## III. BIOLOGIC EFFECTS OF EXPOSURE

### Extent of Exposure

At room temperature and pressure, ammonia is a colorless gas with a distinctive pungent odor. Its water solutions (aqua ammonia) emit ammonia gas. [1] Pertinent properties of ammonia are presented in Table XI-1. [1-3]

In terms of pounds produced each year, ammonia ranked second in 1971 and third in 1972 on a list of the top 50 chemicals produced in the United States. [4] Synthetic ammonia production has risen at an annual rate of 10-12% over the last two decades. [5,6] US production in 1950 was about 1.5 million tons, [6] rising to slightly over 14 million tons in 1971 and 1972. [4] Future annual growth rates were predicted to decline to 6-8%, leading to estimated consumptions of about 20 million tons in 1975 and 30 million tons in 1980. [5]

In 1971, ammonia was produced by approximately 80 companies in the US in as many as 100 separate plants. [6] About 80-85% of current production is used in fertilizer manufacture, with the remainder being taken by other industries. [5] Ammonia is used in a wide variety of industrial processes. A number of occupations with potential exposure to ammonia are listed in Table XI-2. [7-9]

NIOSH estimates that approximately half a million US workers have potential occupational exposure to ammonia.

### Historical Reports

In 1859 Taylor [10] reported a number of poisonings after intentional or accidental ingestion of ammonia solutions. Patients experienced immed-

iate, severe burning pain in the mouth, throat, and stomach which persisted in some cases up to 5 days. The ammonia reportedly "corroded and dissolved" tissues it contacted and caused severe local irritation. In 2 cases, ammonia was aspirated and the patients died as a result of lung damage. One case was cited in which the "vapor of strong ammonia" was applied to the nostrils of an epileptic who died 2 days later with what were described as symptoms of croup.

According to Horvath, [11] Lehmann in 1886 made the first important experiments on the effects of ammonia inhalation. Lehmann exposed himself for 30 minutes to ammonia at a concentration of 330 ppm and concluded that 300-500 ppm could be tolerated for a prolonged period. Horvath criticized the experiment for a number of reasons, including inaccuracies in the reported ammonia levels and the fact that the exposure was for only 30 minutes, and considered that Lehmann's conclusions were unjustified.

Effects on Humans

Ammonium ions are produced in the body as a protein metabolite. [12] Ammonium ions produced by deamination are rapidly converted in the liver into relatively harmless urea and excreted by the kidney or are used to make new amino acids. Ammonium ions are also produced in the kidney, conserving fixed base, thus maintaining electrolyte balance.

A. Odor Threshold

Available odor threshold data show a wide variation. Fieldner et al in 1921 [13] reported a threshold of 50 ppm in human exposure experiments. Smyth [14] found that 1 ppm was detected and identified by 10 subjects. Details of these experiments were not provided. Leonardos et al [15] used

a panel of 4 trained odor analysts, each with more than 1 year of "analytical odor work." Exposures were made in a test room designed to minimize background odor. Ammonia was injected into the test room with a microsyringe and the resultant air concentration was computed based on the room volume. The threshold was taken as the lowest concentration at which the subject could define the odor, provided that he consistently recognized the odor at the next higher concentration. The authors did not report the lowest concentration detected or the threshold level for each test subject, but 46.8 ppm was reported as the lowest concentration which all 4 panel members could consistently recognize. Saifutdinov [16] found the odor threshold for ammonia for the most sensitive subjects in a group of 22 individuals to be 0.50-0.55 mg/cu m (approximately 0.6-0.7 ppm). No description of the method used was given. No data were found on the acclimatization of the odor threshold, but an industrial hygienist reported that "the sense of smell was quickly deadened to the presence of the gas" at a concentration of 9-37 ppm in an ice cream plant survey. [LD Pagnotto, written communication, September 1973]

B. Case Reports

In 1938 Slot [17] reported 6 cases of acute ammonia gas exposure following rupture of a pipe containing ammonia. Varying degrees of symptoms of acute inflammation of the respiratory tract and chemical skin burns were observed. Residual chronic bronchitis was evident in 2 cases. One worker died one month after the accident and the autopsy revealed acute laryngitis, tracheitis, bronchopneumonia, and pulmonary edema. The kidneys showed congestion and early hemorrhagic nephritis, which was attributed to toxemia secondary to chemical skin burns.

In 1941 Caplin [18] published a case report of 47 persons involved in a mass exposure to ammonia in a London air raid shelter when a connecting pipe of an ammonia condenser was ruptured. He divided the exposed individuals into groups depending on the extent of the respiratory involvement. The signs and symptoms ranged from mild upper respiratory irritation to inflammatory processes of the entire respiratory tract with complications of pulmonary edema and bronchopneumonia. The exposed individuals in Caplin's report were affected according to a clinical spectrum depending on their distance from the ammonia source and their time of exposure. Unfortunately, no air concentration estimates were given.

The 9 "mild" cases [18] exhibited only slight eye and upper respiratory irritation with hoarseness and tightness in the throat. They recovered quickly and were discharged from the hospital within a few hours. The 27 "moderately" affected individuals showed more pronounced upper respiratory irritation and, in addition, had a productive cough with tenacious, sometimes blood-stained sputum and moist rales in the lungs suggesting an extension of the inflammatory process into the lower respiratory tract. Three patients in this group developed pulmonary edema within 6 hours and died. Nine patients from the "moderate" group developed bronchopneumonia on the second and third days, and 3 of these died. The remaining 15 "moderately" affected persons made an uneventful recovery within one week. All 11 "severely" affected patients had signs and symptoms of pulmonary edema with cyanosis, persistent cough with frothy sputum, and intense dyspnea. Seven patients of this group died. Autopsy results of 2 of the 3 deaths in the "moderate" group and 2 of 7 deaths in

the "severe" group generally supported the clinical findings. No observations of survivors following their hospital discharge were reported.

Lepine and Soucy [19] presented the results of follow-up pulmonary function tests in a worker who had incurred an acute ammonia gas overexposure of undefined concentration or duration. Over a follow-up period of more than one year, the maximum breathing capacity decreased from 97 to 52 liter/minute, the vital capacity from 3.09 to 2.04 liters, and the ratio of residual volume to total lung capacity increased from 49 to 58%. The diffusion capacity as measured by the carbon monoxide method diminished from 9.4 to 6 ml/min. These results indicate moderately progressive airway obstruction and diminishing diffusion capacity.

