1,2-dihydroxynaphthalene as Biomonitoring of Occupational Exposure to Naphthalene

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ABSTRACT

Introduction: Naphthalene is a chemical exposure found in various industries, including in the manufacture of phthalic anhydride, synthetic resins, lubricants, mothballs, and used as fuel additives. The exposure to naphthalene in humans has several detrimental health effects such as hemolytic anemia, kidney and liver disorders. Therefore, biological monitoring is needed as a health surveillance of naphthalene exposure. Generally, the biomonitoring examination carried out for this is naphthol in the blood. However, 1,2-dihydroxynaphthalene (1,2-DHN) is also known to be another major metabolite. Therefore, this literature review aims to determine whether 1,2-DHN can also be a reliable biomonitoring test on occupational exposure to naphthalene. **Methods:** PubMed, Proquest, and Google Scholar were used to conduct article searches. The articles were chosen based on predetermined inclusion and exclusion criteria. The selected articles were then critically appraised. **Results:** Four cross-sectional articles examining 1,2-DHN in the urine of naphthalene-exposed workers were selected and reviewed. There was a similar result from all selected articles that elevated levels of 1,2-DHN in the urine, indicating workplace exposure to naphthalene. Moreover, apart from having a strong correlation with 1- and 2-naphthol, 1,2-DHN also has a high sensitivity compared to these established metabolites. **Conclusion:** Based on the articles obtained, 1,2-DHN can be a reliable biological monitoring for workers exposed to naphthalene. However, further research is still needed on other industries exposed to naphthalene and is needed to ascertain the correlation between external and internal exposure to naphthalene.

Keywords: 1,2-dihydroxynaphthalene, biological monitoring, biomonitoring, naphthalene, occupational exposure

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INTRODUCTION

Naphthalene is a solid volatile compound that is derived from the coal tar distillation‘s middle fraction which also has substances similar to benzene (Gargiulo *et al*., 2016). This substance is water soluble and readily dissolves in ether, chloroform, alcohol, and oil. Pure naphthalene is white in color, is solid in crystalline or marble-like form, and has a distinctive camphor smell. Naphthalene has high vapor pressure, has low molecular weight, and tends to be associated with the vapor phase. In addition, naphthalene has physical properties such as a large, lustrous, crystal plate with a characteristic odor. In industry, naphthalene is commonly used as a household insecticide and mothballs. It is also used in the manufacture of phthalic and anthranilic acids, synthetic resins, lubricants, wood preservatives, and used as fuel additives (Griego *et al*., 2008; Abdel-Shafy and Mansour, 2016; Gupta, 2016).

Naphthalene exposure to the work environment falls into two ranges. The first range is about 10 – 300 μg/m^3 for the oil refinery industry, the asphalt industry (roads and roofs paving), and industries that require pitch to produce refractory products or graphite electrodes. In the second range, the naphthalene content is around 100 – 3000 μg/m^3 for the creosote production, workers who are exposed to jet fuel, coal tar and fuel industry, the making of naphthalene from coal tar, camphor making, and other chemical industries using naphthalene as a feedstock (Preuss, Angerer and Drexler, 2003; Griego *et al*., 2008; Bailey, Kerper and Rhomberg, 2015). These situations need to consider the Threshold Limit Value - Timex Weighted Average (TLV-TWA) by The American Conference of Governmental Industrial Hygienists (ACGIH) of 10 ppm (TWA) or 52.4 mg/m^3 when converted, which in Indonesia has been adapted in the Minister of

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Health of the Republic of Indonesia Number 70/2016 concerning Standards and Health Requirements for Industrial Work Environment (Ministry of Health of the Republic of Indonesia, 2016; ACGIH, 2021).

