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REVIEW, SUMMARIZATION, AND EVALUATION OF LITERATURE TO SUPPORT THE UPDATE AND REVISION OF CRITERIA DOCUMENTS
III. AMMONIA

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I. INTRODUCTION

This report is designed to present a critical review and evaluation of the recent scientific literature concerning hazards associated with exposure to ammonia. It is intended to provide an update for the existing NIOSH criteria document for ammonia by considering the results of published and unpublished research which have appeared since the preparation of the original document.

In assembling this update, pertinent new information was sought relating to the areas of human and animal toxicity, analytical and sampling methods, work practices and engineering controls, and miscellaneous aspects regarding uses, sources, standards, etc. Identification of relevant articles and documents was accomplished through a search of the scientific literature utilizing both computerized and manual searching of various data bases and published secondary bibliographic sources (see Appendix A).

The production, handling, and use of ammonia has a long history throughout the world. Consequently, there has been ample opportunity to observe the adverse effects of accidental occupational exposures and to design more efficient means to control and measure ammonia exposures. In this report we shall emphasize some of the refinements made possible through recent technological advances which allow for improvements in air sampling and chemical analysis. In addition, data will be presented which suggest that previously unrecognized disruptions of normal physiologic processes may accompany such well known toxic effects of ammonia as irritation and respiratory distress. Ultimately, it will be shown in what areas important information is lacking, and where emphasis for future research should be placed.

II. ANALYTICS

There has been a great deal of interest in the determination of ammonia in ambient air, not only because ammonia is hazardous above certain concentration levels, but also because it is present in air from a number of natural sources. The principal source of NH_3 gas in the atmosphere appears to be the action of the enzyme urease on animal urine. [1] Other sources include rotting organic matter and sewage. Man-made sources include fuel combustion, losses from fertilizer, and chemical processing.

A. Sampling Techniques

Ammonia appears in the atmosphere as the molecule NH_3, a gas, which should not be confused with NH_4^+, ammonium ion, which may also be present in the atmosphere as solids. Various collection and assay methods may not distinguish between ammonia gas and ammonium ion. The health and environmental hazards of these two chemical species, however, are quite different, and little is known about the health effects of ammonium ion in the occupational environment.

The most common method of collecting ammonia in the atmosphere is to pass the gas through an air impinger containing a small volume of dilute aqueous acid, whereupon the ammonia is converted to ammonium ion. Typically, sulfuric acid is used, in the general concentration range of 0.01-0.05 M. The collected sample in the air impinger is brought up to a convenient standard volume and assayed for NH_4^+. If it is desired to distinguish between NH_3 and NH_4^+ in the air, a particle filter must be placed before the air impinger. Ammonium ion can then be extracted from the filter, if that is also desired.

Some questions have been raised as to the low efficiency of dilute acid impingers in collecting ammonia gas quantitatively from ambient air, unless sampling times are kept quite short. [2] A solid state oxalic acid

filter has been developed which has been shown to be extremely effective in collecting ammonia and ammonium salts (although the latter can be excluded by the use of a particulate prefilter), and does not lose efficiency with extended collection times. [2] The filter is made by impregnating Whatman No. 1 or No. 41 filter paper with oxalic acid by soaking it in an ethanolic oxalic acid solution. In tests with two oxalic acid filters in series, ammonia was never detected in the second filter. The tests were conducted over a 0-30% range of relative humidities and a sampling range of 0.200-4 ℓ/min. The ammonia concentration in the air was 10 ppb and the sampling time 24 hours. The authors suggest that increasing the humidity would not substantially affect the results. It was not indicated, however, what the effect of increasing the ammonia concentration to 50 ppm would be.

Regarding the use of filter papers either in samplers or in separatory steps in an ammonia determination, it has been pointed out that filter papers, especially hardened filter papers, often contain significant amounts of ammonia or ammonium ion. [3] Therefore, specific papers should be tested (or at least the manufacturer should be consulted) prior to their use in ammonia collection or determination procedures.

It is possible to determine ammonia in air directly, either by sampling and detecting simultaneously, or by remote detection without sampling. These techniques and their relative value to ambient air monitoring for ammonia are described in the analytical methods section which follows.

B. Analytical Methods

The analytical method specified in the document being reviewed is known as the Nessler Method. Its sensitivity is adequate for the current

specified standard for NH_3 in air (50 ppm). The techniques developed for the determination of ammonia since the writing of the criteria document in many cases offer equal or better sensitivity with fewer interferences and, in some cases, simpler methods and faster results. However, as long as the main purpose of the analytical method is the determination of ammonia in ambient air to approximately 30-50 ppm (with the exception of special situations), it is likely that none of the techniques described below would offer a substantially significant overall advantage to the Nessler Method.

One of the fastest techniques for routine ammonia determinations was developed by Kramer and Sech [4], whereby ammonia is collected in two air impingers connected in series, which contain dioxane and o-(benzenesulfonamido)-p-benzoquinone. After sampling at a rate of 1 ℓ/min, the contents of the impingers are made up to a standard volume, and the dye which forms upon the reaction of two moles of ammonia with one mole of reagent is determined spectrophotometrically at 480 nm. The method is claimed to be 3-4 times more sensitive than the Nessler Method. There was no discussion of interferences.