In 1964 Levy et al [20] reported 4 cases of acute ammonia burns from sudden decompression of ammonia containers. All 4 workers had severe ammonia burns of the face and acute laryngeal edema which was life-threatening and required tracheostomy. The importance of early eye irrigation was also demonstrated in these cases. The only patient who had serious permanent injury to his eyes, resulting in blindness, was the one who did not have early and prompt irrigation. In only one case was there any evidence of residual respiratory symptoms--a persistent, slightly productive cough after 2 years.

In the first case, [20] a 17-year old farm worker was sprayed in the face by a jet of anhydrous ammonia. He had second degree caustic burns of the skin with marked edema of the eyelids. Laryngeal edema developed rapidly, and he quickly became hoarse and dyspneic. He coughed up blood-tinged sputum and expiratory wheezes were heard throughout both lungs. Chest X-rays and routine laboratory tests were normal. He recovered from

his pulmonary distress within 15 days, and no permanent impairment of pulmonary function occurred. However, the patient's eye injury resulted in an almost complete loss of vision. Similar farm accidents involved another 17-year old boy and a 61-year old man. Two years later the 17-year old boy still had a productive cough with mucoid sputum, but in spite of corneal scarring, his vision remained normal. The older man showed no impairment of pulmonary function or vision but suffered some atrophic rhinitis, which subsequently improved. In the fourth case, a 28-year old man was struck by a jet of liquid ammonia from refrigeration equipment. He had a postinjury course similar to the other cases, except that he developed pneumonitis in the base of the right lung. There was no residual damage to the lungs or eyes. Pulmonary function tests, 3 years later, were normal in this fourth case.

Mulder and Van der Zalm in 1967 [21] described an acute case which occurred when a tank of ammonium hydroxide overflowed and exposed a worker to a very high concentration of ammonia. Based on the ammonium hydroxide concentration and weather conditions, the ammonia concentration was estimated as 10,000 ppm. The patient immediately experienced cough and vomiting and had difficulty in breathing. The length of exposure was not stated, but he performed "small jobs" for the remaining 3 hours of work before he was seen at a clinic. At that time, his face was red and swollen, he had conjunctivitis, and his mouth and throat were red and raw. His voice was disappearing and he had labored breathing. The heart appeared to be normal, but while X-rays were being taken the heart stopped. He was revived by massage and artificial respiration and was transferred to a hospital. Six hours after the accident his heart stopped again and he

died. Autopsy showed marked inflammation of the respiratory tract. Surprisingly, no pulmonary edema was present, but the tracheal epithelium was almost completely denuded.

In 1968 Dupuy et al [22] observed a case of severe gastritis after an unknown concentration of ammonia was inhaled. A truck driver was exposed to ammonia gas from a ruptured container and immediately exhibited evidence of dyspnea and lacrimation. The respiratory symptoms cleared up within 1 day, but for reasons which are not apparent he developed severe, acute gastritis which was confirmed by radiography and gastroscopy. The gastritis improved over the next several months but reappeared later. This apparently is the only published report of damage to the gastrointestinal tract attributed to ammonia exposure.

Osmond and Tallents [23] described a case in which aqueous ammonia was thrown in the face of a teller during a bank robbery. The bank employee developed a marked swelling of the nasopharynx and glottis with difficulties in breathing and swallowing. The authors pointed out that edema of the glottis took several hours to develop and that this delay could give a false impression of less severe damage, thus delaying adequate treatment. A mild chemical pneumonia was produced, from which the man recovered within one week. The chemical burn of his lesser affected eye healed promptly, but the other eye showed gradual deterioration over a 3-week period leading to corneal edema and then opacities, uveitis, and marked impairment of visual acuity. The authors emphasized that first aid must be administered at once, and stated that the only effective first aid for eye exposures of this type "is instant copious irrigation of the injured eye with running water...."

In 1971 White [24] reported that a 20-year old worker was found unconscious in a compression room approximately 5 minutes after he had been overcome by ammonia released from a defective safety valve. No estimates of air concentrations were attempted. He had not been wearing his safety mask and had chemical burns on several parts of the body. Rales were heard in both lungs suggesting fluid in the lower respiratory tract. Five hours later the patient was still unresponsive, and respiration was irregular. There was marked conjunctivitis, and pupils were constricted. Lungs revealed generalized rales and rhonchi with expiratory wheezing, which improved over the next 2 weeks. Six months later the patient had no pulmonary symptoms except a mild bronchitis.

Helmers et al [25] in 1971 presented 4 instances of ammonia injuries in agriculture. In all 4 instances farm workers were sprayed with anhydrous ammonia or ammonium hydroxide. The first worker was sprayed with anhydrous ammonia on the face and chest. Besides showing upper respiratory irritation, he developed pulmonary edema and pneumonitis necessitating a tracheotomy. He recovered within 11 days without any residual lung damage. The second worker was squirted on the skin with several gallons of aqua ammonia. He suffered second-degree skin burns on the exposed areas due to his failure to remove contaminated clothing. The third worker was sprayed in the face with anhydrous ammonia and received facial burns and moderate eye irritation with superficial corneal ulcerations. All 3 of these workers had water available and were able to immediately irrigate the eyes and skin. The fourth worker sustained a severe eye injury from an aqua ammonia spray. He was unable to irrigate his eyes with water until 30 minutes after the accident. Sensation in the more seriously affected eye

was lost. Vision was markedly diminished without improvement over the next few months. In spite of cataract surgery four months after the injury, he was left with only light perception. A year later the cornea was considerably vascularized and opacified.

Kass et al [26] in 1972 described 2 cases of bronchiectasis following an unspecified level of exposure to ammonia vapor for a duration of 30-90 minutes. Both cases showed signs and symptoms of severe, acute over-exposure to ammonia following derailment of a railroad tank car containing anhydrous ammonia. They recovered from the acute effects but continued to complain of chronic dyspnea and had a productive cough 2 years after the accident. In the more severe case, the patient was exposed for approximately 90 minutes. Radiologic examination revealed generalized bronchiectatic changes in practically all the segments of the lungs, and pulmonary function tests showed a marked airway obstruction. Hypoxemia was attributed to an uneven distribution between ventilation and perfusion. There was also a marked deterioration of vision with bilateral corneal opacities and early cataract changes. In the less severe case there was radiologic evidence of bronchiectasis involving the left lower lobe and some mild changes in the medial basal segment of the right lower lobe. The results of the pulmonary function tests were interpreted as indicative of obstruction of small airways. In both cases the bronchiectatic changes and the abnormal pulmonary function tests were attributed to ammonia exposure since prior to the accident there was no history of chronic respiratory symptoms, the smoking history was negative, and immunologic disease or genetic defects were not found. The authors emphasized the need

for complete pulmonary physiology studies when patients exhibit persistent cough and dyspnea following ammonia exposure.

