Ventilatory disorders associated with occupational inhalation exposure to nitrogen trihydride (ammonia)

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Abstract: Respiratory effects of long term exposure to low levels of ammonia have not been thoroughly investigated. In this cross sectional study, 124 male subjects (67 high exposed and 57 low exposed), occupationally exposed to low levels of ammonia and 120 male referent individuals were investigated. Airborne concentrations of ammonia were measured and subjects underwent spirometry tests prior to and at end of their daily work shift. Average concentrations of ammonia in the breathing zones of the high and low exposed employees were found to be 1.35 ± 4.59 and 0.29 ± 0.31 ppm, respectively. Additionally, mean baseline values of some parameters of pulmonary function such as Vital Capacity (VC) and Forced Expiratory Volume in the first second (FEV1) in the high exposed group were significantly lower than those of referent individuals. Similarly, significant reversible cross shift decrements were noted in FEV1, VC and Forced Vital Capacity (FVC) of exposed employees. These findings indicate that exposure to low levels of ammonia is associated with significant chronic irreversible and acute reversible decrements in the lungs’ functional capacity.

Key words: Petrochemical plant, Occupational exposure, Ammonia, Lungs’ functional capacity

Introduction

Ammonia is a highly water-soluble, colorless gaseous compound with a characteristic pungent smell, and an odor threshold ranging between 0.05 to 2.6 ppm1, 2). Ammonia is used in farming, textile and fermentation industries, refrigeration operations, fertilizers and in the production of plastics and explosives3, 4). Ammonia is a corrosive agent and dermal exposure to this chemical is associated with severe burns and blisters. Additionally, frostbite may ensue following dermal exposure3, 5). The major effects of acute exposure to ammonia are oronasal and bronchial irritation, airway obstruction, and pulmonary edema6).

This gas is intensely reactive with moist of mucosal surfaces of the eyes, nose, lungs, throat, and skin and produce ammonium hydroxide (NH4OH), causing liquefaction necrosis7, 8).

Recent studies have shown that even exposure to ammonia levels of 0–40 ppm during a 4-h period leads to weak ocular irritation9).
For irritant gases and vapors, threshold limit values (TLVs) are the reference values recommended by ACGIH to prevent complaints of sensory irritation (Alarie, 1981). Sensory irritation of the eyes and nose are a basis for setting of occupational exposure limits (OELs), accounting for about 40% of all OELs.¹⁰

National Institute of Occupational Health and Safety (NIOSH) and American Conference of Governmental Industrial Hygienists (ACGIH) have established a Recommended Exposure Limit (REL) and threshold limit value (TLV) of 25 ppm as an 8-h TWA and a short-term exposure limit (STEL) of 35 ppm for ammonia.⁵

Pulmonary effects of short and long term exposure to high atmospheric concentrations of ammonia have been well documented.¹¹⁻¹⁷

Exposure to high concentrations of ammonia induces nasopharyngeal, tracheal and cutaneous burns, respiratory tract irritation, alveolar edema and death due to cardiac arrest.¹⁸

Close et al.¹⁴, evaluated acute and chronic respiratory effects of accidental exposures to ammonia following accidental spillage of this chemical. Exposure to high concentrations of ammonia over a short period of time (less than 30 min) was associated with upper airway obstruction. Similarly, exposure to lower concentrations of the gas over a longer period of time (more than 30 min) resulted in significant long-term pulmonary sequelae (wheezing) without upper airway obstruction. The symptoms persisted for more than 2 yr.¹⁴ Acute exposure to 5,000–10,000 ppm is rapidly fatal and exposure to 2,500–4,500 ppm is fatal within 30 min.⁵

Extensive burns of the respiratory mucosa, severe tracheobronchitis and a significant reduction in FEV₁ value were reported in a subject following exposure to very high concentrations of ammonia after explosion of a tank of anhydrous ammonia. Severe obstructive pulmonary disease, marked by a remarkable decrease in expiratory flow (FEV₁ values between 41 to 48% of the predicted values) was persistent twelve yr after the accident.¹³

Long-term exposure to lower levels has been associated with sinusitis, mucous membrane inflammation syndrome, chronic bronchitis, and asthma-like symptoms.¹⁹ Results of a cross-sectional study showed that chronic exposure to high cumulative concentrations of ammonia (>70 ppm-yr) compared to lower cumulative exposure levels (≤70 ppm-yr) significantly reduced some parameters of pulmonary function such as FEV₁ and FVC.¹⁶