Naphthalene can be absorbed by inhalation, ingestion, and transdermal by metabolism occurring in the liver. Based on overall evaluation, naphthalene is likely to be carcinogenic to humans. Nausea, vomiting, and abdominal pain are the main gastrointestinal symptoms due to irritation from acute exposure to naphthalene. Naphthalene exposure can also cause a state of naphthalene-induced hemolytic anemia, especially in people with G6PD deficiency. Other effects are irritation, nephrotoxic effects, and hepatotoxic effects. Symptoms and signs that may be experienced in naphthalene toxicity are nausea, vomiting, abdominal pain, hemoglobinuria, nephritis, jaundice, hemolytic anemia, optic neuritis, cyanosis, convulsions, and coma. In addition, symptoms of headache, malaise, and confusion also appear in some people exposed to naphthalene. When exposure is eliminated, symptoms may gradually disappear (Abdel-Shafy and Mansour, 2016; Gupta, 2016; Sucker *et al*., 2021).

Naphthalene is classified as an animal carcinogen (group A3) by ACGIH and is possibly carcinogen to humans (group 2B) as stated by the International Agency for Research on Cancer (IARC). Therefore, personal equipment such as suits, gloves, footwear, and headgear are recommended. It is also recommended to use a NIOSH-approved respirator with a combination organic vapor and P100xcartridge when there is a risk of exposure greater than 2 ppm. Full facepiece powered-air purifying respirators also provide increased protection. Exposure to 250ppm is immediately dangerous for life and health. If there is a possibility of exposure to 250ppm and more, it is recommended to use a self contained breathing apparatus with a full facepiece operated in a pressure-demand or other positive-pressure mode and to have an emergency escape air cylinder (International Agency for Research on Cancer (IARC), 2002; ACGIH, 2021; New Jersey Department of Health, 2012).

There are several ways of biomonitoring exposure to naphthalene. In the event of ingestion, it is possible to use radioluminescense identification of naphthalene insoluble in the stomach or duodenum. Then, through the urine at the end of the shift, naphthalene exposure can be measured through its metabolites such as 1- and 2-naphtol. There are no biological exposure indices (BEI) in biomonitoring of naphthalene exposure (ACGIH, 2021).

According to some studies, the recommended biomonitoring of naphthalene exposure is 1- and 2-naphthol in urine (Sams, 2017; Takeuchi *et al*., 2020; Weiss *et al*., 2020). However, there are several metabolites that can also be detected and used for biomonitoring of exposure. The 1,2-dihydroxynaphthalene (1,2-DHN) is a precursor of 1,2-naphthoquionone, a metabolite of naphthalene that plays a role in toxic action, and is one of the metabolites that can be detected in urine (Bailey *et al*., 2016; Zobel *et al*., 2017). Thus, this scientific review aims to determine whether 1,2-DHN is also an appropriate biological monitoring of exposure as health surveillance for workers exposed to naphthalene.

METHODS

On December 24, 2020, the author performed a literature search using the keywords mentioned in Table 1 in electronic databases, namely PubMed, Proquest, and Google Scholar to answer the scientific review's objective on whether workers exposed to naphthalene can be tested for 1,2-DHN as a biomonitoring of exposure.

The inclusion and exclusion criteria were used to choose the articles. This search strategy's inclusion criteria were meta-analysis, systematic review, cohort study, case-control study, cross-

Table 1. Search Strategy Using Keywords

Database	Keyword	Hit	Selected
PubMed	((((dihydroxynaphthalene[MeSH Terms]) OR (DHN[MeSH Terms])) OR (dihydroxynaphthalene[Title/Abstract])) OR (DHN[Title/Abstract])) AND ((((biological monitoring[MeSH Terms]) OR (biomonitoring[MeSH Terms])) OR (biological monitoring[Title/Abstract])) OR (biomonitoring[Title/Abstract]))	5	3
Proquest	"1,2-dihydroxynaphthalene" AND "biological monitoring" AND "occupational exposure"	4	0
Google Scholar	"1,2-dihydroxynaphthalene" AND "occupational exposure" AND "biological monitoring" AND "naphthalene"	32	1