In 1972 Walton [27] reported 4 ammonia incidents involving 7 men. The autopsy of the one fatal case showed marked laryngeal edema, acute congestion and edema of the lung, and a loss of bronchial epithelium. The remaining 6 were examined at yearly intervals for 5 years. All 6 were classed as "moderate" smokers (15-20 cigarettes a day). Exposures were not described in any detail by the author, however, one man with "light" ammonia exposure exhibited only mild symptoms of bronchospasm and recovered quickly. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV 1) were better than predicted values based on sex, age, and height. However, the gas transfer factor (GTF), a measure of diffusion capacity, was low (about 20 ml/min/mm Hg) throughout the follow-up period. This finding was explained by the author as probably associated with the patient's cigarette smoking.

Five men with "heavy" exposure showed acute symptoms and signs of chemical burns of the nose, mouth, and throat; moderate eye irritation; marked dyspnea with cyanosis, cough with blood stained sputum, and pulmonary congestion. [27] There was little evidence of any radiological abnormalities in the chest. Almost all abnormal pulmonary function tests showed a gradual improvement during the first 2 years after the accident. In one case FVC, FEV 1, and GTF were all above predicted values during the entire 5-year follow-up period. In another, the FVC and FEV 1 remained considerably below normal values throughout the follow-up period, while the GTF recovered to nearly normal. Clinical improvement in this second case was noted during the first 2 years but remained unchanged thereafter. In

the third case the FVC returned to normal, although the FEV 1 and the GTF remained well below normal. The fourth case showed progressive improvement in ventilation, but a consistent depression of the transfer factor. The fifth case showed gradual improvement to normal for the 2 ventilatory measurements, however the GTF stayed at low normal values. The author [27] attributed the residual abnormal pulmonary function tests in 2 cases (the second and third cases) to the ammonia exposure, whereas in 2 other cases (the fourth and fifth cases) the pulmonary function abnormalities were attributed to their continued smoking habit.

Several additional case histories highlight special problems from ammonia exposure. In 1969 Highman [28] described 2 cases of ocular injuries with a rise in intraocular pressure and cataract formation after ammonia of unknown concentration had been squirted into the victims' eyes during robberies. In both cases, the more severely affected eyes showed marked injection and edema of the conjunctiva; diffuse corneal damage; semidilated, oval, and fixed pupils; and a marked increase of the intraocular pressure which persisted and was controlled only with drugs. Glaucoma was observed to be associated with an open angle. Cataract formation was seen in both cases. Visual acuity was reduced to little more than light perception. McGuinness [29] reported a similar exposure during a jewelry robbery with similar effects, except that the victim did not show an increased intraocular pressure.

Morris [30] encountered 2 cases of possible sensitization to ammonia. The first man developed urticaria on 3 occasions when exposed to ammonia gas coming off an ammonium hydroxide solution at his workplace but the condition cleared up when he stayed away from work. The second worker

reported breaking out with the hives once after work and twice when he was riding in a car with workers who had been exposed to ammonia. This apparently is the only report of such an effect, and caution should be exercised before making a causal association.

Shimkin et al [31] observed the development of an epidermoid carcinoma of the nasal septum, which had been burned by an ammonia and oil mixture. They postulated that the corrosive action of ammonia may have prepared, promoted, or exteriorized a latent neoplastic condition. Shimkin et al strongly emphasized that this single case report could not be used to prove causal connections and that additional cases would be required for a critical analysis.

These 15 reports [17-31] involving 81 persons acutely injured by ammonia do not constitute all case reports in the world literature, but do represent a selection displaying the breadth of documented clinical findings from ammonia overexposures, especially those with detailed medical evaluations. In only one instance did the report include an estimate of the air concentration and the duration of exposure for the injured person. Mulder and Van der Zalm [21] reported that a worker died 6 hours following an exposure estimated to be 10,000 ppm for an unspecified time. Of the 81 exposures reported, 16 died, [17,18,21,27] 9 had some evidence of chronic lung disease, [17,19,20,24,26,27] 7 had some evidence of residual visual impairment or a permanent eye lesion, [20,23,25,28,29] 1 had a chronic skin lesion, [31] and 1 had a significant burn scar. [17] All of those with residual lung dysfunction or chronic respiratory symptoms had had documented acute lower respiratory involvement, such as acute tracheitis, bronchitis, bronchopneumonia, or pulmonary edema. Acute symptoms of upper

respiratory inflammation, such as acute laryngitis, pharyngitis, or rhinitis, and complaints of acute eye inflammation were reported by all affected persons almost immediately after exposure. Skin burns were reported after direct contact with anhydrous ammonia, [20,24,25,27] aqua ammonia, [25,27,28] and after exposure to concentrated ammonia gas. [26]

C. Human Exposure Experiments

Schmidt and Vallencourt [32] in 1948 exposed one human subject for 4 hours to an ammonia concentration of 530-560 ppm in order to study biochemical and blood pressure changes. Blood urea nitrogen (BUN) and serum creatinine remained unchanged through the exposure. The carbon dioxide combining power of the blood plasma remained unaltered. Repeated blood pressure readings during the experiment showed a linear drop from 127 mm to 102 mm. The authors made no reference to postexposure blood pressures, and data were not given on any subjective reactions or pulmonary function during or after exposure. During the exposure period, the serum nonprotein nitrogen (NPN) gradually increased from 27 mg/100 g blood to 57 mg/100 g blood and the blood ammonia rose from nondetectable levels to values of 36.4 mg/100 g blood. In response to this finding, Ting [33] noted that rats injected with ammonium citrate died at an ammonia nitrogen level of 8-11 mg N/100 ml of blood. Furthermore, assuming a blood volume of 5 liters, a minute volume of 20 liters, and 100% absorption of inhaled ammonia, Silverman and Whittenberger [34] showed that the blood ammonia levels reported by Schmidt and Vallencourt [32] exceeded what was theoretically possible.