Sims [5] has described a method for determining ammonia in dilute aqueous alkali by gas-liquid chromatography, and in a nitrogen-ethylene environment by gas chromatography. The concentration ranges of these techniques are on the order of thousands of parts per million. While convenient and suitable for analyses such as plant raw effluent, the methods are not sufficiently sensitive for application to trace levels of ammonia in ambient air.

In the Nitrite Method [6], gaseous ammonia is collected in the usual acid impinger, and the ammonium ion obtained is reacted with hypochlorite in the presence of bromide ion (as a catalyst) to form nitrite ion. After destruction of the excess hypochlorite with sodium arsenite, the nitrite is converted

to an azo dye and measured spectrophotometrically. The optimum concentration for ambient air sampled at 1-2 ℓ/min for one hour is 0.02-0.03 ppm ammonia. Higher concentrations may be determined either by taking aliquots of the collected sample solution, reducing sampling time, or some combination of these. The method is suitable for measuring ammonium salts collected with membrane filters, electrostatic precipitators, and high volume samplers. It is less subject to interferences than other chemical methods such as the indophenol method (Health Lab. Sci., 10:115-118, cited in [6]), especially the type of interferences likely to be present in an urban atmosphere, such as formaldehyde, which is tolerable in the Nitrite Method at concentrations up to 100 ppm. Nitrite and hydrolyzable amino compounds (alkyl amines, urea, and some amino acids) do interfere. Particulate matter containing ammonium ion will interfere unless removed by filtration. The method gives good precision, but accuracy data are not available. Therefore, the use of standards and controls are essential.

Matsunaga and Nishimura [7] reported a modification to the Nitrite Method which eliminates interference from amino acids and achieves a much faster reaction time. By increasing hypochlorite and bromide concentrations, the oxidation is accomplished in just two minutes, too short a time to effectively oxidize any amino acids which may be present. Hydroxylamine still interferes, but it is not a likely constituent of ambient air. The precision of the method is estimated to be 2% at the 2 ppb level (ammonia measured as nitrogen), with the sensitivity for 0.001 absorbence in a 1 cm cell 0.03 μg/ℓ, or 3-5 times more sensitive than the indophenol method.

Piezoelectric quartz crystals can detect gaseous pollutants in very small concentrations (ppb). The crystal is made sensitive to a specific gas by a special coating which absorbs the gas to be measured. The absorbed gas increases the weight of the crystal which decreases the frequency of vibration of an oscillating crystal. The decrease in frequency is proportional to the amount of gas absorbed. Ammonia-selective quartz crystals are made by treating the crystals with Ucon coatings manufactured by Union Carbide Corporation, followed by exposure of the coating to NO_2 which sensitizes it to ammonia. [8] The sensitized Ucon coatings are believed to contain R-NO moieties, but their exact structure is presently unknown. The ammonia detectors give linear responses between 1 ppb and 1 ppm. Linearity decreases above 1 ppm and the sensors are not useful above 50 ppm. A major drawback to the use of these sensors for determining ammonia in ambient air is that the crystals are also sensitive to water. The air sample must therefore be dried before it reaches the crystal detector, since it is not possible to distinguish a signal due to moisture from a signal due to ammonia. Other substances which interfere are SO_2, NO, H_2S, acetone, methanol, chloroform, and benzene. However, interferences from these are not noticeable at concentrations ranging from hundreds to thousands of parts per million, much higher concentrations than ever expected in normal air samples. Nevertheless, this state-of-the-art method appears to have little relevance to the monitoring of ambient air for ammonia because of water-interference and also because the useful range of concentrations is far below that of the current standard for ammonia.

Eagan and Dubois [1] have shown that ammonium particles in air can be determined accurately and rapidly with ion selective electrodes. Their

results would also apply to ammonia gas collected in an acid impinger. They studied the Orion ammonia electrode (useful above pH 9) and the Beckman ammonium electrode (useful below pH 7). For a typical air sample of 2000 m^3, ammonium content could be accurately determined down to 0.03 $\mu g/m^3$ ($\sim$40 ppb). In addition to its sensitivity, this method is rapid and efficiently handled on a monitoring basis without the disadvantages of other ppb techniques which require more elaborate and expensive apparatus. Results obtained with specific ion electrodes and with the Nessler and indophenol method compare favorably.

Potentiometric gas sensors sensitive to ammonia have been fabricated from ion selective electrodes for Ag^{+}, Cu^{++}, and Hg^{++}. [10] The sensitivity of these sensors to ammonia is about 10 ppm. They contain an ammonia-permeable membrane around the metal ion selective electrode. They measure the degree of complexation of ammonia with the internal metal ion. Their response to changes in ammonia concentration is relatively rapid, ranging from seconds to less than one minute, making them useful for continuous monitoring systems. Ion selective electrodes designed to measure ammonia or ammonium ion directly are more sensitive than these potentiometric gas sensors. However, the sensitivities of the gas sensors are adequate in ambient air monitoring for purposes of maintaining the current occupational health standard for ammonia.

