IJCOM 2022 March;1(3):189-98

Naphthol as A Biological Monitoring on Naphthalene Exposure in Workers

Arriz Akbar[1*], Muhammad Ilyas[2]

Occupational Medicine Specialist Program, Faculty of Medicine, Universitas Indonesia[1]
Department of Community Medicine, Faculty of Medicine at Universitas Indonesia[2]

*Corresponding address: Arriz Akbar
Email: arriz_dr@yahoo.com

Abstract

Introduction: Naphthalene is one of the chemicals that are widely used throughout the world, such as aircraft fuel, camphor, insecticides, and colouring agents in cosmetics. Exposure to naphthalene can cause health problems ranging from dermatitis and haemolytic anaemia to even the possibility of cancer of the respiratory tract, therefore it is necessary to carry out biological monitoring of workers at risk. The aim of this study is to find out which is the simplest and most reliable biomonitoring to use based on an evidence-based literature review.
Methods: Literature search was conducted through electronic databases from PubMed, ProQuest, and Cochrane. The keywords used are worker, naphthalene, and biomonitoring. Initially, 273 articles were obtained, but after going through a selection process and manual search, seven articles were examined.
Results: Based on the selected evidence-based literature, it was found that there was an increase in the level of naphthol in the urine in workers exposed to naphthalene who were examined during pre-shift and post-shift.
Conclusion: Naphthol concentration in urine can be a non-invasive, easy, and reliable biomonitoring exposure of naphthalene. Although it is currently not possible to do this in Indonesia, this study shows the importance of biomonitoring to prevent occupational diseases due to this exposure.
Keywords: biomonitoring, naphthalene, naphthol, exposure, workers

Abstrak

Pendahuluan: *Naftalena merupakan salah satu bahan kimia yang banyak penggunaannya di seluruh dunia, seperti bahan bakar pesawat, kapur barus, insektisida dan zat pewarna pada kosmetik. Paparan naftalena dapat menyebabkan gangguan kesehatan mulai dari dermatitis dan anemia hemolitik bahkan kemungkinan terjadinya kanker pada saluran nafas, karena itu perlu dilakukan pemantauan biologis pada pekerja yang berisiko. Tujuan dari studi ini adalah untuk mengetahui biomonitoring yang sederhana dan paling andal untuk digunakan berdasarkan tinjauan literatur berbasis bukti.*
Metode: *Pencarian literatur dilakukan melalui database elektronik dari PubMed, ProQuest dan Cochrane. Kata kunci yang digunakan adalah worker, naphthalene dan biomonitoring. Pada awalnya diperoleh 273 artikel, namun setelah melalui proses seleksi dan pencarian manual diperoleh tujuh artikel yang ditelaah.*
Hasil: *Berdasarkan literatur berbasis bukti yang telah dipilih diketahui bahwa terdapat peningkatan kadar naftol dalam urine pada pekerja yang terpapar naftalena yang diperiksa saat pra-shift dan post-shift.*
Simpulan: *Konsentrasi naftol dalam urine dapat menjadi pemantau pajanan biologis naftalena yang non invasif, mudah dan andal untuk dapat diterapkan. Walaupun di Indonesia sekarang belum bisa untuk dilakukan, dari studi ini menunjukan pentingnya biomonitoring untuk mencegah penyakit kerja akibat paparan naftalena.*
Kata kunci: *biomonitoring, naftalena, naftol, pajanan, pekerja*

Introduction

Many workers are exposed to various chemicals while working, one of which is naphthalene and its derivatives. These chemicals are often found in everyday life as airplane fuel in general (it has the most composition). Naphthalene is also known as the main ingredient in the manufacture of camphor with the chemical formula C10H16O and as a constituent of carbamate/carbaryl insecticides with the chemical formula C12H11NO2 which is widely used in Indonesian agriculture. Naphthalene derivatives are also used as an additive in motor fuels, lubricants, epoxy resins and are often used as an intermediate in the manufacture of hair dyes, cosmetics, plastics, and solvents.1

Workers who are exposed to this material will certainly be at risk of causing diseases, some of which are dermatitis, hemolytic anemia, G6PD, damage to epithelial cells in the lung parenchyma (Clara cells) and on repeated exposure it also causes damage to the proximal kidney tubules. In addition, through the respiratory system, it can also attack cells in the nose of experimental animals, triggering the occurrence of neuroblastoma malignancy in the nose, while those given orally can also cause lung malignancies, namely alveolar adenomas, and lung bronchioles.[2,3]