Silverman et al [35] in 1949 reported the physiological studies of 7 human subjects exposed to concentrations of 500 ppm ammonia administered

for 30 minutes using an oral-nasal mask. All 7 volunteers experienced upper respiratory irritation, lasting up to 24 hours in 2. The subjective reactions of upper respiratory irritation in these 2 were graded as severe; and 2 subjects had marked lacrymation in spite of the exposure being by oral-nasal masks, so there was no direct contact of the eyes. No coughing was noted, however, and the average respiratory minute volume was markedly increased above control values. The respiratory rate was slightly increased. Every 4-7 minutes during the exposure, the minute volume shifted down briefly, but was still well above baseline values. The mechanism of this altered respiration was not elucidated in this investigation. After exposure, respiratory minute volumes fell to levels below the preexposure rate, but returned to preexposure values within 5 minutes after exposure. Silverman et al [35] observed that with 500 ppm delivered for 30 minutes by a naso-oral mask ammonia retention decreased progressively until an equilibrium of 24% retention (ranging from 4-30%) was reached at about the 19th minute (from 10-27 minutes). Ammonia in the expired breath was not detectable beyond the 8th minute after exposure. Contrary to the results reported by Schmidt and Vallencourt, [32] the indices of nitrogen metabolism--BUN, NPN, urine urea, and urine ammonia--all remained normal. The carbon dioxide combining power remained unchanged. Pulse rate and blood pressure were measured in 2 of the 7 subjects. In one of these there was a 15% increase in pulse rate and a 10% increase in blood pressure. These changes promptly returned to baseline when exposure was discontinued, and there was no change in the second individual. The limitation of symptoms to the nose and throat suggested to

the authors that ammonia was absorbed largely by the upper respiratory tract.

In 1950, Landahl and Herrmann [36] reported an investigation of the short-term retention of ammonia in the nose of 4 human subjects. A face mask with 2 tubes attached was used. One tube supplied the gas-air mixture, the other was used for air sampling. In this nasal retention experiment, the subject held his breath while a gas-air mixture was drawn in through the nose and out through the mouth. A parallel air stream from the same source was sampled simultaneously to determine the initial ammonia concentration. When a concentration of 0.05 mg/liter (approximately 72 ppm) was drawn through the nose at a rate of 18 liters/minute, an average of 83±5% was retained. A threefold increase of the rate of intranasal flow resulted in a moderate decrease of the percentage retained. When the ammonia gas was inhaled and exhaled through the mouth, bypassing the nasal passage, the total retention was about 92%. In this experiment the subject inhaled through the mouth by a gas-air mixture tube and exhaled into a sampling tube. The percentage retained was not significantly affected by increasing the concentration from 0.04 to 0.35 mg ammonia/liter (approximately 58 ppm to 503 ppm). A threefold increase of the time the ammonia remained in the respiratory tract resulted only in a negligible increase of the percentage retained. No data were given of any subjective reactions or pulmonary function changes during or after exposure.

For comparison with human responses to monomethylhydrazine, MacEwen et al [37] exposed 6 volunteers at ammonia concentrations of 30 and 50 ppm for 10 minutes. Subjects did not know the concentrations to which they were being exposed and exposures were made in random order.

Concentrations, which were continuously monitored, were established and stabilized in a Rochester Chamber. Test subjects then inserted their heads through a rubber diaphragm for the 10 minutes of exposure. The irritation was rated subjectively on a scale of 0-4 and odor on a scale of 0-5. Results for the 2 ammonia concentrations are given in Table XI-3. At 50 ppm, irritation was rated as "moderate" by 4 of the volunteers, but 1 individual reported no detectable irritation. None of the subjects found the irritation at 50 ppm to be "discomforting" or "painful." All of the subjects rated odor as "highly penetrating" at 50 ppm, and 3 volunteers gave the same rating at 30 ppm.

The Industrial Bio-Test Laboratories Inc [38] has also evaluated the irritation threshold of ammonia. Ten human subjects were exposed at 4 different concentrations (32, 50, 72, and 134 ppm) for 5 minutes. The criteria of irritation were any annoyance to the eyes, nose, mouth, throat, or chest which persisted throughout the 5-minute exposure period. The investigators felt that an exposure of 5 minutes was adequate "since irritation with such a material depends more upon concentration than upon time of exposure." The frequency of positive findings out of the 10 subjects exposed to each concentration were as follows: at 32 ppm 1 subject complained of dryness of the nose. At 50 ppm 2 subjects had dryness of the nose. At 72 ppm 3 subjects experienced eye irritation, 2 had nasal irritation, and 3 had throat irritation. At 134 ppm 5 subjects showed signs of lacrimation, 5 had eye irritation, 7 had nasal irritation, 8 had throat irritation, and 1 complained of chest irritation. Because the only reaction noted at 32 and 50 ppm was slight dryness of the nose, the authors concluded that "concentrations of 50 ppm or less did not cause

irritation or discomfort." However, this study involved only a 5-minute exposure, and it is possible that on much longer exposure irritation might have developed; it is also possible that on longer exposure acclimatization could have developed.

Patty [39] stated that he observed that a 1% concentration of ammonia was mildly irritant to the moist skin, at 2% the irritation was more pronounced, and that a concentration of 3% or greater caused a stinging sensation and "may produce chemical burns with blistering after a few minutes exposure." The specifics of this experiment apparently have never been published.

In summary, the above 6 human inhalation studies [13,32,35-38] and the 1 report [39] on skin exposure were directed toward identifying acute responses to ammonia with exposure times of several hours or less. Unfortunately, these studies do not indicate at what air concentrations short-term exposures may result in ventilatory abnormalities, such as significant decrements in FEV 1. In addition, subjective responses of upper respiratory and eye irritation have not been developed into a reliable graded response measurement so as to compare results of various inhalation concentrations and durations of exposure. Thus, only crude indicators of physiologic response were available. Furthermore, the question of skin response to varying concentrations of ammonia appears to be very poorly documented.

Epidemiologic Studies

El Sewefy and Awad [40] evaluated 41 persons employed by an ice manufacturing plant in Egypt. Air concentrations of ammonia were not given, but the authors reported that the workers were exposed to a temperature of -6 C in the ice plant. Workers moved in and out of the refrigerated area, thereby being subject to temperature differences of up to 44 C in the summer. At the time of the study, the workers had an average 16.1 years of exposure and were somewhat older than the 28 control employees, who came from "non-hazardous" work places. For analysis of the data, the subjects were divided into smoker and nonsmoker groups. The exposed workers in both the smoker and nonsmoker groups were slightly older and shorter than the corresponding groups of control workers. Pulmonary function tests (FVC and FEV 1) for smokers vs nonsmokers were compared in both groups and were not significantly different. Therefore, smoker and nonsmoker data were combined to compare control and exposed workers. Values were lower in the exposed group, but the difference was not statistically significant at the 5% level when corrected for age and height differences. Chest symptoms (cough, phlegm, wheeze, and dyspnea) in the ammonia exposed group and control group were not significantly different. The authors concluded that the combination of long-term exposure to ammonia and extreme temperature changes in this plant did not have any adverse effect on ventilatory function or respiratory symptomatology.

