

Bronchial Asthma among Synthetic Fertilizer Factory Workers Exposed to Ammonia

Dwitya Solihati¹, Muhammad Ilyas²

¹Occupational Medicine Specialist Program, Department of Community Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

²Division of Occupational Medicion, Department of Community Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

First and Corresponding author: Dwitya Solihati

E-mail: tyababibi13@gmail.com

Abstract

Background: Ammonia is colorless gaseous compound, lucid and irritating material that is water soluble with a distinctly pungent odor. About 80% of the total usage of ammonia is mainly used to produce synthetic fertilizers. One of the health problems caused by ammonia is bronchial asthma. Ammonia can act as sensitizer or irritant asthmagen depend on their properties, which increased complex interaction of inflammation, airway hyperresponsiveness, and airflow obstruction. However, the causal relationship between ammonia and bronchial asthma is still unclear, so it is necessary to look for some evidence regarding this relationship. The search for evidence also included the seven-step assessment of occupational diagnosis of diseases. Therefore, it can assist occupational medicine doctors who treat patients with bronchial asthma and with a history of ammonia exposure.

Methods: The literature searching using the electronic database “PubMed”, “Scopus”, and “Cochrane” search engine. Keywords used were worker, ammonia, and bronchial asthma, ventilatory disorder, respiratory disorder. The articles were selected using the defined inclusion and exclusion criteria. The selected articles were then be critically reviewed based on etiological studies from the Oxford Center of Evidence-Based Medicine.

Result: From the five literature obtained, there are differences in results. One article stated that ammonia can increase prevalence risk of bronchial asthma, and other four articles found significant associations between ammonia and reduction in the parameters of pulmonary function.

Conclusion: There is a relationship between ammonia exposure and the prevalence of bronchial asthma and reduction of pulmonary function in synthetic fertilizer factory worker. But it is uncertain whether the diagnosis is occupational asthma.

Keywords: worker, ammonia, bronchial asthma, ventilatory disorder, respiratory disorder

Abstrak

Latar belakang: Ammonia adalah senyawa gas yang tidak berwarna, bersifat iritasi, larut dalam air dengan bau yang menyengat. Sekitar 80% dari total penggunaan amonia terutama digunakan untuk memproduksi pupuk sintetis. Salah satu gangguan kesehatan yang dapat ditimbulkan oleh amonia adalah asma bronkhial. Amonia dapat bertindak baik sebagai sensitizer atau iritan tergantung pada bentuk sediaannya. Paparan amonia dapat meningkatkan kejadian interaksi kompleks di saluran napas yaitu peradangan, hiperresponsif saluran napas dan obstruksi aliran udara. Namun, hubungan sebab akibat antara amonia dan asma bronkhial masih belum jelas, sehingga perlu dicari beberapa bukti mengenai hubungan tersebut. Pencarian bukti juga dilengkapi dengan penilaian tujuh langkah penyakit akibat kerja sehingga dapat membantu dokter kesehatan kerja yang mendapatkan pasien dengan asma bronkhial serta memiliki riwayat terpajan amonia.

Metode: Pencarian literatur menggunakan basis data Pubmed, Scopus dan Cochrane. Kata kunci yang digunakan “worker”, “ammonia”, “bronchial asthma”, “ventilatory disorder” and “respiratory disorder”. Pemilihan artikel dilakukan dengan menggunakan kriteria inklusi dan eksklusi yang telah ditentukan. Artikel yang terpilih akan ditelaah secara kritis berdasarkan studi etiologi dari Oxford Centre of Evidence-Based Medicine.

Hasil: Dari kelima literatur yang terpilih, terdapat perbedaan hasil. Satu artikel menyatakan bahwa amonia dapat meningkatkan risiko prevalensi asma bronkhial dan empat artikel lainnya menemukan adanya hubungan yang signifikan antara amonia dan penurunan parameter fungsi paru.

Kesimpulan: Terdapat hubungan antara paparan amonia dengan prevalensi asma bronkhial dan penurunan fungsi paru pada pekerja pabrik pupuk sintetis. Namun, belum dapat dipastikan bahwa diagnosisnya adalah asma akibat kerja.