Additionally, an increase in the prevalence of respiratory symptoms with a diagnosis of chronic bronchitis, bronchial asthma, or both, was reported among subjects exposed to a cumulative ammonia concentration greater than 70-ppm-yr.²⁰

Results of a study (in Bangladesh) showed that exposure to an average concentration of ammonia of about 26.1 ppm was associated with an acute decline in lungs’ functional capacities across the work shift. However, lower concentrations (6.9 ppm) did not induce similar effects.¹⁵

Possible long term effects of occupational exposure to low levels of ammonia have rarely been investigated and are subject of debate and controversy.

In this regard, Preller et al., reported that exposure to low concentrations of ammonia (2.24 ppm) resulted in a decrease in most parameters of pulmonary function except FVC. An increase in exposure to ammonia by a factor of 2.72 reduced FEV₁ value by 270 ml.²¹ Similarly, Donham et al., in two separate studies on swine farmers and poultry workers showed that exposure to 7.5 and 12 ppm of ammonia was associated with an average cross-shift decrement of 3% in FEV₁ value.²², ²³

Conversely, in a study conducted by Heederik et al., the authors did not find any significant association between exposure to low concentrations of ammonia (6.3 ppm) and changes in the parameters of pulmonary function.²⁴

Additionally, Holness et al., did not find any significant difference between the mean values of the parameters of pulmonary function of a group of workers exposed to relatively low ammonia concentrations (9.2 ± 1.4 ppm) and control subjects exposed to a mean concentration of ammonia of 0.3 ± 0.1 ppm.²⁵

Given the above discrepant findings, the main purpose of this study was, to assess toxic response of the respiratory system, if any, following occupational exposure to low levels of this chemical.

**Subjects and Methods**

This cross sectional study was carried out in one of the major Iranian petrochemical industries, producing ammonia, in the South Pars region (Assalouyeh). The studied population consisted of 67 male operational workers (high exposed group) and 57 male repair & maintenance workers (low exposed group) who were selected as exposed group. Both operational workers and repair & maintenance subjects were shift workers engaged in 12-h daily shifts from 7:00 AM to 7:00 PM. A control group of 120 male subjects was recruited by simple random sampling from among 1,500 office workers of the same plant without any
prior or existing exposure to ammonia.

Primary inclusion criteria for selecting the exposed group were as follows:
- History of at least one yr of exposure to ammonia;
- Lack of past history or present exposure to other chemicals with known pulmonotoxic properties and;
- Lack of personal or family history of respiratory illnesses, chest injuries or surgery

With the exception of exposure to ammonia, selection criteria for the referent subjects were similar to those of the exposed workers.

The adherence to the inclusion criteria was checked via completing a questionnaire as well as referring to the medical records of the employees.

Prior to the study, all participants completed an informed consent form and the protocol of the study was approved by the university ethics committee.

Measurement of personal and environmental concentrations of ammonia

The exposure scenario (exposure concentration and daily exposure time) for operational workers was similar (similar exposure group). This was also the case for repair & maintenance workers. Given these similarities, 30 subjects, representative of 67 operational workers and 15 individuals representative of 57 repair & maintenance workers were selected for personal air sampling. These 45 breathing zone samples were collected within several days during autumn 2017 in the plant where, employees used to perform their daily tasks. Additionally, a total of 26 environmental samples were collected during the same time period in parts of the plant where employees used to spend most of their daily working hour. Given the low atmospheric concentration of ammonia, the sampling time extended to 12-h to cover the whole working shift. The concentrations of ammonia were measured according to the NIOSH method 6016.