The International Agency for Research on Cancer (IARC) has classified naphthalene as potentially carcinogenic to humans (Group 2B). The IARC also demonstrated that acute exposure to naphthalene can cause cataracts, hemolytic anemia (as noted above) may occur in children and infants following oral or inhalation exposure or after maternal exposure during pregnancy. Experiments on mice conducted by the US National Toxicology Program (NTP) 1992, showed signs of carcinogenesis with an increased incidence of adenomas and neuroblastomas in the nose, alveolar and bronchioles of experimental animals. So, the NTP also states that naphthalene is anticipated to be a carcinogen for humans.[4,5]

The National Institute of Occupational Safety and Health (NIOSH) has set the recommended exposure limit (REL) for exposure to this naphthalene at 10 ppm (50 mg/m^3) during an 8-hour work period, and the short permissible exposure limit (STEL) at 15 ppm (75 mg/m^3). The American Conference of Governmental Industrial Hygienists (ACGIH) and the Occupational Safety and Health Administration (OSHA) set the permissible exposure limit (PEL) also at 10 ppm (50 mg/m^3).[6]

To protect workers from the possible various health effects of hazardous industrial chemicals including naphthalene, biomonitoring is necessary to identify them in the bodies of workers exposed to it. Several methods are presented by researchers to measure qualitatively and/or quantitatively the exposure to naphthalene from its metabolites contained in biological materials such as blood, adipose tissue, lung fluid and urine.

The aim of this paper is to find out which is the simplest and most reliable biomonitoring to use among the various types of biomonitoring for naphthalene exposure, based on an evidence-based literature review.

Methods

The literature searching was performed via electronic databases from PubMed, ProQuest, and Cochrane to find journals related to naphthalene biomonitoring. The search method was conducted on January 5, 2020. The words used to search as presented in Table 1, were "Biomonitoring", "Jet Propellant", "Carbaryl", "Naphthalene", and "Worker". The search strategy from the results obtained is then selected according to the inclusion and exclusion criteria shown in the flow chart (Figure 1). After the selection, a critical appraisal was carried out using several aspects based on the Center of Evidence-based Medicine, from the University of Oxford for a diagnostic study.[7]

Apart from the electronic database, hand searching was also performed. The results of the appraisal were presented in Tables 2, 3, 4, 5, 6,7 and 8.

Table 1. Search Strategy Using Keywords

Database	***Keyword***	***Hit***
PubMed	((worker) AND (((naphthalene) OR (carbaryl)) OR (jet propellant))) AND ((biomonitoring) OR (biomarker))	95
ProQuest	((worker) AND (naphthalene)) AND (biomonitoring)	177
Cochrane	((worker) AND (((naphthalene) OR (carbaryl)) OR (jet propellant))) AND ((biomonitoring) OR (biomarker))	1