Kata kunci: pekerja, amonia, asma bronkhial, gangguan ventilasi, gangguan respirasi

Introduction

Ammonia is colorless gaseous compound, lucid and irritating material that is water soluble with a distinctly pungent odor. Ammonia in this form is also known as ammonia gas or anhydrous (“without water”) ammonia. Ammonia gas can also be compressed and becomes a liquid under pressure. Ammonia easily dissolved in water. In this form, it is also known as liquid ammonia, aqueous ammonia or ammonia solution. Ammonia is very important to plant, animal and human life. It is found in water, soil and air and is a source of much needed nitrogen for plant and animals.^{1,2,3}

Recently, ammonia is used in farming, textile and fermentation industries, refrigeration operation, fertilizers and in the production of plastics and explosives. Eighty percent of all manufactured ammonia is used as fertilizer.⁴

Ammonia can be absorbed into the human body via inhalation, oral, ocular and dermal routes. Ammonia is absorbed readily through mucous membrane and the intestinal tract but not through the skin. Systemic absorption following dermal or ocular exposure is not considered significant. Ammonia is endogenously produced in the gut from bacterial breakdown of nitrogenous constituent of food. In healthy adults, the physiological ammonia level in blood is typically below 35 µmol/L (approximately 0,67 mg/L). In the liver, ammonium ions are extensively metabolized to urea and glutamin. Ammonia reaching the circulation is principally excreted by humans as urinary urea. Excretion of absorbed ammonia in exhaled breath and faeces is not significant. Small amount of ammonia are excreted in urine, the average daily excretion for human is approximately 2-3 ug, about 0,01 % of the total body burden. Small amount of unabsorbed ammonia may also be excreted from gastrointestinal tract in faeces.^{1,2,3}

The clinical manifestations of acute ammonia exposure are usually immediate in presentation and its toxic effects are mediated through its irritant and corrosive properties. After inhalation of ammonia, the damage to the respiratory tract depends on the concentration, pH, length of exposure and depth of inhalation. Inhalation of ammonia will rapidly cause irritation to the nose, throat and respiratory tract.^{2,5}

There are very few studies of occupational exposure to ammonia. In particular, data on the effects of prolonged exposures to ammonia gas are scarce. Very

few investigators have studied the chronic effects of exposure to low ammonia concentrations and chronic effects on lung function that could be related to length and intensity of exposure have not been investigated.⁵

To determine the causal relationship between ammonia and bronchial asthma, it is necessary to look for some evidence regarding this relationship. The search for evidence is also complemented by seven-step of occupational diagnosis of disease as instituted by the Indonesian Occupational Medicine Specialist Association (IOMA)⁶, to help determine whether there is any causal relationship between a disease and work exposure.

Method

We conducted literature searches using electronic databases, that is, PubMed, Scopus, and Cochrane. The keyword were (“worker”) AND (“ammonia”) AND (“bronchial asthma” OR “ventilatory disorder” OR “respiratory disorder”) The articles were selected using the defined inclusion and exclusion criteria . The search strategy is shown in a flowchart in Figure 1. The selected literature was critically appraised using relevant criteria with the worksheet for etiology study from Oxford Centre of Evidence-Based Medicine.⁷ We used the prevalence value of bronchial asthma from the Riskesdas 2018 as the PEER value (2%), with the assumption that bronchial asthma in the population was not due to ammonia exposure.

Result

The searching was completed on August 27th, 2020. Of the online searches, it resulted in five selected articles that met the inclusion and exclusion criteria. The selected articles consisted of four cross sectional studies by Ballard S.G et al. (1998), Ali B.A et al (2001), Rahman M.A (2007) and Neghab M (2018), and one cohort study by Mahdinia M (2020). Critical appraisal are shown in Table 1.

The first article by Ballard S.G et al (2014)⁸, a cross sectional study, determine the association between a wide ammonia exposure range and respiratory symptoms and bronchial asthma among two chemical fertilizer factory workers in Saudi Arabia. In this article,