In brief, a cellulose ester membrane filter (pore size 0.8 μm) with a diameter of 37 mm (SKC Cat. No. 225-3-01) was placed in a special cassette to remove the interfering particles. Then, an adsorbent tube containing silica gel coated with sulfuric acid (SKC: Cat. No. 226-10-06) was placed into the circuit for absorption of ammonia. The flow rate of the personal sampling pump (SKC: AirChek® XR5000) was adjusted to 200 ml/min. Air samples were collected over one work shift. Samples were then transferred to the laboratory and extracted by deionized water. They were then carefully injected into an ion chromatograph (Metrohm Switzerland, model 850) and the ammonia concentrations were calculated relative to standard solutions. Finally, the results compared to adjusted TLV-TWA by Brief and Scala model. In this model, the reduction factor for a 12-h work shift is 0.526

Peak exposures were measured when there was a leakage or a faulty system (this occurred 10 times during the season). Both operational and repair & maintenance workers were present when there was a leak. However, this type of exposure was limited to a couple of minutes during a working shift and repair & maintenance workers were responsible to fix the faulty system and leakage. Peak exposures were determined by a direct-reading instrument (GasAlert Extreme (GAXT-A2-DL) with a measuring range of 0 to 400 ppm of ammonia.

It has to be reiterated that the industry in which this study was undertaken is a relatively young and new industry and it has not undergone any significant changes in the operating processes over the last few years. Therefore, given the above and in view of the results of periodic air sampling for detection of airborne concentrations of ammonia, it could be tentatively concluded that the ammonia concentrations, more or less, have been constant over the last few years.

Pulmonary Function Tests (PFTs)

Pulmonary function tests (PFT) including Vital capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1), FEV1/FVC ratio and Peak Expiratory Flow (PEF) were measured by a calibrated spirometer device (Spirolab III manufactured by MIR Italy).

Measurements were performed only once for the referent subjects (prior to the shift) and twice for the exposed group (prior to the shift of the first working day of the week (after a week of exposure free period) and at end of shift of the same day) in standing position.

For each subject three measurement were conducted and the largest volumes were selected for analysis.

Data Analysis

Statistical tests were conducted using SPSS V16.0. The data were statistically analyzed using Student’s t-test, $\chi^2$ or Fisher’s exact test, Scheffe Post Hoc test, Mann-Whitney U test and multiple linear regression analysis, where applicable. A $p$ value of less than 0.05 was considered significant. Experimental (descriptive) results are presented as arithmetic means ± SD.

In the regression analyses dependent variable was pre-
Regression analyses were conducted three times (operational vs. referent, repair & maintenance vs. referent and operational vs. repair & maintenance) using binary qualitative (exposure or lack of exposure) data (individuals of exposure free group labeled zero in the model and exposed subjects labeled one). Results of these three analyses merged and formed Table 4.

To conduct multiple linear regression analysis, the main variable was considered to be exposure to ammonia. Other variables such as age, height weight, marital status and smoking habits were considered as potential confounders and their simultaneous effects on changes in the parameters of pulmonary function were controlled.
Results

Some of the main characteristics of the studied groups are provided in Table 1. As shown, the mean values of age, length of employment and the proportion of the smokers and married subjects among the high exposed group were significantly lower than those of the low exposed and referent subjects.

Table 2 presents the results obtained from analysis of samples containing ammonia. The mean concentrations of ammonia in the breathing zones of the operational, repair & maintenance workers and its environmental and peak concentrations were 1.35 ± 4.59, 0.29 ± 0.31, 0.64 ± 1.34, and 94.8 ± 83.1 ppm, respectively. Only the peak exposure exceeded the current TLV-C (ceiling limit) value of 50 ppm. No detectable concentrations of ammonia were present in the breathing zones of the referent group.

Table 3 shows the results of pulmonary function tests (PFTs) prior to and at end of shift as well as those of control subjects. As shown, mean baseline values (pre-shift) of VC and FEV1 in the high exposed group were significantly lower than those of referent individuals.

Exposed subjects experienced a significant cross shift decrement in some parameters of their pulmonary function (acute changes) in that, the mean values of VC, FVC and FEV1 were significantly lower than their corresponding values measured prior to shift.

On the other hand, pre-shift spirometry which was performed after a 7-d exposure free period showed significant improvement in PFT values. This indicates that the acute cross shift changes are reversible in nature, although still significantly lower than those of referent group (chronic irreversible effect).

Using multiple linear regression analysis, association between exposure to ammonia and changes in the parameters of pulmonary function was investigated. Results showed that after adjusting for important confounders including age, height, weight, marital status and smoking habits in the model, a significant negative correlation exists between exposure to ammonia and pre-shift VC and FEV1 values (Table 4).