Bittersohl [41] reported that in the German chemical industry cancer morbidity and mortality among male and female workers for the period from 1958-1967 was very high, especially in the ammonia and amine plants. The average air concentration in these 2 plants was estimated to be 2-3 times

the German Democratic Republic (East Germany) maximum allowable concentration (MAK) of 25 mg/cu m (approximately 35 ppm). The duration of employment was more than 10 years for about 80% of the work force. The 10-year cancer morbidity rate for the entire chemical factory of about 30,000 workers was approximately 160/10,000/year. In 1 of the 2 ammonia plants, the morbidity rate per 10,000 employees was reported to be about 1,250 in males and about 370 in females. The male cancer morbidity rate was about 1,000 for the second plant (precise rates were not given, but must be read from bar diagrams). The author suggested that the average ammonia exposure dose had been greater for male workers in the ammonia plants. Cancer deaths reportedly accounted for 40% of all deaths among employees of the ammonia plants during this 10-year period. Bittersohl also noted that his analysis of the distribution of cancer deaths by site suggested an excess of lung, urinary tract, gastric, and lymphatic neoplasms.

Details in this paper are very poor. The author did not include the background information necessary to judge the accuracy of his conclusions. This isolated and poorly documented report is not adequate to implicate ammonia as a suspected carcinogen, but it does make more urgent the need for follow-up epidemiological studies. Until thorough studies are completed, the validity of this single report cannot be evaluated.

Elkins [42] stated briefly without giving any details that ammonia concentrations of 125 ppm in a mildew-proofing process were definitely irritating, while 55 ppm in an electroplating plant "were judged not to be excessive."

In 1955 Vigliani and Zurlo [43] reported on their investigations of exposures to 24 substances. They reported that in an "ammonia works"

concentrations of 100 ppm could not be continuously inhaled for lengthy periods without irritation of the upper respiratory tract and eyes. They also reported that workers accustomed to 20 ppm of ammonia did not complain but showed slight redness of the conjunctiva. Those not accustomed did have eye and respiratory discomfort and irritation. The authors recommended a MAC of 50 ppm. It is not clear whether respiratory complaints pertained to the upper or lower respiratory tract or whether conjunctivitis was more severe in the nonaccustomed workers. Unfortunately, the details of these surveys were not provided, namely, the numbers of workers at risk at 100 and 20 ppm, the numbers and matching of controls, the environmental measurement data, the methods of measurement of clinical effects and subjective responses, the proportions and persistence of those showing effects, or the presence of confounding variables such as other irritants or preexisting chronic diseases.

Mangold [44] in an unpublished report evaluated complaints of eye irritation in a blueprint shop. Two 2-hour samples on each of 2 days and 10 15-minute samples of air on each of 2 later days during a 1-week period when eye complaints were occurring showed concentrations of ammonia ranging from 4-29 ppm. No reference was made to the type or level of any respiratory complaints, if any, of the workers in the blueprint shop. Previous evaluation 6 months earlier in the same shop had reported air levels below 5 ppm of ammonia associated by the workers and/or the hygienist with barely noticeable eye irritation. It was concluded that intermittent peak exposures in the range of 20 ppm of ammonia caused moderate eye irritation. The author considered these to be strictly irritating or annoying but not injurious exposures. This was a very small

survey (8 workers) in which the effects were entirely subjective and were given only in descriptive, not quantitative, terms. There are no data on how many of the 8 workers were affected, the possible presence of other irritants such as coupling agents or cigarette smoke was not acknowledged, the association of peaks with acute responses was not documented, and there was no clinical verification of any of the responses.

Pagnotto [written communication, September 1973] reviewed the files of surveys performed by the Division of Occupational Hygiene of the Commonwealth of Massachusetts from 1940 to 1972. Several plant surveys mentioned irritating effects. A survey of refrigeration equipment in an ice cream plant disclosed that ammonia concentrations in air ranged from 9-37 ppm. Odor fatigue was reported at these concentrations by the industrial hygienist, who stated that the odor of ammonia was noticeable but that "the sense of smell was quickly deadened to the presence of the gas." In an insole cementing operation, ammonia concentrations were 15-28 ppm in the work area, and very slight eye irritation was reported. A concentration of 45 ppm was found in a blueprint machine room, and the industrial hygienist commented that there was "some eye irritation, but one quickly becomes accustomed to it." Samples ranging from 3-29 ppm were collected near a printing machine with the comment from the industrial hygienist that the "odor of ammonia was quite marked, but not disagreeable." In another survey at a printing machine, the range was 2-45 ppm, but the hygienist commented only that the "odor of ammonia was strong" when taking the sample of 45 ppm. None of these brief reports were epidemiologic studies in which the investigator used systematic methods for evaluating the effects, used control groups, noted the frequency of

clinically substantiated or reliable subjective responses among workers at risk and controls, documented carefully the environmental exposures of all those at risk including confounding exposures, or attempted statistical comparisons of the incidence of the various acute effects.

In the preceeding 4 reports, [42-44, and LD Pagnotto, written communication, September 1973] irritation was associated with a wide range of ammonia exposure. The highest concentration reported, 125 ppm, [42] was "definitely irritating," while "barely noticeable" eye irritation was reported [44] at 5 ppm. However, in one survey mentioned by Pagnotto, [written communication, September 1973] the hygienist who collected a sample of 45 ppm noted the strong odor of ammonia but mentioned no irritation. Elkins [42] considered exposure at 55 ppm not to be "excessive," and Vigliani and Zurlo [43] recommended 50 ppm as a MAK.

## Animal Toxicity

### A. High Exposure Studies

In 1933, the Underwriters Laboratory [45] reported exposures of 8 guinea pigs to concentrations of 0.5-0.6% by volume (5,000-6,000 ppm). Two animals were removed from the test chamber at the end of 5, 30, 60, and 120 minutes and all were observed for 10 days. Within 30 seconds, all 8 were lachrymating profusely, discharging from their noses, and exhibiting labored breathing. At the end of 5 minutes, their eyes and noses were intensely inflamed, respiration was irregular, and frequent retching movements were noted. Violent coughing occurred after 30 minutes, breathing was shallow at 60 minutes, and barely perceptible at 120 minutes. All animals survived but showed increasing severity of respiratory

irritation depending on exposure time. All 8 animals were blind, as judged by corneal opacities, when first removed from the chamber, but those exposed only 5 minutes recovered their sight within a week. Sight was recovered by 1 animal exposed for 30 minutes and in only 1 eye of 1 animal exposed for 60 minutes. Aside from this permanent blindness in 5, all animals recovered and showed consistent weight gain during the 10-day observation period.