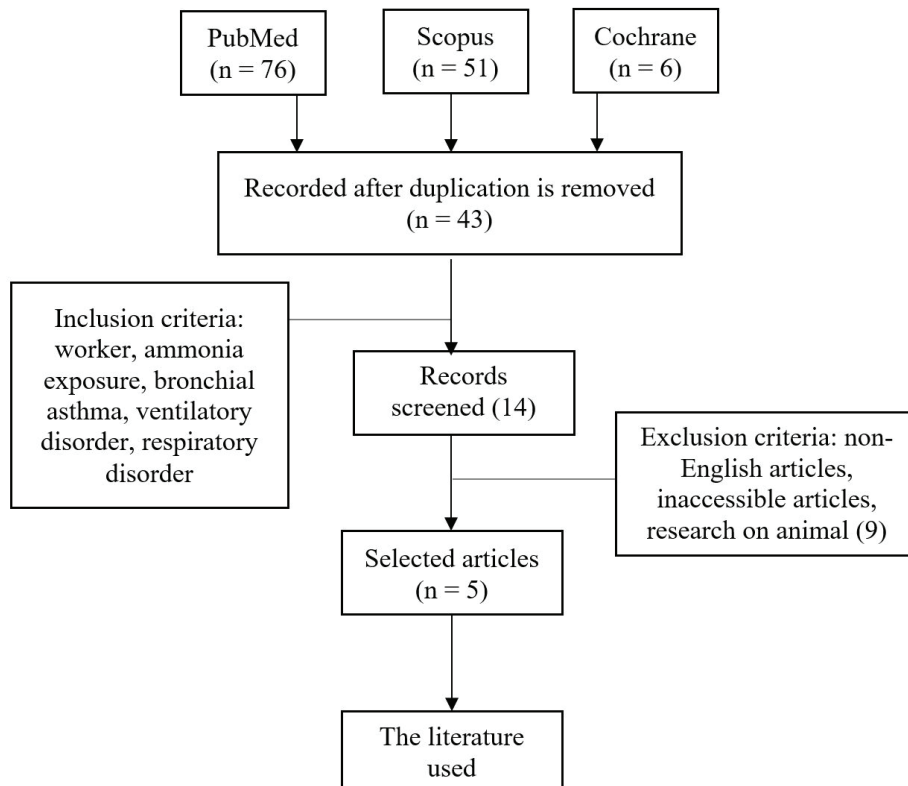


Figure 1. Flowchart of literature search

161 exposed worker and 355 control which selected by sytematic sampling, completed a respiratory symptoms questionnaire with additional questions on present and past occupations. Ammonia concentrations were measured in the different sections of the factories. The ammonia concentration in factory A ranged from 2,0 – 130,4 mg/m³ of air and in factory B from 0,02 – 7,0 mg/m³. Distribution of symptom by ammonia exposure level (\geq the ACGIH Treshold Limit Value (TLV) of 18 mg/m³ of air) shows significantly higher relative risks for all four symptoms (cough, wheezing, phlegm, dyspnoea) among those exposed to ammonia levels above the TLV, but wheezing was also high among those exposed to ammonia levels at or below TLV. A diagnosis of bronchial asthma was statistically significant among workers exposed to ammonia level above the TLV (> 18 mg/m³) and cummulative ammonia concentration > 50 mg/m³ of air years (RR 4,32 ; 95% CI 2,08-8,98 and RR 5,32; 95% CI 1,72-16,08).

The second article by Ali B.A et al⁹ (2001), a cross sectional studies, determine effect of chronic exposure to ammonia on pulmonary function among ammonia workers in Saudi Arabia. 77 workers were randomly selected from an ammonia factory in the Eastern Province of Saudi Arabia and 355 were selected as control from the administrative staff of four industrial groups in Eastern Province. The ammonia level in the working environment was determined spectrophotometrically. Pulmonary Function Testing (PFI) of control and exposed workers was performed in the morning using a dry below portable spirometer. At least three acceptable spirometric tracings were recorded for every subject and the highest FEV₁, FVC and FEV₁/FVC were selected. Significantly lower FEV₁% predicted (p < 0,010) and FVC% predicted (p < 0,05) but not FEV₁/FVC% were observed in the group with cummulative ammonia exposure (above 50 mg/m³ of air years). Comparison of PFIs between symptomatic

Table 1. The Critical Appraisal of The Study

| Question | Article 1 | Article 2 | Article 3 | Article 4 | Article 5 |
|--|-----------|-----------|-----------|-----------|-----------|
| Is the result of this harm study valid? | | | | | |
| Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause? | Yes | Yes | Yes | Yes | Yes |
| Were treatments/exposures and clinical outcomes measured in the same ways in both groups (was the assessment of outcomes either objective or blinded to exposure)? | Yes | Yes | Yes | Yes | Yes |
| Was the follow-up of study patients sufficiently long and complete? | No | No | No | No | Yes |
| Do the results satisfy some “diagnostic tests for causation”? | | | | | |
| Is it clear that the exposure preceded the onset of the outcome? | No | No | No | No | Yes |
| Is there a dose-response gradient? | Yes | Yes | Yes | Yes | Yes |
| Is there positive evidence from a “dechallenge-rechallenge” study? | No | No | No | No | No |
| Is the association consistent from study to study? | Yes | Yes | Yes | Yes | Yes |
| Does the association make biological sense? | Yes | Yes | Yes | Yes | Yes |

and asymptomatic exposed worker revealed significantly lower FEV1% predicted ($p < 0,05$) and FEV1/FVC% predicted ($p < 0,05$) among the symptomatic workers.