Discussion

The present study was designed to determine whether long term occupational exposure to low levels of ammonia is associated with acute and/or chronic pulmonary disorders.

In this study, a significantly higher proportion of the operational workers were single and their length of employment was significantly lower than their counterparts. Additionally, they were significantly younger and a significantly lower proportion of them were smokers.

While operational workers were exposed to significantly higher concentrations of ammonia than the maintenance workers, mean atmospheric concentrations of ammonia for both groups were lower than the adjusted TLV-TWA of 12.5 ppm for this compound.

The levels of ammonia observed in this investigation were far below those observed by Rahman et al., in a urea fertilizer factory and Ali et al., who found concentrations higher than 25 ppm in 30% of the air samples in the ammonia factory.

Although the exact reason(s) for these apparent discrepancies are not known, they could be explained, at least in part, by the fact that the plant in which this study was undertaken was a relatively young industry and the equipment and machineries were new and properly maintained. Consequently, leakage of the chemical was negligible and finally, engineering measures such as local exhaust ventilation systems were strictly enforced.

Furthermore, the results of ion chromatography method, used in this study, may not necessarily be directly comparable with those of direct-reading diffusion method reported in Rahman’s study or spectrophotometric technique based on a peak absorbance of about 440 nm.
reported in Ali’s study\textsuperscript{16}. Even in the study of Rahman \textit{et al.}, in which the authors used two different analytical methods, concentrations measured by Drager tubes were 4−5-fold higher than Drager PAC III\textsuperscript{15}.

Significant cross shift decrements in most parameters of pulmonary function of the exposed subjects were noted. Interestingly, after a short exposure free period (7 d), a full recovery in lungs’ functional capacity was observed, indicating that nature of the spirometry changes was acute and reversible. Similar findings have been reported by Rahman \textit{et al.}\textsuperscript{15}.

However, some investigators have not observed any cross shift decline in the parameters of pulmonary function following exposure to 9.2 ppm of ammonia\textsuperscript{25}.

The base line values of VC and FEV1 in the operational workers (prior to shift and after a 7-d exposure-free period) were shown to be significantly lower than those of the referent group indicating that, under the exposure scenario explained in this study, even exposure to low levels of ammonia, over years, may induce chronic irreversible pulmonary disorders.

In line with these findings, Bhat and Ramaswamys showed that FEV1, FVC and peak expiratory flow rate (PEFR/minute) in fertilizer workers were significantly lower than control subjects, although in their study ammonia levels were not quantified\textsuperscript{27}.

Conversely, Ali \textit{et al.},\textsuperscript{16} showed that some parameters of pulmonary function such as FEV1, FVC, and FEV1/FVC in the ammonia exposed workers were higher than those of the control group. This peculiar result may be explained by a significantly higher proportion of smokers among the controls in Ali’s study and lack of control for important potential confounders such as smoking\textsuperscript{16}.

Interestingly, the proportion of the smokers, length of employment and the mean age of the high exposed, operational workers were significantly lower than those of repair and maintenance and control subjects. Therefore, it is unlikely that confounding variables of age and cigarette smoking account for the significantly lower values noted in the parameters of pulmonary function of this group compared to their counterparts.

This conclusion is further supported by the results of multiple linear regression analysis where significant associations were found between exposure to ammonia and a reduction in lungs’ functional capacities after adjusting for the role of potential confounders of age, height, weight, marital status and smoking.

Interestingly, despite the fact that the proportion of the smokers of the referent subjects was about 4-fold higher than that of high exposed subjects, the mean baseline values (pre-shift) of VC and FEV1 were significantly higher in referent subjects than in high exposed subjects. This finding indicates that ventilatory disorders observed among the high exposed group may well be attributed to their exposure to ammonia.

Exposure to low atmospheric concentrations (1.35 ppm) of ammonia for about 5 yr was associated with 6.61 and 3.95 units decline in VC and FEV1 values, respectively.

Assuming a linear trend, one would expect a significant cumulative decline of about 40\% and 24\% in FEV1 and FVC values, respectively, over the working lifetime of the employees.

Quantitatively, similar findings have been reported by Rahman \textit{et al.}, where each year of exposure to ammonia was shown to be associated with a decrement of about 0.6\% in FEV1 value\textsuperscript{15}.