A second group of 4 guinea pigs was exposed [45] to concentrations of 2.0-2.5% by volume (20,000-25,000 ppm). Two animals removed after 5 minutes were blind and showed signs of marked respiratory irritation. Except for permanent blindness in 1 of the 2 guinea pigs, both recovered fully within one week. One animal died after 9 minutes of exposure, apparently as a result of a reflex stoppage of the respiration since autopsy findings were minimal. The fourth animal, exposed for 30 minutes, displayed marked respiratory difficulties, but recovered except for permanent blindness.

Silver and McGrath [46] in 1948 exposed 9 groups of 20 mice to ammonia for 10 minutes, each group at a different concentration. Exposures ranged from 6.1-9.0 mg/liter (approximately 8,770-12,940 ppm). The LC50 was estimated to be 7.06±0.32 mg/liter (about 10,150 ppm). All test animals exhibited great excitement and severe eye and upper respiratory tract irritation. They closed their eyes immediately and within one minute they were gasping, pawing, and scratching their noses. Death with convulsions occurred after about 5 minutes, and 100 of 180 animals died before the 10-minute exposure was completed. The 80 surviving animals recovered rapidly after removal from the chamber, showing normal behavior

in many cases within 10 minutes. Between the 6th and 10th postexposure days, 7 of the 80 died, compared with no deaths in controls. Autopsies were not performed.

Boyd et al [47] in 1944 reported an experiment in which they exposed an unstated number of rabbits and cats for 1 hour to initial concentrations of 3.5-8.7 mg/liter (approximately 5,200-12,800 ppm) with an average concentration of 7.0 mg/liter (approximately 10,360 ppm). This was reported to be the "approximate LC50." The authors estimated that the static method of gassing used probably resulted in an average concentration of half the initial concentrations or less. Boyd and associates also evaluated the gas absorption of the nasobuccopharyngeal section of the respiratory tract. One group of rabbits inhaled directly through a tracheal cannula, and a second group inhaled normally through nose, mouth, and throat. The numbers of rabbits in the 2 groups were not indicated by the authors. The mean survival time in the second group was reported to be almost twice that of the first group, 33 hours versus 18 hours. On microscopic examination, the trachea was congested and edematous. The mucosa was necrotic and sloughed off in 80-90% of the animals in which the upper respiratory tract had been bypassed, while the trachea was normal in appearance in the second group of test animals. Similar differential findings, but to a lesser degree, were shown in the bronchial mucosa. The damage to the bronchioles and alveoli surprisingly appeared to be identical in both groups. It was described as congestion, edema, hemorrhage, and atelectasis with emphysema. The authors concluded that the upper respiratory tract acted as a protection only to the trachea and bronchi, and that small airways and alveoli were less resistant to ammonia injury

than the upper airways. The data are difficult to interpret because of lack of information on the number of animals used and the number affected.

B. Low and Moderate Exposure Studies

Weedon et al [48] in 1940 reported on continuous flow chamber studies in which they exposed 8 rats and 4 mice for 16 hours to an ammonia gas concentration of 1,000 ppm. They reported no noticeable effects during exposure. One rat died 12 hours after exposure and showed congestion of the brain, liver, and kidneys, plus large hemorrhages in the lungs and pulmonary edema. The other 11 animals showed no gross abnormalities during the subsequent 5 months of observation. Two rats and 2 mice were killed at that time, and autopsy results were negative.

Weatherby [49] in 1952 reported an experiment in which he exposed 12 guinea pigs to about 170 ppm ammonia for 6 hours a day, 5 days a week for up to 18 weeks. Chamber concentrations were monitored and ranged from 140-200 ppm. The 12 exposed animals and 6 controls were weighed weekly. No adverse effects were observed by autopsy of the 4 exposed and 2 control animals killed after 6 weeks or after 12 weeks. In 4 animals exposed for 18 weeks, there was congestion of spleens, livers, and kidneys with early degenerative changes in suprarenal glands. Increased blood destruction was suggested by higher quantities of hemosiderin in the spleens. In the upper tubules of the kidneys there was cloudy swelling with precipitated albumin in the lumen and some casts. These changes were also seen in the lower tubules of 2 animals. The cells of the suprarenal glands were swollen and the cytoplasm in some areas had lost its normal granular structure. The author considered all changes to be relatively mild, though definite.

Coon et al [50] in 1970 reported experiments in which they exposed 15 rats, 15 guinea pigs, 3 rabbits, 2 dogs, and 3 monkeys to an ammonia concentration of 155 mg/cu m (about 220 ppm) for 8 hours a day, 5 days a week for 6 weeks. This concentration did not produce any abnormal pathologic findings in any of the species except evidence of focal pneumonitis in the lung of 1 of the monkeys. Exposure of the same numbers and species of animals to 770 mg/cu m (approximately 1,110 ppm) for the same duration produced mild to moderate eye irritation and labored breathing in the rabbits and dogs at the beginning of exposure, but these disappeared by the second week and no other signs of irritation or toxicity were noted. Necropsy revealed nonspecific inflammatory changes in the lungs of the rats and guinea pigs at the end of the exposure period.

In addition to these studies, several experiments were undertaken by Coon et al [50] involving continuous (24 hours a day, 7 days a week) exposure to ammonia. Continuous exposure to 40 mg/cu m (about 60 ppm) for 114 days showed no sign of toxicity in any of the species referred to above. Macro- and microscopic examination showed no lung abnormalities. Forty-eight rats continuously exposed to 127 mg/cu m (about 180 ppm) for 90 days did not reveal any abnormalities of organs or tissue. Inhalation of 262 mg/cu m (approximately 380 ppm) for 90 days produced mild nasal irritation in about 25% of 49 rats and a slightly elevated leucocyte count in 4 of the rats. Fifty of 51 rats continuously exposed to 455 mg/cu m (about 650 ppm) died by the 65th day of exposure. Mild nasal discharge and labored breathing were exhibited by all animals, but no microscopic examinations were made on these animals. In a final experiment, all species mentioned above were continuously exposed to 470 mg/cu m

(approximately 680 ppm) for 90 days. Four of 15 guinea pigs died and 13 of 15 rats died. Marked eye irritation was noted in dogs and rabbits, with corneal opacities in about one-third of the rabbits. At necropsy all test animals examined had more extensive focal or diffuse interstitial inflammatory processes in the lungs than did controls.