The third article by Rahman H et al¹⁰(2007), a cross sectional study in Bangladesh which aimed to assess the association between personal exposure to ammonia (breathing zone) and acute respiratory symptoms and lung function changes among workers across the work shift in urea fertilizer factory. 63 operators in the ammonia plant and 77 operators in urea plant were included in this study as the exposed group and 25 administrative workers were included in this study as control group. Personal ammonia exposure was measured by two direct-reading methods: the drager PAC III monitoring instrument and the Drager diffusion tube. Prevalence of acute respiratory symptoms such as cough and chest tightness was higher

among worker who exposed to an average concentration of ammonia of about 26,1 ppm ($p = 0,05$ dan $p = 0,02$). This study also found a significant decrease in FVC ($p = 0,01$) and FEV₁ ($p = 0,05$) during the work shift among workers in urea factory. However, lower concentration (6,9 ppm) did not induce similar effect.

The fourth article by Neghab et al¹¹(2018), a cross sectional study, determine association between long term exposure to low levels of ammonia and ventilatory disorder among workers in Iranian petrochemical industries, producing ammonia. The studies population consisted of 67 male operational workers and 57 male repair and maintenance workers as exposed group and 120 male office workers of the same plant as control group. The mean concentration of ammonia in the breathing zones of the operational, repair and maintenance workers and its environmental

Table 2. The Critical Appraisal of The Study (continued)

| Question | Article 1 | Article 2 | Article 3 | Article 4 | Article 5 |
|---|-------------------------|-----------|-----------|--|-----------|
| Are the valid results from this harm study important? | | | | | |
| What is the magnitude of the association between the exposure and outcome? | RR 4,32 | p < 0,05 | p < 0,05 | VC : β -6,61 FEV : β -3,95 | P < 0,05 |
| What is the precision of the estimate of the association between exposure and outcome? | 95% CI (2.08 – 8,98) | - | - | VC : 95% CI (-11, 19 to -2,12) FEV1 : 95% CI (-7,23 to -0,68) | - |
| Should these be valid, potentially important results change the treatment of your patient | | | | | |
| Do the results apply to our patient? | Yes | Yes | Yes | Yes | Yes |
| Is our patient so different from those in the study that its results don't apply? | No | No | No | No | No |
| What are our patient's risks of the adverse event? | PEER = 0,02 | - | - | - | - |
| To calculate the NNH (number of patients we need to treat to harm one of them) for any odds ratio (OR) and our patient's expected event rate for this adverse event if they were not exposed to this treatment (PEER): $NNH = \frac{PEER(\theta - 1) + 1}{PEER(\theta - 1) \times (1 - PEER)}$ | NNH = 16 | | | | |

and peak concentration were $1,35 \pm 4,59$, $0,29 \pm 0,31$, $0,64 \pm 1,34$, and $94,8 \pm 83,1$ ppm. The result study show that exposed subjek experienced a significant cross shift decrement in some parameter of their pulmonary function (acute changes) and mean baseline value (preshift) of VC, FVC and FEV1 in the high exposed group were significantly lower than those of referent individuals . Exposure to low atmospheric concentrations (1,35 ppm) of ammonia for about 5 years was associated with 6,61 and 3,95 units decline in VC and FEV1 value, respectively { β (95% CI yaitu -6,61 (-11, 19 to -2,12), p=0,004 and -3,95 (-7,23 to -0,68) p = 0,02 }.