It is possible to simultaneously sample and assay gaseous ammonia in air with gas chromatography. [11] A column packed with Chromosorb 102 impregnated with tetrahydroxy-ethyl-ethylenediamine can simultaneously determine O_2, N_2, N_2O, NO_2, NH_3, and H_2O. The detection limit of ammonia is about 1000 ppm (0.1%), which means the technique is not sufficiently sensitive for environmental monitoring.

Menzies and Shumate [12] have used an infrared heterodyne radiometer with a CO_2 laser as a local oscillator to remotely detect laboratory samples of several pollutant gases, including ammonia. The sensitivity of the method to ammonia is in the range of several parts per billion. The heterodyne radiometer is well suited for remote observation and measurement of atmospheric constituents whenever high spectral resolution is desired. The instrument is also very selective. Applications include monitoring air pollution from the ground, or global pollution from spacecraft. The system is probably too complex for routine monitoring of ammonia on industrial sites or workplaces, although it would have the advantage of not requiring sampling and the consequent potential for sample losses characteristic of other available assay techniques.

The ring oven method developed by Weisz (cited in West et al. [13]) has been used to determine ammonia in air in an efficient and sensitive method suggested by Shendrikar and Lodge. [2] The technique involves placing a drop of liquid or a speck of dust containing the sample at the center of a filter paper maintained at 95°C in a trace oven. Reagents are added which diffuse from the center of the filter paper and produce colored rings upon reacting with the sample. The color of the rings is characteristic of the species to be determined. The intensity of the ring color is proportional to the concentration of the sought species, which can therefore be measured by comparison with rings made from samples of known concentration. In the case of the ammonia ring oven method, the technique has a detection limit of 50 ng, while the recommended range for quantitative determination is 0.1-1.00 μg of ammonia (this cannot be related to ppm of ammonia in air unless a sampling technique

is specified). The only interference noted by the authors is formaldehyde, which is serious even in concentrations on the same order of magnitude as ammonia. However, this can be overcome by the use of oxalic acid ammonia collectors (see previous section), which do not retain formaldehyde.

Pym and Milham [14] studied pH effects on a salicylate-dichloroisocyanate procedure attributed to Reardon et al. (cited in [14]), which is said to be more sensitive than the phenol-hypochlorite method for ammonia. It is subject to interference from iron and manganese, although this can be avoided by additional steps. It does not seem that this method offers any substantial benefits over the indophenol or other chemical methods for the purpose of environmental monitoring of ammonia.

Ion exchange chromatography, a new technique developed by Small et al. (1975) has been applied to a number of cations including ammonium, sodium, potassium, lithium, magnesium, and calcium. The cations are trapped on an ion exchange resin. They are resolved during elution with dilute hydrochloric acid. As each ion type leaves the column, the solution is passed through a stripped column which removes the chloride background anions, exchanging them for hydroxide ions which react with the excess hydrogen ions to produce water. The final ionic content of the solution is therefore dependent solely on the concentration of the sample component, which is determined by a simple conductance measurement. The system can also be adapted to determine anions in a mixture by substituting NaOH for the HCl eluant.

As Anderson (1976) has pointed out, the advantages and disadvantages of ion exchange chromatography are the same as for other chromatographic techniques. It is possible to analyze many components of a mixture in a short time

if all can be eluted and separated from one another. The method of determination (conductance) is general purpose and equally sensitive to all ions. However, all components of a sample must be eluted from the separatory column before another sample is added, even if it is desired to determine only one component of each sample. Also, compounds with similar separatory characteristics will overlap, making measurement impossible.

Bouyoucos (1977) has applied ion exchange chromatography specifically to the determination of ammonium ion. A recovery of 98-103% was achieved with spiked samples of about 50 µℓ. By modifying the original method of Small et al. (1975), it was possible to obtain excellent linearity of response of the system between approximately 10-120 ppm NH_4^+ in the injected samples.

III. HUMAN EFFECTS

A. Observed Effects

Exposure to ammonia in the occupational environment may occur when working with either anhydrous ammonia or aqueous solutions of ammonia (ammonium hydroxide). In the latter case, however, exposure actually results to the ammonium ion. Unfortunately, the toxic effects in humans attributable to exogenous exposure specifically to ammonium ion are not well understood.

Direct human contact with anhydrous ammonia produces characteristic lesions of several tissues, particularly the eyes and respiratory tract. Johnson [15] has summarized the available evidence regarding the nature, incidence, and severity of injuries resulting from accidental ammonia exposure. Due to its high solubility and alkalinity, anhydrous ammonia readily attacks the moist tissues of the body (mucous membranes, eyes, respiratory tract), producing tissue liquefaction accompanied by blistering. First and second degree burns of the skin are not uncommon when the chemical contacts the neck, face, or chest. Ammonia burns of the eye can be extremely damaging, causing destruction of the cornea which may leave permanent corneal clouding or progress to eventual blindness. The mechanism of action in producing corneal damage is apparently characteristic of all alkalis, that being saponification and disruption of the epithelial layer, allowing the chemical to traverse the stroma where it produces serious lesions of the endothelium. Corneal transplants are reportedly not successful in most cases of ammonia injury.