Stombaugh et al [51] in 1969 evaluated the effects of ammonia on pigs. One pig exposed to 280 ppm showed immediate irritation of the nose and mouth and abnormal respiratory patterns, and by the 36th hour of exposure had convulsions and extremely shallow and irregular breathing. Convulsions continued for 3 hours after exposure ended but the animal appeared normal several hours later. In each of 2 trials, 4 exposure groups of 9 pigs each were continuously exposed to ammonia for 5 weeks. Data from both trials were combined for analysis. Concentrations of ammonia were measured daily, and the average exposures of the groups were 12, 61, 103, and 145 ppm. Feed consumption and average daily weight gain were adversely affected by increasing ammonia concentrations. Pigs exposed to the 3 higher concentrations had excessive nasal, lacrymal, and oral secretions, but these were less pronounced in those exposed to 61 ppm. Pigs exposed to 61 ppm appeared to adjust within 3-4 days, so that their secretory rate was only slightly higher than that of animals exposed to 12 ppm. Pigs in the 2 higher concentrations coughed approximately 3 times as much as those in the lower, and coughing at 61 ppm was slightly more frequent than at 12 ppm. Five animals from each exposure group were autopsied and all gross and microscopic findings were normal.

Doig and Willoughby [52] found no adverse effects on food intake, weight gain, or frequency of coughing when weanling pigs were continuously

exposed to ammonia for up to 6 weeks at an average concentration of 106 ppm, with a range from 52-160 ppm. Slight eye irritation with evidence of photophobia and excessive lacrimation were noticed during the first week of exposure, but thereafter the pigs appeared to be acclimatized. The hematocrit, total white blood cell count, differential white cell count, and serum lactic dehydrogenase activity were unchanged. Bacterial flora in the trachea of exposed pigs did not differ from that of control animals, but pathologic changes were noted in the tracheal epithelium with an increase in epithelial thickness and a decrease in the number of goblet cells. Effects on bronchi, bronchioles, and alveoli were not observed. One pig was randomly selected each week for autopsy studies that included estimating the thickness of the tracheal epithelium. The 6-week mean for exposed pigs was 32.9 μm vs 19.4 μm in controls. Likewise, the mean number of goblet cells per 500 μm was 10.6 for exposed animals and 18.9 for controls. These changes were not evident in the animal autopsied after 1 week, but they were seen in all 5 animals examined in succeeding weeks.

Corn starch dust and corn dust were studied [52] for interaction with ammonia by replicating the ammonia exposure with simultaneous exposure either to corn starch dust or to corn dust. The authors concluded that the dust inhibited the effects of ammonia on the trachea. The average corn starch dust concentration was approximately 70 mg/cu m with a median particle size of about 3 μm, and the corn dust concentration was approximately 3 mg/cu m with a median particle size of about 1 μm. Limited data were presented to indicate that the epithelium of the nasal turbinates also underwent changes suggestive of chronic inflammation.

Mayan and Merilan [53] in 1972 used thermocouples in plastic masks secured over test animals' noses and thereby recorded respiration on magnetic tape. In 5 animals BUN, blood pH, and blood carbon dioxide were measured prior to exposure and immediately following exposure to 100 ppm of ammonia. Using 2.5-3.0 hour exposure times, 9 rabbits were exposed to 50 ppm in a total of 22 trials, and 7 rabbits were exposed to 100 ppm in 16 trials. Five animals of the latter group were included in the biochemical studies. A significant decrease of about 33% in the respiration rate of rabbits exposed to both concentrations was reported. Respiratory depth was measured indirectly by the thermocouple sensors, and the authors reported that respiratory depth increased with time during exposure to ammonia. In 5 rabbits exposed to 100 ppm ammonia, BUN disclosed significant increases from 19.4 to 24.6 mg/100 ml (P less than 0.005) and blood carbon dioxide rose from 14.3 to 18.9 meq/liter plasma (P less than 0.07). The blood pH was not significantly altered. No pathological changes in lungs, liver, spleen, or kidneys were found.

C. Ciliary Function and Related Studies

Cralley [54] noted a cessation of ciliary activity without recovery in resected sections of rabbit trachea exposed in a tissue chamber to 500 ppm ammonia for 5 minutes and 400 ppm for 10 minutes. Temporary cessation was observed at 200 ppm after 9.5 minutes of exposure of the trachea.

Dalhamn [55] in 1956 studied rats whose incised tracheas were exposed directly to ammonia without passage through the upper respiratory tract and microscopically observed ciliary activity in vivo. Control preparations using moist, warm air showed no effect on ciliary movement or mucosal drying with a 10-minute treatment. Ciliary activity of the trachea ceased

after exposure for 5 seconds at 90 ppm, after 10 seconds at 45 ppm, after 20 seconds at 20 ppm, after 150 seconds at 6.5 ppm, and after 7-8 minutes at 3 ppm. Recovery occurred in all cases 10-30 seconds after exposure was discontinued. All reported data were based on the average of 3 observations for each exposure. Findings at the 2 lower concentrations were, according to the author, inadequate because the gas sampling method used was applicable only to concentrations of 5 ppm or more. The following studies by the same author did not verify the findings of this earliest experiment.

In 1963, Dalhamn and Sjoholm, [56] using the same in vivo preparation, reported that 500-1,000 ppm caused arrest of ciliary activity in an excised trachea of a rabbit following a 5-minute exposure. Also in 1963, Dalhamn [57] reported that, in resected rabbit tracheas, concentrations of about 1,000 down to 460 ppm stopped ciliary activity, and at 400 down to 270 ppm the ciliary beat either ceased or was greatly reduced. Below 260 ppm an effect could be detected only by counting ciliary beats. In this way, 100 ppm was established as the approximate level at which a reduction first occurred. Dalhamn [57] then exposed excised tracheas to 75-169 ppm. Using cinematographic recordings of microscopic images, the range of initial ciliary beat rates was established as 1,111-1,603 beats/min. Postexposure rates averaged 7.5% lower than initial ciliary beat rates for concentrations between 112 and 169 ppm. No mean difference was observed between 88 and 75 ppm. The author estimated that 100 ppm was the lowest concentration that would produce a significant reduction in ciliary motility using this technique.