The fifth article by Mahdinia et al¹² (2020) was a historical cohort study conducted on the 122 workers of four synthetic fertilizer industries in 5 years from 2015

to 2019. This study aimed to investigate respiratory disorders associated with exposure to low concentrations of ammonia. The prevalence rate of respiratory disorder significantly increased in the exposure group over 5 years (P < 0,05) and frequencies of these symptoms in the exposure group were significantly higher than non exposure group (P<0,05). Respiratory function were decrease significantly in the exposure group and were lower than non exposure group (P < 0,05). Exposure and the amount of exposure to ammonia had a significant relationship with respiratory disorders and respiratory function (P < 0,05)

After critically assessed, there was only one article, a cohort study, conducted by Mahdinia et al.¹² It was the best study to establish a causal relationship between exposure and outcome and has reliable data collection

method and outcome measures, and long-term and complete follow-up of the study. Meanwhile, the other four articles have limitations in determining a causal relationship.⁸⁻¹¹ This is due to the study designs used (cross sectional study) were not suitable to determine whether the exposure happened prior to the outcome occurred. However, these four articles are valid enough to be used as illustrations to determine if there is any possibility of a causal relationship between ammonia exposure and the prevalence of bronchial asthma in synthetic fertilizer factory workers. The validity of each article can be assessed from the method is used. All articles determined or divided the respondents' groups clearly, and assessed the outcome and the exposure using respiratory symptoms questionnaire and spirometry test to assess reduction in the parameters of pulmonary function.

Ballal S.G et al⁸, declare that the exposed workers were at high risk of respiratory symptoms which is bronchial asthma. This article stated as valid studies and the magnitude of the relationship between ammonia and bronchial asthma is considered of importance. The study by Ali B.A et al⁹ raise the possibility that exposure to a high cumulative ammonia level produces a combined restrictive / obstructive ventilatory defect. Another findings have been reported by Rahman et al¹⁰, that significant cross shift decrement were noted in most parameters of pulmonary function of exposed worker and after a 7 day exposure free period, acute decrements in the parameters of pulmonary function were found to be reversible and each year exposure to ammonia was shown to be associated with a decrement of about 0,6% in FEV₁ value. In line with these finding, Neghab et al¹¹ showed that low levels of ammonia is associated with significant chronic irreversible and acute reversible decrements in the lung' functional capacity.

Discussion

We used the seven steps of occupational diagnosis as instituted by IOMA⁶ in order to determine the relationship between diseases with workers if we found that the workers are with bronchial asthma exposed to ammonia.

The first step was to determine the clinical diagnosis. Bronchial asthma can be diagnosed through history-taking, physical examination and supportive examination such as spirometry test or lung function test. History-taking reveals more than one of these typical symptoms

such as wheeze, shortness of breath, chest tightness and cough,^{13,14} and a history of exposure to allergen substances.¹⁵ Physical examination in people with asthma is often normal, but the most frequent finding is wheezing on auscultation, especially on forced expiration. Spirometry test or lung function test showed an evidence of variable expiratory airflow limitation. At least once during the diagnostic process (e.g. when FEV₁ is low), document that the FEV₁/FVC ratio is below the lower limit of normal. Document that variation in lung function is greater than in healthy people. For example, excess variability is recorded if FEV₁ increased by 200 ml and > 12% of the baseline value after inhaling a bronchodilator and FEV₁ increased by 200 ml and > 12% of the baseline value after 4 weeks of anti inflammatory treatment (outside respiratory infections).^{13,14}

The second step was to determine exposure in the workplace or work environment. All physical, chemical, biological, ergonomics, and psychosocial hazards in the workplace that potentially causes occupational disease or increases the risk of occupational disease must be listed. In this case, ammonia of which has the risk of causing bronchial asthma, will be investigated. Details needed include the company, its products, the material used for the process, worksite, job description, and the usage of protective devices and equipment while working. The history-taking has to cover a complete anamnesis of the job description, including a description of all the work in chronological order, such as the time needed doing each task, the product resulted, the material used, and how it works. It is better to be guided by MSDS (Material Safety Data Sheet) of material used.

Workers can be exposed to ammonia through inhalation, skin, eyes and ingestion. In this case, we can ask the worker about ammonia exposure in the workplace and then we can measured ammonia concentration in the working environment. We also monitor ammonia concentration in breathing zone or whole blood ammonia, so biomonitoring is needed.^{1,2,3}

The third step was to determine whether there was any relationship between exposure to the disease. Make sure to identify any exposure-related disease. This relationship should be based on the result of previous epidemiological studies (evidence-based). Identifying whether or not there is any relationship between ammonia and bronchial asthma, can be done by reviewing existing literature or references and applying Bradford Hill's Criteria:

1. Strength of association

Of the five appraised articles, one articles suggested a significant relationship between ammonia and bronchial asthma, namely a study conducted by Ballad S.G et al.⁸ with RR 4,32 (95% CI 2.08 – 8,98, $p < 0.001$). Other article by Neghab M et al¹¹ showed that exposure to low atmospheric concentrations (1,35 ppm) of ammonia for about 5 years was associated with 6,61 and 3,95 units decline in VC and FEV1 value respectively { β (95% CI yaitu -6,61 (-11, 19 to -2,12), $p=0,004$ and -3,95 (-7,23 to -0,68) $p = 0,02$ }.