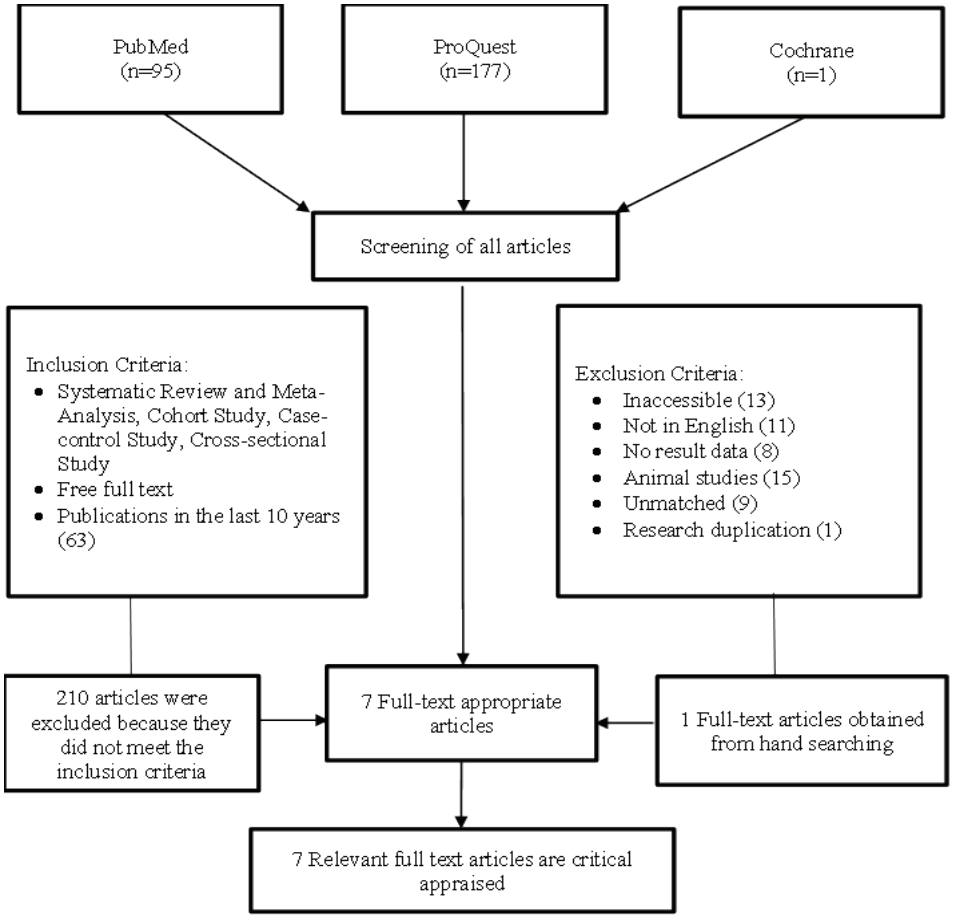

Figure 1. The Process of Article Selection

Result

The first study by Smith KW, et al (2012), performed a urinary biomarker of occupational jet fuel exposure among US air force personnel. They measured naphthol levels (NAP); 1-NAP and 2-NAP in urine were found to be increased during shift work in the naphthalene-exposed group. Post-shift urinary 1-, 2-NAP levels reflecting JP8 aircraft fuel exposure during work shifts were significant predictors. Job-related predictors of post-shift 1-, 2-NAP in the high-exposure group emphasized the importance of reducing skin exposure (other than inhalation exposure) with PPE such as wearing gloves when working in an environment with exposure to JP8 aircraft fuel.

The results showed that the naphthalene exposure group was a significant predictor of post-shift 1-NAP and 2-NAP, so the levels in the high-exposure group were 5.2 and 2.9 times higher than in the low-exposure group for 1-NAP, respectively and 2-NAP, while levels in the moderate group were 1.4 and 1.2 times higher than the low group for 1-NAP and 2-NAP, respectively.

Tabel 2. Critical Appraisal Checklist for Diagnosis Study (Article 1)

Title	**Urinary biomarkers of occupational jet fuel exposure among airforce personnel[8]**
Author(s)	Smith KW, et al (2012)
Level of Evidence	3b

Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes. Samples were taken from 24 US Air Force personnel (divided into 6 people with low exposure, 9 medium exposure and 9 high exposure).
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in urine samples was analyzed where sampling was active for duration of the work shift.
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	It is not clear, but the authors confirmed the analysis by measuring accrording to the metodh of the NIOSH 1501 (NIOSH, 2003)
Are test characteristics presented?	Yes, test result are analyzed and presented using descriptive statistics, scatter plots, correlation coefficients, and linear mixed effects models.
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological monitoring from urine sampling and air measurements are described in sufficient detail.

The study by Rodrigues EG, et al (2014) is to evaluate the association between inhalation exposure to jet propulsion fuel 8 (JP-8) and urinary metabolites among US Air Force (USAF) personnel and investigate the role of glutathione S-transferase polymorphisms. Measurement of airborne naphthalene levels in the workplace with metabolites in the urine of 73 USAF personnel for 4 consecutive working days and analyzed from exposure to JP-8. Pre- and post-shift urine samples were collected daily and analyzed for polycyclic aromatic hydrocarbon urine metabolites.

The result was that naphthalene levels in the work area were statistically significant predictors for the concentrations of 1-NAP (β = 0.22; P = <0.0001), and 2-NAP (β = 0.11; P = 0.0006) in the post-shift urinary tract. work, with an estimated effect slightly larger than that observed for the total hydrocarbon concentration. Urine levels of 1-NAP and 2-NAP represent occupational exposure to JP-8 during the workday among US Air Force personnel and can be used as biological markers for jet fuel exposure.