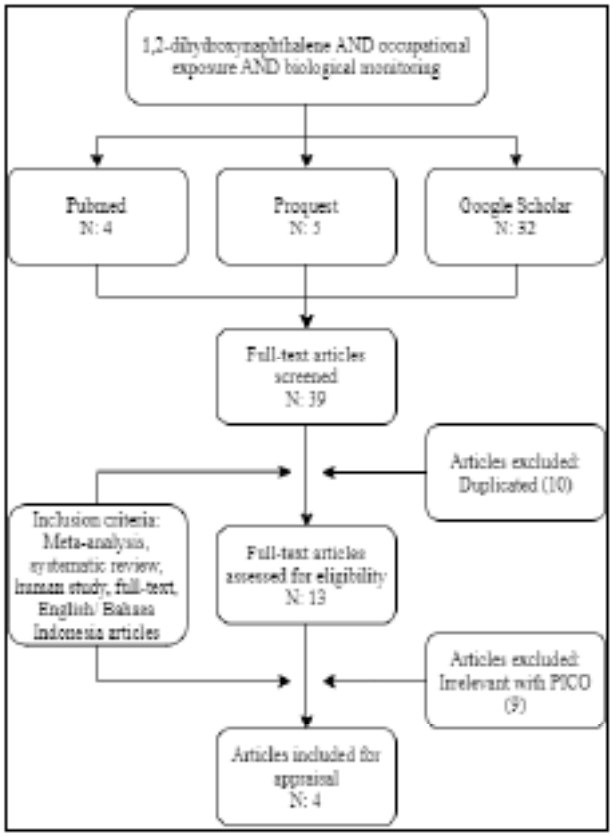

Figure 1. Article Selection Strategy

sectional study, human studies, full-text articles, and English/ Indonesian articles. Meanwhile, the exclusion criteria were duplicated and articles irrelevant with the title of this scientific review. The validity, relevance of the result, and applicability of the articles that have been chosen were then assessed. There were 4 final articles selected for appraisal. The Center for Evidence-Based Medicine's Diagnostic Study Appraisal Worksheet was used to evaluate the selected articles (CEBM), University of Oxford.

RESULTS

From the article search, there were 5 articles from PubMed, 4 articles from Proquest, and 32 articles from Google Scholar. There were four cross-sectional articles with different publication years applicable to this scientific review's goal based on the inclusion and exclusion criteria. Figure 1 depicts the article selection strategy. Table 2 describes the characteristics of the four selected cross-sectional articles. All of the selected articles examine 1,2-DHN as a biomonitoring of naphthalene exposure using the GC-MS method. Critical appraisal was carried out on selected articles using several questions adapted from the Diagnostic Study Appraisal Worksheet, which can be seen in Table 2 (Oxford Centre for Evidence Based Medicine, 2020).

In all articles, patients whose urine samples were taken for 1,2-DHN examination were randomly selected so as to minimize bias. In addition, all articles can be considered valid even though there are some shortcomings, such as uncertainty regarding the existence of independent, blind comparisons between the index test and an appropriate reference examination. Then, from the assessment on importance and applicability, it was found that the four articles have the characteristics of a good test and a sufficient description to allow their replication and also interpretation of the research results, which makes all the selected articles eligible to be used as literature for this review.