Jarudi and Golden [16] have reviewed the problem of ammonia eye injuries and noted that more permanent disabilities result from eye damage than from any other consequence of ammonia exposure. These authors described the

pathologic progression of eye damage resulting from severe contact. Initially, cataractous changes occur in the lens with marked edema of the cornea appearing within a few minutes after exposure. In a matter of weeks, the cornea becomes infiltrated by inflammatory cells resulting in fibrosis and neovascularization. Ultimately, the cornea, iris, and lens may become indiscriminately fused into a mass of vascular granulation tissue. A particularly dangerous feature of ammonia burns to the eye is the delayed breakdown of the cornea leading to corneal ulcers which appear after one to three weeks of relative inactivity. This results from the corneal release of collagenase (a tissue self-destructive enzyme) in response to the chemical-induced trauma.

Johnson [15] has emphasized that the greatest threat to life by ammonia exposure is from damage to the respiratory tissues. Death can result when ammonia paralyzes the respiratory cilia, mucous secretions increase, and airway obstruction subsequently occurs. Others have reported that ammonia burns may cause ulceration and desquamation of the bronchial epithelium, with complications by bronchitis, bronchiolitis, pneumonia, and atelectasis. [17] It has recently been suggested [15] that susceptibility to burns of the respiratory tract may involve a genetic component. Observation of various individuals demonstrated that two persons, equally exposed, may suffer widely different respiratory tract damage from anhydrous ammonia. Further experimental or epidemiologic evidence to support this observation is not presently available.

Through the use of a radionuclidic lung-imaging procedure, Taplan and coworkers [17] were able to critically assess the pulmonary function of a man accidentally sprayed with ammonia. The injury produced sloughing of the lining of the upper airways and posterior pharynx which rendered the patient

unable to swallow and necessitated a tracheostomy. Initial assessments of pulmonary function indicated a severe restrictive ventilatory defect with marked impairment of diffusion. Lung volumes returned to normal within two months and diffusing capacity was limited only upon exertion. At six months postexposure to ammonia, the patient underwent a more extensive examination which revealed abnormal pulmonary arterial perfusion, especially in the posterior projection of the left lung. Administration of a radioactive aerosol at this time demonstrated excessive deposition in the major airways with poor penetration to the periphery of the lung. These results indicated partial airway obstruction characteristic of the chronic bronchitic type of obstructive airway disease. In addition, a distinctly abnormal retention of radioactive xenon was encountered throughout the entire left lung at five minutes, accompanied by less severe air trapping at the right base. A subsequent fiberoptic bronchoscopic examination revealed the presence of two tracheal strictures and stenosis of the orifices of the subsegmental basal bronchi on the left accompanied by mucopurulent secretions. The mucosa was edematous and friable, and bled easily when suctioned. The administration of isoproterenol produced a sufficient bronchodilation to significantly improve aerosol distribution and wash-out of radioactive xenon.

B. Experimental Studies

A controlled study with humans has recently been conducted by the Allied Chemical Corporation [18] to evaluate the responses to inhaled ammonia at concentrations of 25, 50, and 100 ppm. Six adult subjects, not acclimated to ammonia exposure, comprised three groups which were exposed for two to six hours each day, five days per week, for six weeks. One pair of subjects was

exposed only to 50 ppm ammonia for six-hour periods throughout the test. Subjects were examined daily for irritation of the eyes, nose, or throat, and periodically for pulse rate, respiration rate, pulmonary function (forced vital capacity and forced expiratory volume in one second), blood pressures, neurological responses, and interference of task performance ability. A statistical analysis of the results demonstrated that the only significant change among the vital functions measured was an increase in forced expiratory volume in one second with increasing ammonia concentration. In addition, the rate of mild eye, nose, or throat irritations over the last three weeks of the test was significantly less than during the first two weeks. This observation indicated that an acclimation process occurs whereby an increased tolerance to the irritant effects of ammonia develops with increasing time of exposure. Overall, the ammonia exposure produced 2 incidents of mild irritation (78 observations made) at 25 ppm, 22 incidents (198 observations made) at 50 ppm, and 11 incidents (84 observations made) at 100 ppm. Among control subjects, 4 irritation incidents were recorded during 45 observations. When ammonia concentrations exceeded 150 ppm, all subjects experienced watering of the eyes accompanied by dryness of the nose and throat. No measurements were made during this study of biochemical parameters or other effects on homeostatic mechanisms.