Tabel 3. Critical Appraisal Checklist for Diagnosis Study (Article 2)

Title	**Urinary Polycyclic Aromatic Hydrocarbon (OH-PAH) Metabolite Concentrations and the Effect of GST Polymorphisms Among US Air Force Personnel Exposed to Jet Fuel[9]**
Author(s)	Rodrigues EG, et al (2014)
Level of Evidence	3b
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes. samples were drawn from 73 US Air Force personnel (divided into high exposure/tank maintenance, distribution and low exposure/administration, health care workers).
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in urine samples was analyzed where sampling was active for duration of the work shift.
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	It is unclear, bue the authors reassured the analysis was in accordance with US CDC approval
Are test characteristics presented?	Yes, test result are analyzed and presented using Chi-square and Fisher exact tests. Airbone naphthalene concentration was a statistically significant predictor of posts-shift urine concentration of 1-naphthol (β = 0.15; P = <0.0001), 2-naphthol (β = 0.09; P = 0.005).
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological monitoring from urine sampling and air measurements are described in sufficient detail.

This study from Craig Sam's (2017) is an experimental study conducted on five volunteers who were given carbamate insecticide orally containing naphthalene, and the level of naphthol in the urine was measured. A single oral dose of Carbaryl according to the acceptable daily intake (ADI: 0.008 mg/kg) was given dissolved in ethanol and diluted with a soft drink. Details of participants including gender, age, height, weight, and body mass index (BMI) were recorded. The total urine collection was collected into a series of individual vials per 2 hours to 48 hours post-exposure.

After oral exposure to carbaryl, urinary 1-NAP levels rise rapidly analyzed using HP-LC, peaking between 2 and 6 hours after dosing. The median excretion half-life is 3.6 hours, and the elimination of 1-NAP is complete in 24 hours. Metabolite levels recovered in the total urine collection for 24 hours post-dose represent between 11% and 43% of the administered dose. The two volunteers with the lowest recovery had the highest BMI. This could indicate that there is an increase in Carbaryl storage in body fat. The level of 1-NAP in urine is a suitable biomarker to assess naphthalene exposure to carbamate insecticides.

The study from Klotz (2019) aims to evaluate the validity of several different biomarkers from several biomonitoring of naphthalene exposure in abrasive industrial work environments. They measured naphthalene in the workplace air and determined it during one work shift and then bio monitored the urine samples before and after the shift which were collected 2 days a week. Metabolites were analyzed 1,2-dihydroxynaphthalene (DHN), 1- and 2-naphthol (NAP), 1- and 2-naphthylmercapturic acid (NMA) using GC-MS and HPLC-MS.

Tabel 4. Critical Appraisal Checklist for Diagnosis Study (Article 3)

Title	**Urinary Naphthol as a Biomaker of Exposure: Results from an Oral Exposure to Carbaryl and Workers Occupationally Exposed to Naphthalene[10]**
Author(s)	Sam's C (2017)
Level of Evidence	1c
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes. Samples were taken from 5 volunteers who received a single oral dose of carbamate insecticide according to the daily intake that was still allowed. (Acceptable Daily Intake/ADI: 0.008 mg/kg).
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in urine samples was analyzed where sampling was taken after oral carbamate ingestion.
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	Unclear, but author approved by Health and Safety Executive HSE Research Ethics Committee UK.
Are test characteristics presented?	Yes, test result are analyzed and presented using a statistical mean of 27.1 levels of 1-NAP and 8.1 levels of 2-NAP, a median of 4.2 and 4.0 levels of 1,2-NAP, coefficient of variation.
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological monitoring from urine sampling are described in sufficient detail.

Airborne naphthalene concentrations ranged from 0.5 to 11.6 mg/m^3 and an increase in post-shift urine biomarkers at 1,2-DHN, 1-NMA, 1,2-NAP, except that 2-NMA was not detected. Significantly positive correlations were found for 1,2-DHN, 1-NMA, and 1,2-NAP in post-shift urine samples due to exposure to naphthalene in the work environment. 1-NMA and 1,2-DHN, 1,2-NAP have been demonstrated to be suitable biomarkers for monitoring naphthalene exposure.