It is not exactly clear whether intermittent exposure to high concentrations of ammonia or continuous exposure to low levels of this chemical is responsible for the chronic effects observed in this study. However, it is thought that sporadic short exposure to high concentrations of irritant gases does not usually result in chronic respiratory disorders. Therefore, it is possible that an inflammatory reaction occurs following the initial exposure and then does not resolve due to continual repeated exposure\textsuperscript{28}. This is likely to explain the reason of chronic respiratory changes in the high exposed group.

It should be noted that a 5\% cross shift decrement in FEV1 value is thought to be clinically significant\textsuperscript{29}. In the present study, 20.9\% of the operational workers had a 5\% decrease in FEV1 value.

Nature of the cross shift changes in the parameters of pulmonary function (significant decreases in VC, FVC and FEV1) are consistent with combined obstructive and restrictive pulmonary disorders\textsuperscript{30}. These results are in accord with the findings of studies showing that exposure to ammonia produces both restrictive and obstructive pulmonary disorders\textsuperscript{16, 27}.

Cross sectional epidemiological studies such as the present study lack the ability to establish cause and effect relationship.

Therefore, due to this inherent limitation, one might argue that the observed effects could not necessarily be attributed to exposure to ammonia. While we do not refute this view, we believe that the following lines of circumstantial evidence indicate that these are very likely to be the direct consequence of exposure to ammonia:

1) Exposed subjects had no history of exposure to
chemical causing respiratory disorders or history of injury and chest operation once they commenced working in the plant

2) Significant cross shift decrements were noted in most parameters of pulmonary function of exposed workers

3) Mean baseline values of some parameters of pulmonary function of high exposed group were significantly lower than their corresponding values for referent subjects

4) After a 7-d exposure-free period, acute decrements in the parameters of pulmonary function were found to be reversible

5) Significant associations were found between exposure to ammonia and reduction in the parameters of pulmonary function after adjusting for potential confounders.

The occupational exposure limit (OEL) for ammonia has been set at 25 ppm by both ACGIH and NIOSH. Although mean airborne concentration of ammonia in this study was below this value, both acute and chronic significant decrements were noted in some parameters of pulmonary function of the high exposed group.

Given the above, one might tentatively conclude that the existing TLV does not provide sufficient protection against respiratory effects of this irritant gas. This is in agreement with the views expressed by Donham et al., where the authors have shown that a TLV of about 7.5 to 12 ppm would be more reasonable for ammonia.

In line with this proposition it has been suggested that the RD50 (the concentration of ammonia producing a 50% decrease in respiratory rate) test for sensory irritation in the mouse could be useful in setting “acceptable” levels of airborne industrial chemicals to prevent burning sensation of the throat, eye and nose in humans. The author reported good correlations between RD50s and TLVs for 26 industrial chemicals including. The Alarie test was adopted in 1984 as a standard test by the American Society for Testing and Materials (ASTM).

This relationship, TLV=0.03×RD50, may be used to predict sensory irritation effects at workplace exposures. Alari showed that RD50 of ammonia is 303 ppm in Swiss Webster mice and the acceptable TLV-TWA value using 0.03×RD50 would be 9.1 ppm for ammonia.

Additionally, in a study conducted by Sundblad’s on volunteers exposed to 25 ppm of ammonia and a sham group, symptoms of eye, throat and nose discomfort, breathing difficulty, solvent smell, headache, fatigue, nausea, dizziness and feeling of intoxication were found to be significantly higher during exposure to 25 ppm of ammonia than during the control exposure. Similarly, symptoms including burning eyes, solvent smell, headache, dizziness, and feeling of intoxication were significantly higher in volunteers exposed to 5 ppm ammonia than in a sham group. Based on these findings the authors maintain that there is a need to reconsider the present occupational exposure limit of 25 ppm for ammonia.

Conclusions

Taken together, our findings indicate that exposure to low levels of ammonia is associated with both acute reversible and chronic irreversible decrements in the lungs’ functional capacity. Additional studies are needed to further substantiate these preliminary observations and to ascertain whether these findings are related to long term exposure to low levels of ammonia or to sporadic intermittent peak exposure to this compound or both.

Under any circumstances, engineering controls and use of personal protective equipment is needed to reduce workers’ exposure to ammonia, particularly, to peak exposures.

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Conflict of Interest

The authors declare that they have no conflicting interests.

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