Article 1 (Klotz, Schindler and Angerer, 2011) examines 1,2-, 1,4-, 1,5-, 1,6-, 1,7-, 2,6-, and 2,7-dihydroxynaphthalene (DHN) as biomonitoring of naphthalene exposure. Although using urine samples from a previous study, samples were obtained through the urine of workers and the general population as controls, both smokers and non-smokers. The GC-MS method was used to calculate the DHN after solid phase extraction and derivatization with bis (trimethylsilyl) acetamide and 5% TMCS. The results showed that 1,2-DHN served as the main metabolite in 54 of the 55 analyzed samples and had the highest quantification result in the group of workers with median values (range) of 1012 µg/L (22–6477 µg/L) for workers and 8 µg/L (<LOD – 62 µg/L) for controls. Moreover 1,4-, 1,7-2,6- and 2,7-DHN were quantified in 61–89% of the samples (range <LOD – 113 µg/L). Meanwhile, 1,5- and 1,6-DHN were not detected in human urine. There was a ten-fold difference in the median results of the 1,2-DHN measurements compared with biomarkers of 1- and 2-naphthol in the worker group, while the control group appeared comparable. Furthermore, 1,2-DHN is a precursor to the potentially carcinogenic naphthalene metabolite, 1,2-naphthoquinone. Through this article, it was found that 1,2-DHN was the most sensitive biomonitoring of exposure to naphthalene. The 1,2-DHN appeared to be the most promising biomarker for estimating naphthalene internal exposures caused by environmental and occupational factors.

Article 2 (Wu *et al*., 2005) examines 1,2-DHN and 1,4-DHN in urine using gas chromatography – mass spectrometry (GC– MS) method in coke workers as an exposed group and in steel

Table 2. Critical Appraisal Results of the Selected Articles

		Article 1	Article 2	Article 3	Article 4
Author		Klotz K, Schindler BK, Angerer J (2011)	Wu et al., (2005)	Klotz et al. (2019)	Klotz et al. (2018)
Study design		Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Number of participants		26	28	10	9
Validity	Diagnostic test evaluated in the representative spectrum of patients	Yes	Yes	Yes	Yes
	The reference was applied	Yes	No	Yes	Yes
	Independent, blind, comparison between the index test and an appropriate reference	Unclear	Unclear	Unclear	Yes
Importance	Test characteristic presented	Yes	Yes	Yes	Yes
Applicability	The method for performing test described to permit replication	Yes	Yes	Yes	Yes
Level of evidence		3b	3b	3b	3b

industry workers as a control group using the same examination method as Article 1. Enzymatic digestion of urinary conjugates was used to release the DHNs, which were then analyzed as trimethylsilyl derivatives by GC–MS. The assay limits of detection for 1,2-DHN and 1,4-DHN, were 0.21 and 0.15 g/l respectively, the assay limits of quantitation were 0.69 and 0.44 g/l, and the coefficients of variation were 14.7 and 10.9 percent. This method was successfully used to determine urinary levels of 1,2-DHN and 1,4-DHN in coke workers (14 top workers and 13 side-bottom workers) and 21 matching control workers from the northern Chinese steel industry. The results showed that 1,2- and 1,4-DHN significantly and strongly correlated with 1- and 2-naphthol, which is a long-used exposure biomonitoring method ($rs \geq 0.623$; $p < 0.0001$). The 1,2-DHN significantly ($p \leq 0.0031$) had a geometric mean level that was 100 times higher than that of 1,4-DHN in the exposed group and 30 times greater in the control group. Then, the DHN measurement results were marginally greater in the exposed workers who smoked ($p = 0.0646$). The findings of this study indicated that 1,2-DHN and 1,4-DHN were useful biomarkers for assessing naphthalene exposure in coke workers. Because DHNs are precursors of naphthoquinones, which have been implicated as toxic elements of naphthalene metabolism, urinary DHN measurements may have toxicological implications.

The purpose of Article 3 (Klotz *et al*., 2019) is to investigate the correlation between occupational naphthalene exposure and biological exposure markers. It collected urine samples from workers who had been exposed to naphthalene in industrial abrasives. Ten workers from the abrasives industry, both lowly and highly exposed, were chosen to represent a wide range of exposure. Airborne naphthalene exposure was also measured using the GGP mini-sampling system for personal air monitoring for one shift and for biological monitoring before and after shift urine samples collected on 2 days of a working week. The data were then measured using gas chromatography – flame ionization detector (GC-FID). The airborne naphthalene was found to be 0.5 - 11.6 mg/m^3. Some of the metabolites analyzed in urine showed that after shift concentrations, including 1,2-DHN, were found to be 114–51,809 µg/L, 1-naphthol of 2–2698 µg/L, 2-naphthol of 4–1135 µg/L, and 1-naphthylmercapturic acid (NMA) of 0.8–666 µg/L. Meanwhile, 2-NMA was not detected. In the article, it was found that the levels of naphthalene metabolites in the urine increased significantly from before the shift to after the shift and at the beginning