Tabel 5. Critical Appraisal Checklist for Diagnosis Study (Article 4)

Title	**Validility of different monitoring parameters in human urine for assessment of occupational exposure to naphthalene**[11]
Author(s)	Klotz K, et al (2019)
Level of Evidence	3b
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes. Samples were taken from 10 workers who were the subject of the previous study (63 workers in the abrasive industry. 32 exposed to naphthalene and 31 controls).
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in the urine samples was analyzed. In addition, other metabolites also investigated in this study such as 1,2-naphthylmercapturic acid
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	It is not clear, but the authors confirmed the analysis with internal quality control measures.
Are test characteristics presented?	Yes, test result are analyzed and presented with the Pearson correlation coefficient and p-value
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological monitoring and aerial monitoring are describe in sufficient detail.

The study by Thaia PK (2020) was conducted to measure levels of polycyclic aromatic hydrocarbon chain metabolites (PAHs) in urine samples collected from the Australian population (stratified and pooled by age and sex) over two consecutive collection periods from 2014-2015 and 2016 -2017. The collected urine samples were extracted and analyzed for ten PAHs using a modified GC-isotope dilution-MS method. Four samples from previous studies were used as quality control (QC) samples. The 1-NAP and 2-NAP concentrations of each sample collected were used to calculate the ratio between 1-NAP/2-NAP. This ratio is used as a parameter to evaluate whether a person or group (in this case) is exposed to carbamate insecticides or not.

Among the OH-PAHs measured in this study, 1-NAP is known not only as a metabolite/biomarker of naphthalene but also Carbaryl, which is a broad-spectrum carbamate insecticide. While 2-NAP only emerged from exposure to naphthalene. The consequence of increasing 1-NAP levels is that the 1-NAP/2-NAP ratio in Australia is > 1 may indicate exposure to Carbaryl in addition to naphthalene.

This study provides information on PAH exposure in Australian residents including young children. The urine 1-NAP concentration (and consequently the 1-NAP/2-NAP ratio) was relatively high in some samples, possibly due to exposure to Carbaryl and naphthalene derivatives in cosmetic products.

Tabel 6. Critical Appraisal Checklist for Diagnosis Study (Article 5)

Title	**Analysis of urinary metabolites of polycyclic aromatic hydrocarbons and cotinine in pooled urine samples to determine the exposure to PAHs in an Australian population**[12]
Author(s)	Thaia PK, et al (2020)
Level of Evidence	4
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes. urine samples were taken from more than 3 million Australians
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in urine samples was analyzed
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	It is not clear, but the authors confirm the analysis is in accordance with the University of Queensland's approval

Are test characteristics presented?	Yes, test result are analyzed and presented using mean and median statistics
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological monitoring, starting from urine sampling, is explained in detail

The study of Weiss et al (2020) was carried out to obtain data on exposure to naphthalene in the work environment air (personal shift measurement) by biomonitoring (amount of naphthalene metabolite 1,2-naphthol in urine post-shift work).

Air naphthalene measurements are carried out at 3 abrasive plants every Thursday during the work shift. Urine samples were taken daily during the measurement week before and after the work shift from subjects assessed as exposed. And for control, urine sampling was only carried out on Mondays before shifts and on Thursdays after work shifts. For biomonitoring, urine metabolites of naphthalene 1- and 2-NAP were quantified by stable isotope dilution analysis using GC-EI-MS.

The average concentration of naphthalene measurements in the work environment was obtained from 0.4 to 11.1 mg/m3. There was a statistically close linear correlation between personal shift measurements recorded on Thursdays (Airborne Monitoring) and naphthol concentrations obtained on Thursdays after the end of the shift (Biological Monitoring).

Studies show a strong correlation between naphthalene in workplace air, which is found exclusively in the vapor phase, and the amount of its metabolite 1,2-NAP in post-shift urine. This implies the main absorption of naphthalene from exposure to air.

Tabel 7. Critical Appraisal Checklist for Diagnosis Study (Article 6)

Title	**(Mono-) Exposure to Naphthalene in the Abrasives Industry Air Monitoring and Biological Monitoring**
Author(s)	Weiss T et al (2020)
Level of Evidence	3b
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes. a sample of 63 workers was drawn from 3 factories in Germany and 2 in Austria where naphthalene exposure was present in the workplace
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in urine sample was analyzed
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	It is not clear, but the accuracy of the test is proven in the German External Quality Assessment Scheme (G-EQUAS)
Are test characteristics presented?	The test result were statistically analyzed and presented with a Spearman's correlation coefficient and a significant p-value
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological and aerial monitoring are described in sufficient detail

This study from Takeuchi (2020) was aimed at developing and validating a simple and reliable gas chromatography mass spectrometry (GC-MS) method for determining the levels of 1-NAP and 2-NAP in urine for biomonitoring. occupational naphthalene exposure. Both NAPs were derivatized in situ with acetic anhydride after enzymatic hydrolysis, extracted with n-hexane, and analyzed using GC-MS.