IV. ANIMAL STUDIES

A. Metabolic and Physiologic Effects

Vagal nerve endings in the lungs known as pulmonary irritant receptors are said to be responsible for the tachypnea arising in anaphylactic- or histamine-induced bronchial asthma attacks. [19] These same receptors, when excited by chemical irritants, were shown in rabbits to produce respiratory effects closely resembling those evoked in guinea pigs by bronchial asthma attacks. Studies with guinea pigs demonstrated that uneven ventilation resulting in expiratory self-compression of the lungs is responsible for the stimulation of these vagal fibers. Buff and Koller [19] administered an ammonia aerosol (0.5 to 2.0%) for 2 to 30 seconds to guinea pigs and measured its effect on respiratory function and the production of uneven ventilation as determined by the argon wash-out rate. A slow wash-out rate was regarded as evidence for uneven ventilation. Among 17 treated animals, most responded to the inhaled ammonia vapor with a successively increasing respiratory frequency accompanied by decreased tidal volume and an increase in lung volume. Intermittent cough attacks and phases of bradypnea were associated with the initial hyperpnea. Normal breathing was restored several minutes after the attack onset. Initially, the argon wash-out rate was significantly diminished ($P<.01$) compared with the control. When the same ammonia exposures were made with bilaterally vagotomized guinea pigs, respiration did not generally change with ammonia inhalation, nor did the argon wash-out rate differ before and after exposure. These results showed that the respiratory responses to inhaled ammonia are mediated by the vagus nerve. The mechanism responsible for activation of vagal endings by ammonia is apparently lung deflation or compression caused by uneven ventilation.

Experiments conducted by Egle [20] confirmed that the uptake and retention of inhaled ammonia vapor by the total respiratory tract of the dog are quite similar to the values in humans. He was able to show that uptake of inhaled ammonia in air (∿216 to 719 ppm) averaged 73.7 $\pm$ 1.5 to 82.6 $\pm$ 1.3 percent at ventilation rates ranging from 4 to 40 per minute. No significant correlation was demonstrated between ventilation rate and respiratory tract retention of ammonia. Furthermore, ammonia uptake was not affected by concentration nor by tidal volume. When a second gas, acetaldehyde, was administered concurrently with ammonia, the uptake of acetaldehyde was decreased at lower ventilatory rates and increased at higher rates. However, when inhaled alone, acetaldehyde uptake was greater at low ventilatory rates than at high rates. Therefore, interaction with ammonia can apparently alter the respiratory uptake and retention pattern of certain compounds.

A recent report from the Russian literature [21] described the respiratory effects in rats produced by inhalation of ammonia. Animals exposed to gradually increasing concentrations starting from ∿72 ppm or to a constant ammonia level of ∿164 ppm responded with a decrease in respiration frequency. In addition, rats exposed to gradually increasing ammonia concentrations did not display a compensation period in respiratory function. This observation suggests that exposure to gradually increasing ammonia levels in air may present a greater toxic hazard than exposure to constant levels. These results are somewhat in contrast with those obtained by Buff and Koller [19], who demonstrated that an initial increase in respiratory frequency accompanied by decreased tidal volume and increased lung volume usually resulted from ammonia exposure in guinea pigs.

The effect of ammonia on ventilation may be mediated by the action of ammonium ion in the brain. Studies conducted with dogs during intravenous and intraventricular infusion of ammonium chloride demonstrated that brain ammonia levels were correlated with the hyperventilation response to treatment. [27] Varying blood levels of ammonia did not influence respiration. These investigators suggested that ammonia neurotoxicity may be mediated by either an ammonia-induced formation of lactic acid in the brain or by the depletion of high energy phosphates during the enhanced amidation of glutamate to glutamine in the brain stem. Nevertheless, the stimulation of respiration by ammonium ion may be a direct effect and thus separate from these proposed mechanisms for ammonia neurotoxicity.

B. Biochemical and Pharmacologic Effects

Evidence obtained from the foreign literature suggests that exposure to gaseous ammonia by inhalation or contact with the skin can effectively disrupt normal biochemical and neurological processes. Russian investigators [22] examined the effect of brief (15- and 60-minute) ammonia exposures repeated every 48 hours for a period of two and one-half or three months. Rats were subjected to ammonia inhalation at concentrations of about 43 and 144 ppm, and to the isolated effect of the gas on the skin in average concentrations of 72 and 719 ppm (15-minute exposures), as well as to 36 and 360 ppm (60-minute exposures).

Over a period of one month, rats exposed to 144 ppm ammonia displayed elevated leukocyte counts, but no other changes in oxygen consumption, neuromuscular excitation threshold, heart rate, blood sugar, residual nitrogen in the blood, or total serum protein. Two months after the initiation of inhalations, rats exposed to 144 ppm ammonia, with either 15- or 60-minute exposures,

showed an increase in latent time of an unconditioned pain reflex. Among animals inhaling 43 ppm ammonia, those with 60-minute exposures also displayed an increase in reflex time (86.9 $\pm$ 1.5 ms vs. 68.6 $\pm$ 0.96 ms in controls), which remained quite high to the end of the treatment period. Additional toxic effects were noted only among the animals exposed to ammonia at 144 ppm. These included slight congestion of the blood vessels in the lungs after two months and small areas of interstitial pneumonia with signs of peribronchitis and perivasculitis after three months. In the liver, an elevation of cytochrome oxidase activity was discovered, primarily around the central veins. No other organs were affected.