The confidence interval of the study by Ali B.A et al.⁹ and Rahman H et al and Mahdina et al could not be assessed statistically, even though Ali B.A study showed that chronic exposure to high cumulative concentrations of ammonia ($> 50\text{mg}/\text{m}^3$ years) was statistically significant reduced some parameters of pulmonary function such as FEV₁ ($p = 0,006$) and FVC ($p = 0,03$). Rahman et al¹⁰ study showed that prevalence of acute respiratory symptoms such as cough and chest tightness was higher among worker who exposed to an average concentration of ammonia of about 26,1 ppm ($p = 0,05$ dan $p = 0,02$). This study also found a significant decrease in FVC ($p = 0,01$) and FEV₁ ($p=0,05$) during the work shift among workers in urea factory. Study by Mahdina et al¹² showed that exposure and the amount of exposure to ammonia had a significant relationship with respiratory disorders and respiratory function ($P < 0,05$).

2. Consistency

The results of 2 out of 5 articles consistently stated that ammonia can increase risk in the prevalence of respiratory symptoms with diagnosis of bronchial asthma and reduction in the parameters of pulmonary function. Three article could not be assessed because there is no magnitude association value.

3. Specificity

Not only ammonia can caused bronchial asthma. Ammonia exposure is known to be one of the 522 asthma agents identified by the Association of Occupational and Environmental

Clinics (AOEC).¹⁶

4. Temporality:

Mahdina M et al.¹² followed the subjects for five years and obtained exposure and the amount of exposure to ammonia had a significant relationship with respiratory disorders and respiratory function ($P < 0,05$). Meanwhile, the other four articles did not follow their subjects for a certain period of time.

5. Dose response

Article 1, 2, 3, 4 and 5 revealed that there are association between dose of ammonia exposure and diagnosis of bronchial asthma or reduction in the parameters of pulmonary function.

6. Plausibility.

Ammonia can act as sensitizer or irritant asthmagen depend on their properties, which increases complex interaction of inflammation, airway hyperresponsiveness, and airflow obstruction.¹⁵

7. Coherent

Of five articles, one article use respiratory symptoms questionnaire to diagnosis bronchial asthma and another four article uses spirometry test to asses reduction in the parameters of pulmonary function.

8. Reversibility (experimental evidence)

All articles did not conducts an experiment.

9. Analogy

Ammonia does not only cause bronchial asthma and vice versa. Bronchial asthma is not cause specifically by ammonia alone.

The fourth step was to determine the sufficiency of exposure in the workplace. In this step, we have to know the length of working in ammonia exposure area in workplace, duration time exposed to ammonia per day, measurement of ammonia level in the workplace and personal protective equipment used in workers. An odor ammonia treshold ranging between 0,05 to 2,6 ppm. For irritant gases and vapors, threshold limit value (TLV) are the reference value recommended by ACGIH to prevent complaints of sensory irritation. Sensory irritation of the eyes and nose are a basis for setting of Occupational Exposure Limits (EOL), accounting for about 40% of all EOLs. National Institute of Occupational Health and Safety (NIOSH) and American Conference of Governmental Industrial

Hygienist (ACGIH) have established a Recommended Exposure Limit (REL) and Threshold Limit Value (TLV) of 25 ppm as an 8h TWA and a short term exposure limit (STEL) of 35 ppm for ammonia.^{1,2,3}

The fifth step was to determine the individual factors that play a role. The patient / family history of atopy does not exclude the possibility of occupational asthma.

The sixth step was to determine the factors outside workplace. Beside workplace, exposure to ammonia comes from cleaning product, farming, textile and fermentation industries, refrigeration operation, and in the production of plastics and explosives. Ammonia in the environment comes from the natural breakdown of mature and dead plants and animals.

The seventh step was to determine the occupational diagnosis. If steps 2, 3, and 4 were appropriate, and there was no factor outside of work to be found, the bronchial asthma is an occupational disease.