Accurate determination using the GC method with derivatization of acetic anhydride to convert naphthol (NAP) into a less polar compound to obtain better chromatographic results with a fast and simple sample

preparation procedure. An important determinant of the success of acetylation is the formation of naphtholate anion in solution because this anion reacts with acetic anhydride in aqueous solution. Method validation was carried out in accordance with US Food and Drug Administration guidelines and met the specified criteria. The results of the ClinChek® analysis also show that the method used is quite accurate because the mean ± SD is within the confidence interval.

The proposed method is simple, reliable, and suitable for routine analysis, and is useful for naphthol biomonitoring (NAP) of naphthalene exposure in occupational health practice.

Table 8. Critical Appraisal Checklist for Diagnostic Study (Article 7)

Title	**Simple and reliable method for simultaneously determining urine 1- and 2-naphthol using in situ derivatization and gas chromatography mass spectrometry for biological monitoring of naphthalene exposure in occupational health practice[14]**
Author(s)	Takeuchi A, et al (2020)
Level of Evidence	2c
Was the diagnostic test evaluated in a representative spectrum of patients (like those in whom it would be used in practice)?	Yes, samples were taken from 10 workers who were the subject of the previous study (63 workers in the abrasive industry: 32 exposed to naphthalene and 31 controls).
Was the reference standard applied regardless of the index test result?	Yes, 1,2-naphthol in the urine sample was analyzed. In addition, other metabolites also investigated in this study such as 1,2-naphthylmercapturic acid
Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis?	It is not clear, but the authors confirm the analysis with internal quality control measures.
Are test characteristics presented?	No, the test results were analyzed and then presented with the Pearson correlation coefficient and p-value.
Were the methods for performing the test described in sufficient detail to permit replication?	Yes, the methods for carrying out biological and aerial monitoring are described in sufficient detail.

Discussion

Based on the literature review in the seven journals conducted above, information was obtained that researchers have reported a strong correlation between the concentration of naphthol in the urine of workers exposed to naphthalene in the air of the work environment as contained in articles one, two and six. Peak concentrations of naphthalene in urine may occur soon after the end of the exposure period and decrease thereafter. Several studies conducted on US American Air Force workers/personnel who worked in the process of filling and repairing aircraft fuel tank leaks also found a significant relationship to an increase in naphthol levels in urine due to exposure to jet fuel that contains a lot of naphthalene (article 1 and 2).

Likewise, the sixth article, a recent study by Weiss (2020) measuring naphthol levels in the urine of humans working in the abrasive industry who were only exposed to naphthalene chemicals had a positive correlation. Statistically, there is a close linear correlation between the measurement of naphthalene in the working air environment and the naphthol concentration obtained after the end of the work shift.

In humans, naphthalene is metabolized to 1- and 2-naphthol in approximately equal amounts. In general, 2-NAP metabolites appear to be a more specific parameter for naphthalene exposure, as 1-NAP metabolites are more likely to be caused by exposure to insecticides and hair dyes. This is in line with research conducted by Sams (2017) which in the third article and Meeker (2007) who is measuring the ratio between 1-NAP/2-NAP > 2 is used as a threshold indicating exposure to carbaryl.[15]

This is also corroborated by the fifth article, in Thaia's study (2020) it was found that the results of urine measurements in the Australian population in general (not just workers) from adults to young children found that PAH exposure in Australian residents showed a relative concentration of 1-NAP in urine high in some

samples resulting ratio >1; this may be due to the source of exposure to naphthalene in carbamate insecticides and cosmetic products (hair dyes) used by Australians.

The latest research is shown in the fourth article by Klotz (2020). Among more than 30 metabolites in urine that can be measured, 1-,2-NAP have been the most commonly used urinary parameters for the purpose of assessing naphthalene exposure. Klotz attempted to validate biomarkers for naphthalene exposure by measuring airborne naphthalene concentrations and found increased post-shift urine biomarkers at 1,2-DHN, 1-NMA, 1,2-NAP , except 2-NMA is not detected. This significant positive correlation proves that naphthol can be used as a suitable biomarker for monitoring naphthalene exposure.