The isolated exposure of the skin to ammonia at about 360 ppm (60-minute exposures every 48 hours) and 719 ppm (15-minute exposures every 48 hours) caused several significant effects in rats. [22] After two and one-half months of treatment, the experimental animals showed a statistically significant lag (12-15%) in body weight gain. However, no changes were observed in the hemoglobin content, or numbers of erythrocytes and leukocytes. Upon termination of the treatment, there was found an increase in relative weight of the heart at both dose levels, and a slight (17%), but statistically significant, enlargement of the adrenals in rats exposed to 719 ppm ammonia. Histological examination of various organs revealed congestion of the blood vessels in the kidneys, lungs, portal system of the liver, and veins of the myocardium. In addition, there were observed in the kidneys initial signs of epithelial dystrophy of the convoluted tubules (of the turbid swelling type); in the skin there was increased desquamation of the epidermal cells, as well as some edema of the superficial layers of the dermis. A histochemical examination of the liver revealed an increased activity of succinic dehydrogenase

and alkaline phosphatase along with increased glycogen content. The activity of succinic dehydrogenase and alkaline phosphatase was also elevated in the skin. The investigators noted that skin exposures to gaseous ammonia at 36 and 72 ppm produced no toxic effects in comparisons with controls. Furthermore, one month after cessation of inhalations or skin exposures, there were no signs of intoxication among the experimental animals.

In a previous study [23], these investigators examined the acute actions of ammonia on rats resulting from single exposures of 5, 15, 30, or 60 minutes. Inhalation of ammonia at levels of about 1438 to 8628 ppm caused dyspnea, respiratory irritation, cyanosis of the extremeties, and increased excitability leading to death by convulsions. During inhalation of lower concentrations (approximately 431, 1438, or 4314 ppm), there were noted a drop in the static muscular tension, leukocytosis, prolonged latent reflex time, increased total oxygen consumption, and increased serum total protein and sugar. These changes were not seen at ammonia exposures equivalent to 144 ppm.

When ammonia exposure was limited to skin contact only, concentrations on the order of 79,000 ppm (15-minute exposure) caused excitation followed by sluggishness, decreased respiration rate, and often accompanied by tonic-clonic spasms. [23] Ammonia levels were increased in the urine, as was urea in both urine and blood. Elevated activity of alanine aminotransferase, indicative of liver damage, was noted in the first 24 hours, while the number of leukocytes practically doubled in comparison to control rats. In concentrations greater than 20,000 ppm, acute exposure of the skin to ammonia produced histochemical changes which included increased activities of cytochrome oxidase,

succinic dehydrogenase, lactate dehydrogenase, and alkaline phosphatase in the liver. No changes were seen with ammonia exposures equal to 1869 ppm (5 minutes) or 288 ppm (60 minutes).

Enzymatic alterations in rats have also been reported to result from inhalation of ammonia at low levels. [24] At concentrations of approximately 29 to 173 ppm, a decrease was noted in the activities of liver succinic dehydrogenase, lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and adenosine triphosphatase. Acid phosphatase activity was increased in response to ammonia exposure.

C. Acute Toxicity

1. Inhalation Studies

The acute lethal dose for ammonia by inhalation has been determined in both rats and mice. [25] One hour exposures to ammonia were conducted at several concentrations using male CFE rats ranging from 200-300 grams and 20-30 gram male CF1 mice (ICR derived). Inhalation of ammonia vapor produced immediate nasal and eye irritation followed by labored breathing and gasping in both rats (6210-9840 ppm) and mice (3600-5720 ppm). In addition, convulsions were seen in mice. The results, as summarized in Table IV-1, indicate subnormal weight gains among rats and actual weight losses among mice during a 14-day observation period. Surviving rats necropsied after 14 days showed moderate mottling of the liver regarded as probable fatty change at the 7820 and 9840 ppm dose levels. Mice surviving the two highest dose levels (4550 and 5720 ppm) showed mild congestion of the liver. Pathologic lesions were not seen in rats exposed to 6210 ppm or mice exposed to 3600 ppm. The calculated one-hour LC_{50} values for rats and mice were 7338 (6822-7893) and 4837 (4409-5305) ppm, respectively.

Table IV-1. Effects of One-Hour Exposures of Ammonia on Rats and Mice (Source: MacEwen and Vernot [25])

Measured Concentration (ppm)	Species	Mortality Ratio*	Mean Weight Gain of Survivors at 14-Days (grams)
6210	Rats	0/10	3.5
7820	Rats	8/10	**
9840	Rats	9/10	**
Controls	Rats	-	21.4
3600	Mice	0/10	-0.2
4550	Mice	3/10	-0.7
5720	Mice	9/10	**
Controls	Mice	-	1.6

* Number dead/Number exposed.