Conclusion

We conducted a critical appraisal using the Evidence-Based Medicine etiology study worksheet and Austin Bradford Hill's criteria to determine the causal relationship. To establish an occupational diagnosis in synthetic fertilizer factory workers exposed to ammonia, we can use the seven-step occupational diagnosis of disease - from the first step of determining clinical diagnosis to the step of determining whether there are other factors outside of work considering ammonia still be found on the market.

The five articles stated relationship between ammonia exposure and the prevalence of bronchial asthma and reduction in the parameters of pulmonary function. However, due to limitation from the study design, it is uncertain whether the diagnosis is occupational asthma.

Finally, we recommend that synthetic fertilizer factory, using ammonia should have better knowledge about the health effects of ammonia exposure on their workers. Implement appropriate controls of technique, administration, and personal protective equipment (PPE) to reduce ammonia exposure. Regular monitoring of ammonia exposure in the working environment should be established and work process associated with peak exposures should be identified. In addition, the

workers should be educated and trained to improve their awareness about the respiratory effects of ammonia.

References

1. ATSDR (Agency for Toxic Substance and Disease Registry). (2004). Toxicological profile for ammonia (ATSDR Tox Profile). Atlanta, GA: U.S Department of Health and Human Services, Public Health Service.
2. Public Health England. Ammonia Toxicological Overview. PHE publications gateway number: 2014790. Published August 2015.
3. Toxicological Review of Ammonia. Non Cancer Inhalation: Executive Summary {CASRN 7664-41-7}. Integrated Risk Information System. National Center for Environmental Assessment Office of Research and Development. U.S Environmental Protection Agency. Washington, DC. September 2016.
4. Aika K-I, Christiansen L, Dybkjaer I, et al. Ammonia: Catalysis and Manufacture. Springer Science & Business Media; 2012.
5. Mohamed H et al. Irritation Effect of Ammonia Gas on Workers in Ammonia Factoru at Elberga Petroleum Company During 2017. Scholar Journal of Applied Sciences and Research. 2018. Volume 1-5.
6. Perhimpunan Spesialis Kedokteran Okupasi Indonesia. Pedoman Klinis Diagnosis Dan Tatalaksana Kasus Penyakit Akibat Kerja. Jilid 1.
7. CEBM, Oxford University. Critical Appraisal of Diagnostic Accuracy Studies. 2019;4. Available from: <https://www.cebm.net/wp-content/uploads/2018/11/Diagnostic-Accuracy-Studies.pdf>.
8. Ballal SG, Ali BA, Albar AA, Ahmed HO, Al Hasan AY (1998). Bronchial asthma in two chemical fertilizer producing factories in eastern Saudi Arabia. Int J Tuberc Lung Dis 2, 330-5.
9. Ali BA, Ahmed HO, Ballal SG, Albar AA (2001). Pulmonary function of workers exposed to ammonia : a study in the Eastern Province of Saudi Arabia. Int J Occup Environment Health 7, 19-22.
10. Rahman MH, Brätveit M, Moen BE (2007) Exposure to ammonia and acute respiratory effects in a urea fertilizer factory. Int J Occup Environ Health 13, 153-9.
11. Neghab M, Mirzaei A, Shouroki FK, Jahangiri M, Zare M, and Yousefinejad S. Ventilatory disorders associated with occupational inhalation exposure to nitrogen trihydride (ammonia). Industrial Health. National Institute of Occupational Safety and Health. 2018, 56, 427-435.
12. Mahdinia M, Adeli SH, Mohammad beige A, Heidari H, Ghamari F, Soltanzadeh A. Respiratory Disorders Resulting From Exposure to Low Concentrations of Ammonia. A 5 years historical cohort study. Journal Occupational and Environmental Medicine. Volume 62. Number 8. 2020.
13. Perhimpunan Dokter Paru Indonesia. Asma: pedoman diagnosis dan penatalaksanaan di Indonesia. Edisi ke 1. Jakarta, 2004.
14. Global Initiative for Asthma. Asthma Management and

- Prevention (for adult and Children Older than 5 years). A pocket Guide for Health Professionals. Updated 2020.
15. Malo J.L and Vandenplas O. Definitions and Classification of Work-Related Asthma Jean- Immunol Allergy Clin N Am 31 (2011) 645–662.
 16. www.aoecdata.org/expcodelookup.aspx.