Meanwhile, Takeuchi (2020) in the 7th article tried to research a reliable and simple technical examination of naphthol in urine using the GC-MS tool without modification so that it might be replicated and the implementation process done in helping to assess naphthalene exposure in the work environment.

Several researchers have previously developed biomonitoring of naphthalene exposure by measuring the binding of hemoglobin to naphthalene present in the blood by measuring the cysteine bond formed from the reaction between hemoglobin and albumin with reactive metabolites of naphthalene. However, the difficulty of measuring the levels of reactive metabolites of naphthalene in vivo is one of the reasons why this technique was not developed.[16,17]

Hemolytic anemia as a biomonitoring effect has also been reported frequently as a result of naphthalene exposure. However, this effect can also occur in patients without exposure to naphthalene, making it less useful as a biomarker for exposure to this substance. Damage to Clara cells in the lung can also be identified by the presence of naphthalene binding to proteins in lung lavage fluid, but additional research is needed to increase the specificity of this technique as an alternative to biomonitoring. And it is also necessary to prioritize the comfort of the patient to develop a non-invasive biomonitoring examination (urine) compared to an invasive examination (blood or lung fluid).[3]

As limitation, although there have been quite a number of studies that discuss the biomonitoring of naphthalene exposure, until now there has been no clear determination of the biomarkers that will be used as metabolites; NAP, DHN or NMA. So there is no official reference / 'gold standard' used as a biomarker for naphthalene exposure, as indicated by the fourth article by Klotz (2020). However, in general, 2-naphthol metabolites seem to be a more specific parameter for naphthalene exposure, because 1-naphthol metabolites are more likely to be caused by exposure to insecticides/ pesticides and hair dyes.

In addition, there are several types of tools used to examine these biomarkers GC-MS, LC-MS or some modifications of the GC-MS used as in articles one, three and six. This is what Takeuchi (2020) tries to bridge in the seventh article, where he tries to show how to measure naphthol levels in urine with a simple and reliable method using GC-MS without modification so as to try to reduce examination costs and can be used widely.

Table 9. Summary of critical assessments on selected articles

Articles	Validity		Importancy	Applicability	Level of Evidence
	Study Design	Population	Result	Measure and Replication Detail	
Takeuchi A, et al (2020)	+	-	+	+	2c
Weiss T, et al (2020)	+	+	+	+	3b
Thaia PK, et al (2020)	+	+	+	+	4
Klotz K, et al (2019)	+	+	+	+	3b
Sams C (2017)	+	-	+	+	1c
Rodrigues EG, et al (2014)	+	+	+	+	3b
Smith KW, et al (2012)	+	+	+	+	3b

Notes: + Clearly mentioned in the article; - Not done; Not so clear

Conclusion

From this scientific review, we have reported a strong correlation between naphthol concentrations in the urine of workers exposed to naphthalene in work environment air. Determination of naphthol levels in the urine of workers exposed to naphthalene can be recommended to monitor the presence of naphthalene metabolites in workers. This examination is more reliable and comfortable for the patient when compared to invasive tests on blood or lung lavage fluids. Examination using GC-MS without modification can also be simple and reduce examination costs.

Some recommendations can be made by the company by establishing a medical surveillance program for all employees whose workers have been exposed, are suspected of being exposed to, or are concerned about being exposed to naphthalene. Medical surveillance begins with an initial examination of each employee which includes not only medical and occupational history but also biological monitoring and provision of PPE.

Further studies with better quality are needed to provide stronger evidence regarding the biomonitoring of workers exposed to naphthalene.