of the week to the end of the working week. In addition, there was a significant positive correlation between naphthalene personal exposure in air and1,2-DHN, 1-NMA, 1-naphthol and 2-naphthol tested in urine after shift. The metabolite with the highest concentration in urine samples was 1,2-DHN, by far the most abundant of the biomarkers identified.

In Article 4 by Klotz *et al*. (2018), nine workers exposed to naphthalene handling with creosote were examined for the naphthalene metabolites 1,2-DHN, 1-NMA and 2-NMA as well as 1-naphthol and 2-naphthol. At various workplaces, air sampling was used to characterize the exposure in task-related exposure situations. The main metabolite in the 51 urine samples studied was 1,2-DHN, which had concentrations ranging from 2.3 to 886 µg/g-creatinine (median 34 µg/g creatinine). Meanwhile, the concentrations of 1-naphthol and 2-naphthol ranged from 2.6 to 174 µg/g-creatinine (median 15 µg/g-creatinine). Concentrations of 1-NMA ranged from < LOD (Limit of Detection) to 2.4 µg/g creatinine (61 percent greater than LOD), where as 2-NMA was not detected in the urine samples tested. Significant correlations were found between the biomarkers 1,2-DHN, 1- and 2-naphthol, and 1-NMA, indicating that naphthalene was the common exposure source. However, there was no significant correlation between the concentration of naphthalene metabolites and the concentration of naphthalene in air in this article. This is probably due to fluctuating exposures during the shift and the absence of personal air monitoring during the whole shift. Even so, this still shows that 1,2-DHN was the most sensitive and precise parameter of the biological monitoring of naphthalene exposure at workplace, along with 1-NMA.

DISCUSSION

Naphthalene is commercially produced from coal tar and petroleum. It is used to make a variety of chemicals, including phthalate plasticizers, naphthalene sulfonates and dyes, the insecticide carbaryl, and synthetic leather tanning chemicals. It is used as an intermediate in the production of several pharmaceuticals. As a moth repellent, crystalline naphthalene has been largely used. Workers may be exposed to it through inhalation or dermal absorption in environments such as naphthalene production, coal coking operations, and creosote wood treatment (National Biomonitoring Program, 2017).

In the articles reviewed, samples of workers come from various industrial fields who have experienced exposure to naphthalene with the aim to obtain a representative picture to determine whether 1,2-dihydroxynaphthalene (DHN) can be used as a biomarker in exposed workers.

Based on its metabolism, 1,2-DHN is the precursor of the possibly carcinogenic metabolite of naphthalene, which is 1,2-naphthoquinone. Thus, 1,2-DHN is also thought to be a promising biomarker in humans exposed to naphthalene. In article 2 (Wu *et al*., 2005), it was found that the urinary level of 1,2-DHN from side-bottom coke workers was strongly correlated with 1- and 2-naphthol in urine. The result indicates that 1,2-DHN was a good biomarker for assessing naphthalene exposure in workers. In Article 2, it was found that the urinary level of 1,2-DHN from side-bottom coke workers was 30 times and that of top coke workers was 100 times higher than the control. In addition, when correlated with 1- and 2-naphthol, 1,2-DHN and 1,4-DHN had a high correlation ($r_s > 0.623$; $p < 0.0001$). It is also noteworthy that the levels of 1,2-DHN were marginally more correlated with those of 1-hydroxynaphthalene ($r_s = 0.920$) than of 2-hydroxynaphthalene ($r_s = 0.870$) (Wu *et al*., 2005) .