** Not enough survivors for comparison.

Russian investigators [23] have evaluated the acute toxicity of ammonia to rats resulting from both inhalation exposures and isolated contact with the skin. The average lethal concentrations (LC_{50}) for inhalation exposures of 5 and 15 minutes were about 26,780 $\pm$ 992 and 17,429 $\pm$ 2071 ppm, respectively. For exposures lasting 30 and 60 minutes, the LC_{50}'s were about 10,123 $\pm$ 1352 and 11,317 $\pm$ 1136 ppm, respectively. Inhalation of ammonia in lethal concentrations typically produced pneumonia, which was not evident in some cases until 14 days after exposure. In addition, three to seven days after exposure there appeared congestive hyperemia in the liver with a faint turbid swelling of the parenchymal cells.

2. Dermal Studies

Lethal concentrations of ammonia when administered to the skin of rats were considerably higher than for exposure by inhalation. [23] The LC_{50}'s varied with time of exposure as follows: $\sim$69,599 $\pm$ 8398 ppm (60 minutes), $\sim$103,392 $\pm$ 7478 ppm (30 minutes) and $\sim$161,056 $\pm$ 6831 ppm (15 minutes). An LC_{50} for a five-minute exposure to ammonia could not be obtained by isolated skin exposure. At concentrations in excess of about 28,760 ppm, ammonia produced skin lesions in the form of burns in the region of the external genitals. Pathologic analysis of tissues taken from rats exposed to $\sim$20,132 ppm and higher revealed hemorrhaging of the internal organs; primarily in the heart and liver, less frequently in kidneys, lungs, and brain. Examination of the liver revealed edema, cellular vacuolization, and turbid swelling of the parenchymal cells. The lungs were described as having edema of the vascular walls and focal thickening of the interalveolar septa.

V. WORK PRACTICES AND ENGINEERING CONTROLS

A. Safety Measures

The hazards associated with the handling and use of anhydrous ammonia have long been used for many years to insure that leakage of liquid ammonia, especially when pressurized, does not occur. Accident prevention generally consists of paying special attention to the condition of hoses, valves, and fittings used in the movement of ammonia during production, transfer, or application. It has been recognized [16] that a most common accident situation involves the transfer of the pressurized liquid from tank to tank.

A further hazard involving ammonia is related to its extremely high solubility in water. Cicolella [26] has studied the sudden decompression in a vessel containing liquid ammonia when water was added. The large decrease in volume occurring with the mixture of the two substances is conceivably sufficient to cause a collapse of the ammonia-containing vessel. The author, therefore, recommends that a cement-lined trough be used under vessels containing ammonia, and that a light thermal insulating substance, such as vermiculite, be used to protect against sudden ammonia leakage.

B. Worker Protection

Persons working with liquid anhydrous ammonia are advised to observe several precautions to avoid direct contact with the material. [16] These include:

1. The use of tight fitting goggles and rubber gloves
2. Have ready access to a protective garment in case of leak
3. Stay out of line of valves or hose couplings
4. Stand upwind during a transfer operation
5. Have access to an ample water supply for immediate irrigation in case of exposure

VI. SUMMARY AND CONCLUSIONS

It appears from the evidence available that dry oxalic acid filters for collecting ammonia are superior to the wet acid impingers generally used, especially for low concentrations of ammonia which require long sampling times. [2] Oxalic acid filters are capable of collecting ammonia quantitatively over longer sampling times than wet acid impingers, and also do not retain formaldehyde, which interferes with some colorimetric assays. In addition, dry oxalic acid filters would probably be simpler to use and less subject to physical abuse than a sampler containing a liquid.

The standard colorimetric wet chemical assays for ammonia and ammonium ion appear to remain perfectly adequate for the purpose of ambient air monitoring for an ammonia standard of 30-50 ppm. Of the various wet methods, the modified nitrite method appears to be least subject to interferences, as well as offering more than adequate sensitivity. [6]

Techniques based on the use of ion selective electrodes are probably more practical than the colorimetric methods because they are faster and more easily adaptable to continuous monitoring and automated processes. [1,9,10] A choice between the two general approaches, however, would be dictated mainly by circumstances of convenience and personal preference, as the precision and accuracy of both types of methods are within the requirements of the current ammonia standard.

While the potential future of ion chromatography as a general analytical tool appears bright, it is obviously not superior in environmental monitoring applications to other available techniques. It is much slower, for example, than ion selective electrode methods, especially if the goal is to determine only ammonium ion in the presence of many other components.

The more exotic techniques are perhaps better suited to trace level studies of natural ammonia sources rather than environmental monitoring for health purposes. Below about 10 ppm, humans cannot detect ammonia in the air and it is not an apparent irritant. It is unlikely, therefore, that ammonia-selective quartz crystals [8] or infrared radiometry [12] would be cost effective techniques for the routine monitoring of ambient air.

