arch Occup Environ Health ; 94: 487–94.DOI: 10.1007/s00420-020-01599-2.
14. Heeley-Hill AC, Stuart KW, Martyn W, Alastair C, Neil O, et al.(2021): Frequency of use of household products containing VOCs and indoor atmospheric concentrations in homes. Environ Sci Processes Impacts ;(23):699- 713. DOI: 10.1039/d0em00504e.
15. Hideki F, Haruna D, Tetsuhisa K, Taito F, Toru K, et al. (2020): Frequently abnormal serum gamma- glutamyl transferase activity is associated with future development of fatty liver: a retrospective cohort study. BMC Gastroenterology; 20(1):217. DOI:10.1186/s12876-020-01369-x.
16. Huai K, Rafael S, Jerome B, Rodolphe A, Wah K , et al. (2023): Hepatocyte apoptosis fragment product cytokeratin-18 M30 level and non-alcoholic steatohepatitis risk diagnosis: an international registry study. Chin Med J (Engl); 5;136(3):341-50. DOI: 10.1097/CM9.0000000000002603.
17. Jayavardhan V, Varun S, Pazhanivel M,

Sadishkumar K, Jayaprakash Sahoo, et al. (2023): Obesity and Metabolic Dysfunction-associated Fatty Liver Disease: Understanding the Intricate Link. Journal of Translation Gastroenterology; 1(2):74-86. DOI: 10.14218/JTG.2023.00043

18. Jones D and Brischke C (2017): Performance of Bio-based Building Materials. Volume 7 Cost European Corporation in Science and Technology, Woodhead Publishing; Sawston, UK. ISBN: 0081009925, 9780081009925[Google Scholar]
19. Jung H , Chang Y, Kwon M, Sung E, Yun K, et al. (2019): Smoking and the risk of non-alcoholic fatty liver disease: A cohort study. Am J Gastroenterol; 114:453–63.DOI: 10.1038/s41395-018-0283-5.
20. Lee J, Vali Y, Boursier J, Duffin K, Verheij J, et al. (2020): Accuracy of cytokeratin 18 (M30 and M65) in detecting non-alcoholic steatohepatitis and fibrosis a systematic review and meta-analysis. PLoS One; 15(9): e0238717, PMID: 32915852. DOI: org/10.1371/journal.pone.0238717.
21. Lingling Q, Lei Z, Liang W, Jing Z, Qichen F, et al. (2020): Elevated Serum Level of Cytokeratin 18 M65ED Is an Independent Indicator of Cardiometabolic Disorders. J Diabetes Res: 5198359. DOI: 10.1155/2020/5198359.
22. Liu J, Drane W, Liu, X, and Wu T (2009): Examination of the relationships between environmental exposures to volatile organic compounds and bio- chemical liver tests: application of canonical correlation analysis. Environ Res; 109:193-9.DOI: org/10.1016/j.envres.2008.11.002.
23. Matt C, Keith C, Latasha H, Brittany C, Bonnie G, et al. (2011): Serum Cytokeratin 18 and cytokine elevations suggest a high prevalence of occupational liver disease in highly exposed elastomer/polymers. J Occup Environ Med; 53(10):1128–33. DOI: 10.1097/JOM.0b013e31822cfd68
24. Miwa K, Yoshihiro K, Hirokazu T, Michihiro I, Ken N, et al. (2024): Serum Cytokeratin 18 Fragment Is an Indicator for Treating Metabolic Dysfunction-Associated Steatotic Liver Disease. Gastro Hep Advances; 3 :1120–8. DOI: 10.1016/j.gastha.2024.08.008.
25. Perez C , Bosia J , Cantore M , Chiera A, Cocozzella D, et al. (2006): Liver damage in workers exposed to hydrocarbons. Gastroenterol Hepatol; 29(6):334–7.DOI: 10.1157/13089716.
26. Qianyong S, Yalin L, Guiying L, and Taicheng A (2024): A review of disrupted biological response associated with volatile organic compound exposure: Insight into identification of biomarkers. Sci Total Environ; 248:174924. DOI: org/10.1016/j.scitotenv. 2024.174924..
27. Sabrina P, Stephan J, Catherine J, Robin P, and Nicolas V (2023): Serum Level of Cytokeratin 18 (M65) as a Prognostic Marker of High Cardiovascular Disease Risk in Individuals with Non-Alcoholic Fatty Liver Disease. Biomolecules; 13(7):1128. DOI: 10.3390/biom13071128
28. Safiye G, Amir H, Simone M, and Ashraf M T (2023): exposure to volatile organic compounds in paint production plants: levels and potential Human health risks. Toxics; 24; 11(2):111. DOI: 10.3390/toxics 11020111.
29. Saito Y, Nishio K, Ogawa Y, Kimata J, Kinumi T, et al. (2006): Turning point in apoptosis/necrosis induced by hydrogen peroxide. Free Radic Res; 40: 619–30.DOI: 10.1080/10715760600632552.
30. Simian T, Vishal K, Rina D, Vishal S, and Dinesh K (2024): Biomarkers of Hepatic Toxicity: An Overview. Curr Ther Res Clin Exp; 26(100):100737. DOI: 10.1016/j.curtheres.2024.100737.
31. Swait J, Irina K, Cave C, Luis S, and Craig J (2015) : Alcoholic, Nonalcoholic, and Toxicant-Associated Steatohepatitis: Mechanistic Similarities and Differences. Cell Mol Gastroenterol Hepatol; 3:1(4):356–67.DOI: 10.1016/j.jcmgh.2015.05.006.

32. Tony Kolotov (2022): TVOC monitoring in commercial and office buildings. Available at:https://atmotube.com/blog/tvoc-monitoring-in-commercial-and-office-buildings .
33. Veeral A, Emily RP, Nathan MB, Norah AT, Katherine PY, et al. (2017): Novel Plasma Biomarkers Associated with Liver Disease Severity in Adults with Nonalcoholic Fatty Liver Disease. Hepatology; 65(1):65 -77. DOI: 10.1002/hep.28776.
34. Wahlang B, Beier J, Clair H, Bellis-Jones H, Falkner K, et al. (2013): Toxicant- associated steatohepatitis. Toxicol Pathol; 41: 343-60. DOI: 10.1177/0192623312468517.
35. Weber S, Allgeier J, Denk G, and Gerbes A (2022): Marked increase of gamma-glutamyltransferase as an indicator of drug-induced liver injury in patients without conventional diagnostic criteria of acute liver injury. Visc Med; 38 (3):223-8.
36. Wei L, Shuting C, Da S, Linling Y, Weihong Q, et al. (2023): Single-chemical and mixture effects of multiple volatile organic compounds exposure on liver injury and risk of non-alcoholic fatty liver disease in a representative general adult population. Chemosphere; 339: 139753. DOI:10.1016/j.chemosphere.2023. 139753.
37. WHO (World Health Organization) (2024): Global assessment of occupational liver disease burden: 2024 update. WHO Press.