Based on Article 1 (Klotz, Schindler and Angerer, 2011), further method development regarding the instability of the analytical standards 1,2-DHN is required for the development of a robust analytical method. The method used, however, is sufficiently valid to assess the environmental as well as occupational medical diagnostic specificity. Article 1 (Klotz, Schindler and Angerer, 2011) also showed that 1,2-DHN as major naphthalene metabolite in humans can be used as a biomarker. However, compared to the long-established biomarkers of 1- and 2- naphthol, 1,2-DHN is a more complex parameter to analyze, despite its higher diagnostic specificity (Hartwig, Arand and Commission, 2020). Moreover, 1- and 2- naphthol as established biomarkers were approved by the commission, and an established methodology would be needed to assess 1,2-DHN (Sams, 2017; Omidi, Dehghani and Jamaleddin Shahtaheri, 2020). In workplaces with high PAH exposures, such as infeed converter 1,2-DHN excretion is about tenfold higher than 1- and 2-naphthol (median 1012 µg/L for 1,2-DHN, 122 µg/L for 1-naphthol and 80 µg/L for

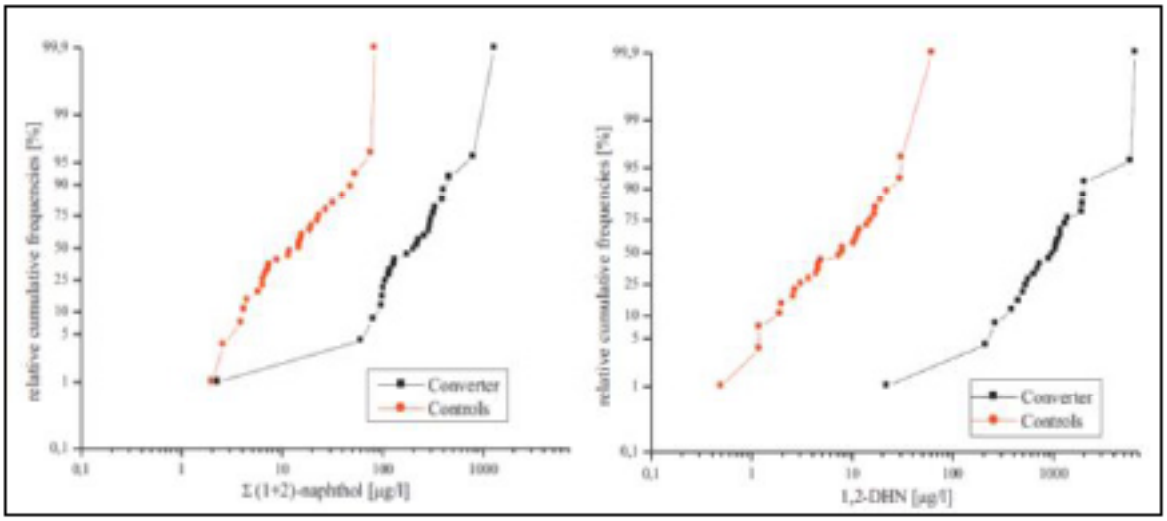

Figure 2. Relative cumulative frequencies of naphthol and 1,2-DHN (Klotz, Schindler and Angerer, 2011)

2-naphthol). The relative cumulative frequencies of 1- and 2-naphthol (left) and 1,2-DHN (bottom) in urine of controls with no occupational PAH-exposure and infeed converter workers are depicted in Figure 2 (Klotz *et al*., 2018).