There exists ample evidence to indicate that human contact with vapors of anhydrous ammonia can produce serious burns of the skin and eyes [16] and damage to the respiratory tissues. [17] These effects result primarily from acute accidental exposures at high concentrations. Relatively little information pertaining to chronic human exposures at low ammonia levels has appeared in the recent literature. A controlled study with six volunteer subjects exposed to ammonia at 25, 50, and 100 ppm intermittently for six weeks has provided some indication of dose-response parameters for respiratory effects and mucous membrane irritation. [18] The results suggested that, at the concentrations employed, ammonia did not cause significant alterations in pulmonary function, pulse rate, blood pressures, selected neurological responses, or task performance ability. Mild irritation of the eyes, nose, and throat was evident, however, in a dose-related fashion at all exposure levels. Acclimation to the irritant effects of ammonia occurred with increasing time of exposure. Ammonia concentrations in excess of 150 ppm produced watering of the eyes accompanied by dryness of the nose and throat in all exposed subjects. The contribution of ammonium ion to the toxic effects elicited by ammonia exposure are poorly understood.

Several investigators have recently shown that rats periodically inhaling relatively low levels of ammonia vapor (~144 ppm) for two months respond with hematologic and neurologic disturbances. [22] Moreover, it was demonstrated that exposure to ammonia by inhalation or contact with the skin can alter the activity of certain enzymes. [23,24] It is reported [24] that inhaled ammonia at concentrations of about 29-173 ppm caused reductions in the activity of liver succinate dehydrogenase, lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and adenosine triphosphatase. After contact with the skin, elevations have been noted in liver cytochrome oxidase [22], alkaline phosphatase [22], and succinate dehydrogenase [22], and in blood alanine aminotransferase. [23] These findings have particular relevance insofar as they indicate that disturbances of the citric acid cycle, glycolysis, oxidation phosphorylation, and active transport processes may occur at exposure levels below the currently recommended standard of 50 ppm. Reports of leukocytosis in rats exposed to ammonia [22,23] may be significant in light of evidence presented in the NIOSH Criteria Document on ammonia concerning an excess of lymphatic neoplasms among workers in ammonia and amine plants.

The disruption of biochemical processes in the human as a consequence of exposure to ammonia remains essentially an open question. However, the current literature does not provide any evidence of adverse effects on worker health from exposures at the presently recommended threshold limit. Whether this is a reflection of the failure to monitor for biochemical disturbances or a confirmation of the adequacy of the present threshold limit cannot be determined from current knowledge. Although limited evidence from human studies suggests that moderate excursions of ammonia vapor above 50 ppm may not cause significant

mucous membrane irritation or decreased respiratory function, results from the animal studies cited above indicate that other physiologic responses remain to be investigated. Complicating factors arising in the definitive evaluation of ammonia toxicity pertain to the degree and permanence of biochemical alterations produced by excessive exposures, and the nature of the detriment to health posed by disruption of enzymatic, hematologic, and neurologic parameters.

VII. RESEARCH NEEDS

The presently recommended threshold limit for exposure to ammonia is based, for the most part, on subjective symptoms of irritation or annoyance. Experimental verification of the chronic effects of low-level exposures is required, particularly in light of recent evidence from animal studies to suggest that biochemical alterations may occur. A final and definitive analysis of the occupational hazard to health associated with ammonia would be greatly expedited by undertaking the following investigations:

(a) Animal studies conducted to characterize the dose-response relationships for ammonia-induced alterations in the activities of a wide spectrum of serum and tissue enzymes.

(b) Identification of homeostatic mechanisms (vis-à-vis, biochemical reactions) potentially disrupted by exposure to ammonia in humans. (Blood levels of ammonia, blood urea, nitrogen, and urea in the urine should be correlated with specific responses).

(c) Epidemiologic and/or retrospective worker investigations to detect possible biochemical or neurologic disturbances resulting from ammonia exposure.

(d) Chronic toxicity investigations designed to evaluate pathologic, physiologic, biochemical, carcinogenic, or neurological consequences of long-term exposure.

(e) Evaluation of the possible toxic synergisms resulting from ammonia exposure concomitant with other volatile chemicals or particulate matter.

(f) Investigations to determine the interference by ammonia with normal nitrogen balance in pregnancy and the effects on the fetus.

(g) Use of stable ^{15}N-isotope ($^{15}NH_3$ and urea) studies to determine the tissue distribution and enzymatic pathways of detoxification.

Insofar as research into analytical methods for ammonia is concerned, currently available techniques are adequate for current exposure level standards, as well as for concentrations of ammonia several orders of magnitude below

current standards. Therefore, research into analytical methods is not necessary for the purpose of ambient air monitoring at presently recommended threshold levels.

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APPENDIX A - LITERATURE SEARCH

The literature search strategy employed in preparing this update consisted of both computerized and manual techniques. Major reliance for bibliographic information was placed on a computer-generated NIOSHTIC search. In order to supplement this citation source, several steps were taken to insure that: (1) all relevant articles would be retrieved, and (2) very recent articles of relevance to the literature review would not be overlooked.

An on-line search using ammonia and related keywords was undertaken using the following data bases.

1. Chemical Abstracts (1973 to present)
2. U.S. National Technical Information Service (1973 to present)
3. Biological Abstracts (1973 to present)
4. Science Citation Index (1973 to present)

In addition to the computer-readable data bases detailed above, a manual search of Current Contents was conducted for the period November 1975 through August 1976. Pertinent articles located by manual and computer searching were examined to determine whether additional references could be located.