References

1. Preuss, R., Angerer, J. & Drexler, H. Naphthalene—an environmental and occupational toxicant. *Int Arch Occup Environ Health* 7**6,** 556–576 (2003).
2. Coman G, Zinsmeister C, Norris P. Occupational Contact Dermatitis: Workers' Compensation Patch Test Results of Portland, Oregon, 2005-2014. Dermatitis. 2015 Nov-Dec;26(6):276-83. doi: 10.1097/DER.0000000000000142. PMID: 26551607.
3. Santucci K, Shah B (Jan 2000). "Association Naphthalene with Acute Hemolytic Anemia". Acad Emergency Med. 7(1): 42-7.
4. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some Traditional Herbal Medicines, Some Mycotoxin, Naphthalene and Sytrene. Vol 82 (2002) (p. 367)
5. ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological profile for naphthalene (update). Atlanta: ASTDR, 1995.
6. Preuss, R., Angerer, J. & Drexler, H. Naphthalene—an environmental and occupational toxicant. *Int Arch Occup Environ Health* **76,** 556–576 (2003).
7. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009) (online). 7 Januari 2021. Center for Evidence Based Medicine. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.
8. Smith KW, Proctor SP, Ozonoff AL, McClean MD. Urinary biomarkers of occupational jet fuel exposure among Air Force personnel. J Expo Sci Environ Epidemiol. 2012 Jan-Feb;22(1):35-45. doi: 10.1038/jes.2011.38. Epub 2011 Nov 2. PMID: 22044926.
9. Rodrigues EG, Smith K, Maule AL, Sjodin A, Li Z, Romanoff L, Kelsey K, Proctor S, McClean MD. Urinary polycyclic aromatic hydrocarbon (OH-PAH) metabolite concentrations and the effect of GST polymorphisms among US Air Force personnel exposed to jet fuel. J Occup Environ Med. 2014 May;56(5):465-71. doi: 10.1097/JOM.0000000000000142. PMID: 24806557; PMCID: PMC5137189.
10. Sams C. Urinary Naphthol as a Biomarker of Exposure: Results from an Oral Exposure to Carbaryl and Workers Occupationally Exposed to Naphthalene. Toxics. 2017 Jan 6;5(1):3. doi: 10.3390/toxics5010003. PMID: 29051435; PMCID: PMC5606673.
11. Klotz K, Weiß T, Zobel M, Bury D, Breuer D, Werner S, Sucker K, Zschiesche W, Göen T, Brüning T, Drexler H. Validity of different biomonitoring parameters in human urine for the assessment of occupational exposure to naphthalene. Arch Toxicol. 2019 Aug;93(8):2185-2195. doi: 10.1007/s00204-019-02468-9. Epub 2019 Jun 20. PMID: 31222524.
12. Thai PK, Banks APW, Toms LL, Choi PM, Wang X, Hobson P, Mueller JF. Analysis of urinary metabolites of polycyclic aromatic hydrocarbons and cotinine in pooled urine samples to determine the exposure to PAHs in an Australian population. Environ Res. 2020 Mar;182:109048. doi: 10.1016/j.envres.2019.109048. Epub 2019 Dec 16. PMID: 31865166.
13. Weiss T, Breuer D, Bury D, Friedrich C, Werner S, Aziz M, Hummel T, Raulf M, Zschiesche W, Sucker K, Pallapies D, Bünger J, Brüning T. (Mono-) Exposure to Naphthalene in the Abrasives Industry: Air Monitoring and Biological Monitoring. Ann Work Expo Health. 2020 Nov 16;64(9):982-992. doi: 10.1093/annweh/wxaa062. PMID: 32656562.
14. Takeuchi A, Nakamura S, Namera A, Kondo T, Onuki H, Yamamoto S, Okamura S, Nishinoiri O, Endo Y, Miyauchi H, Endo G. Simple and reliable method to simultaneously determine urinary 1- and 2-naphthol using in situ derivatization and gas chromatography-mass spectrometry for biological monitoring of naphthalene exposure in occupational health practice. J Occup Health. 2020 Jan;62(1):e12144. doi: 10.1002/1348-9585.12144. PMID: 32713100; PMCID: PMC7382817.
15. Meeker J, Barr D, Serdar B. *et al.* Utility of urinary 1-naphthol and 2-naphthol levels to assess environmental carbaryl and naphthalene exposure in an epidemiology study. *J Expo Sci Environ Epidemiol* **17,** 314–320 (2007).
16. Troester MA, Lindstrom AB, Rappaport SM. Measurement of hemoglobin and albumin adducts of naphthalene-1,2-oxide, 1,2-naphthoquinone and 1,4-naphthoquinone after administration of naphthalene to F344 rats. Chemico-biological Interactions. 2002 Oct;141(3):189-210.
17. Waidyanatha S, Rappaport SM. Hemoglobin and albumin adducts of naphthalene-1,2-oxide, 1,2-naphthoquinone and 1,4-naphthoquinone in Swiss Webster mice. Chem Biol Interact. 2008 Mar 27;172(2):105-14. doi: 10.1016/j.cbi.2008.01.004. Epub 2008 Jan 16. PMID: 18291356.