In further experiments on 6 rabbits, Dalhamn [57] reported that a concentration of about 2,000 ppm introduced for 45 minutes into the nasal cavity produced concentrations of about 100 ppm in the rabbit trachea. Ten rabbits were then exposed to an average concentration of about 2,200 ppm for 45 minutes. Cinematographic recordings of ciliary activity were obtained after 15, 30, and 45 minutes of exposure. A significant mean decrement of 17% in ciliary activity was noted after 45 minutes. Ten rabbits were also exposed to ammonia at about 2,000 ppm and pulverized carbon particles at an average concentration of about 2.0 mg/cu m and with a median particle size of about 1 μm. After 45 minutes the mean decrement in ciliary activity was 33%. Dalhamn did not consider this interaction to be of practical significance.

Dalhamn and Reid [58] also examined the interaction between ammonia and carbon particles. Four groups of 10 rats each were exposed either to air alone, carbon particles (median diameter slightly under 1.0 μm) at a concentration of 7 mg carbon/cu m, ammonia at a mean concentration of 102 ppm, or to ammonia plus carbon particles at concentrations of 119 ppm and 3.5 mg carbon/cu m, respectively. Exposures lasted 5 hours a day, 5 days a week for 60 days. At the end of that time, ciliary activity was determined and sections of trachea were taken for microscopic examination of the mucosa. Neither ammonia alone nor carbon alone had a significant effect on ciliary activity, but the combination of ammonia and carbon produced a significant reduction in ciliary activity. On microscopic examination, the tracheal mucosa was classified as "normal," "moderately damaged," or "severely damaged." Among the air controls and the rats exposed to carbon alone, none of the tracheas were severely damaged and 2 in each group were

considered to be moderately damaged. The remainder, 8 of the air controls and 7 of those exposed to carbon, had normal tracheas (the section from 1 rat exposed to carbon alone was not suitable for microscopic examination). Of those exposed to ammonia alone, 4 rats had normal mucosa, 3 had moderately damaged, and 3 had severely damaged mucosa. In contrast, there were no normal tracheas in rats exposed to ammonia plus carbon particles. Two of these rats showed moderate damage and 8 rats had severe damage.

In summary, animal experiments indicate that the main toxic effect of ammonia is on the respiratory tract and on the eyes. Exposure at concentrations of 5,000-6,000 ppm for up to 2 hours produced marked irritation of the respiratory system and produced blindness in many animals exposed for 30 minutes or more. One of 2 guinea pigs exposed at 20,000-25,000 ppm for 5 minutes was permanently blinded, 1 died after 9 minutes, and 1 which survived for 30 minutes was permanently blinded. [45] The LC50 for the animals exposed for 10 minutes [46] and for 1 hour [47] was reported to be in the range of 10,000 ppm. Simulating a workweek, intermittent exposure to concentrations of about 1,000 ppm for 6 weeks, produced mild to moderate eye inflammation and labored breathing in some animals, and inflammatory lung changes in others. [50] Similar intermittent exposures to concentrations of about 200 ppm were reported to have no adverse effects on the respiratory system of rats, guinea pigs, rabbits, and dogs, but 1 of 3 monkeys showed focal pneumonitis. [50] Intermittent inhalation exposures of rats to about 100 ppm for almost 10 weeks showed chronic inflammation of the trachea and a ciliary motility effect, potentiated by activated carbon particles. [58]

In continuous 24-hour exposures over prolonged periods the effects of ammonia were, as might be expected, more severe. Exposure up to about 180 ppm for several months did not produce adverse effects, but 380 ppm and more produced nasal discharge, labored breathing, and, at 680 ppm, inflammatory processes in the lungs. [50] At concentrations in the range of 100-150 ppm, slight eye and upper respiratory irritation were noted early in the exposure, [51,52] and marked thickening of the tracheal epithelium was found at autopsy. [52]

Correlation of Exposure and Effect

A worker exposed to an ammonia concentration estimated at about 10,000 ppm experienced immediate coughing, dyspnea, and vomiting. [21] The worker died of heart failure 6 hours following the exposure. The autopsy showed denudation of the tracheal epithelium.

During controlled human exposures at about 500 ppm for 30 minutes [35] the following were observed: irregular minute ventilation with a cyclic pattern of hyperpnea, increases in blood pressure and pulse rate, variable lacrimation, and general complaints of upper respiratory irritation, some of these persisting for 24 hours following exposure.

Exposures of human subjects to 134 ppm for 5 minutes produced lacrimation, eye irritation, discomfort of the nose and throat in some individuals, and 1 complaint of discomfort in the chest. [38] In plant surveys with exposures at 100-125 ppm, [42,43] definite upper respiratory and eye irritation have been reported. At 72 ppm for 5 minutes a "discomfort" level of nasal and throat irritation plus eye irritation were reported by some subjects. [38]

MacEwen et al [37] exposed volunteers to ammonia concentrations of 30 and 50 ppm for 10 minutes and reported 4 of 6 subjects felt "moderate" irritation at 50 ppm, while the remaining 2 volunteers felt no irritation and "just perceptible" irritation, respectively. There was no or "just perceptible" irritation at 30 ppm. The odor was considered to be "highly penetrating" at 50 ppm by all subjects and by 3 at 30 ppm, including one who reported irritation to be imperceptible at both 30 and 50 ppm (Table XI-3).

Exposures of 5 minutes at 32 and 50 ppm produced no eye irritation but some complaints of dryness of the nose. The investigators reported the latter effect was not one of discomfort. [38] In a survey of an electroplating plant, the industrial hygienist was aware of "no adverse effects" at an average concentration of 55 ppm. [42]

On the other hand, a number of plant surveys have suggested that lower concentrations do produce an adverse response in some workers. In one plant with average concentrations of 20 ppm, [43] some workers displayed conjunctivitis, and "unaccustomed" workers complained of eye and respiratory irritation. In a blueprint shop [44] several workers noted only "barely noticeable eye irritation" at 5 ppm or less. The industrial hygienist associated eye irritation with peaks of about 20 ppm. [44] "Very slight eye irritation" was reported by workers in an insole cementing operation with exposures ranging from 15-25 ppm, and in another blueprint room with concentrations of 45 ppm there were complaints of eye irritation. [LD Pagnotto, written communication, September 1973]

Animal studies suggest that some airborne particulates can potentiate the effect of ammonia, apparently by carrying adsorbed ammonia deeper into

the respiratory tract. Doig and Willoughly [52] found that corn starch dust and corn dust inhibited the effect of ammonia on pig tracheas. In contrast, Dalhamn [57] and Dalhamn and Reid [58] found that activated carbon particles increased the tracheal damage in rats.