In Article 4 (Klotz *et al*., 2018), the correlation between external and internal naphthalene exposure was investigated using linear regression analysis, but no significant correlations were found. It is estimated that the fluctuating PAH exposure during a shift with a peak situation is thought to result in workers being exposed in a non-continuous manner. However, statistically significant associations were found across all of the biomarkers tested, with the Pearson's correlation coefficients varying from 0.432 to 0.957 ($p < 0.01$), indicating that naphthalene is one of the significant exposure in the workplace. There was also a significant increase in the concentration of 1,2-DHN in exposed employees from pre-shift to post-shift ($p < 0.05$). Meanwhile, there were no major differences in 1- and 2-naphthol concentrations before and after the shift. In this article, 1,2-DHN was compared to 1- and 2-naphthol, as well as 1- and 2-naphthylmercapturicx acids (NMA), as a sensitive and specific biomonitoring parameter of naphthalene exposure. The results showed the overall sensitivity of I,2-DHN is the highest among other metabolites in indicating naphthalene exposure, which is possible because 1,2 and 1,4-DHN is the reduction product of 1,2- and 1,4- naphthoquinone (Wu *et al*., 2005; Cho, Rose and Hodgson, 2006). Even though its metabolites may be more stable, Wang (2020) found that 1,2-DHN was present in the highest concentrations in humans compared to other naphthalene metabolites. In addition, 1-naphthol also increased in humans but had no difference in mice (Wang *et al*., 2020). Thus 1,2 DHN may better describe the metabolites of naphthalene in humans.

Article 3 (Klotz *et al*., 2019) and Article 4 (Klotz *et al*., 2018) were produced by the same first author. Previously it was stated that Article 4 (Klotz *et al*., 2018) did not find correlations between external and internal naphthalene exposure, so in Article 3 (Klotz *et al*., 2019) the data were re-analyzed statistically, resulting in a significant correlation ($p<0.01$) with a strong Pearson's correlation coefficient ($R2=0.944$). Using the correlation, the biomarker equivalent concentration in urine can be calculated in relation to occupational exposure limits in workplace's water. The biomarker equivalent concentration for the occupational exposure limit (OEL) of 2 mg/m^3 can be calculated up to 4940 µg/L for 1,2-DHN (Klotz *et al*., 2019).

Since 1,2-DHN is a new parameter, there are only a few studies in the literature that present biomonitoring results. Furthermore, the high-cost and complex analysis on 1,2 DHN might be re-considered as the first-line method in naphthalene intoxication diagnosis (Johnsen *et al*., 2017). Biomonitoring results for 1- and 2-naphthol, on the other hand, can be compared and analyzed with extensive data reported in occupational medicine for collectives. Another biomarker that has been widely studied even until recent years is 1- and 2- hydroxynaphthalene (Wang *et al*., 2017; Nie *et al*., 2018; Du *et al*., 2020). Simulations carried out by Li *et al*. showed excellent sensitivity to 1-hydroxynaphthalene (1-OHN) and 2-hydroxynaphthalene (2-OHN) levels as a

prospective biomarker (Li *et al*., 2021). Further study on 1,2-DHN is urgently needed to gain attention of this new parameter and lower the cost.

CONCLUSION

Naphthalene is colorless and white solid with a camphor odor, and it can also be found in coal tar, gasoline, and diesel fuel. Naphthalene is used to make phthalic anhydride, moth repellent, and lubricants. In addition, naphthalene is used in the production of synthetic tanning, preservatives, textile chemicals, abrasives, emulsion breakers, and motor fuel. Exposure to naphthalene is associated with hemolytic anemia, damage to the liver and kidney, and cataracts. Naphthalene is, therefore, considered as possibly carcinogen to humans.

Based on the four scientifically reviewed articles, 1,2-dihydroxynaphthalene (DHN), as one of the major metabolites of naphthalene, is very likely to be a biomarker that is routinely tested in exposed workers. Nevertheless, 1,2-DHN in urine is still a more demanding parameter than the tests recommended for biomonitoring exposure to naphthalene, 1- and 2-naphthol. This scientific review demonstrates the potential of using 1,2-DHN either alone or in combination with other available biomarkers to assess the uptake and metabolism of naphthalene in workers as a health surveillance. Further research is still needed to develop the analysis method for 1,2-DHN to confirm the different results on the correlation between internal and external exposure of naphthalene in workplace, and to determine changes in 1,2-DHN levels in the body by increasing the dose or duration of naphthalene exposure.

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