

## VI. COMPATIBILITY WITH AMBIENT AIR QUALITY STANDARDS

National primary and secondary air quality standards for nitrogen dioxide were published by the Environmental Protection Agency in the Federal Register 30:8186-8201, April 30, 1971 (present codification in 40 CFR 50.1-50.3, 50.11) The national primary air quality standards define levels of air quality which are judged necessary, with an adequate margin of safety, to protect the public health. The national secondary air quality standards define levels of air quality which are judged necessary to protect the public welfare from any known or anticipated effects of a pollutant. The term "ambient air", as used in the air quality standards, means that portion of the atmosphere, external to buildings, to which the general public has access.

The national primary and secondary ambient air quality standards for nitrogen dioxide are  $100 \mu\text{g}/\text{cu m}$  (0.05 ppm) annual arithmetic mean, measured by a specified reference method. However, on June 14, 1972 (Federal Register 37:11826, June 14, 1972), it was announced that the reference method would be reevaluated because of apparent deficiencies. On June 8, 1973, tentative candidate methods from which to select a replacement reference method were published. (40 CFR Part 50)

No direct comparison can be made between the national primary and secondary ambient air quality standards and the recommended standard for occupational exposure because the levels of exposure to the general public involve varying health status and age on a 24-hours/day, 7-days/week basis. The ambient air quality standards should be substantially lower than the occupational standards which are based on a workday of up to 10 hours and a workweek of 40 hours.

## VII. RESEARCH NEEDS

### Epidemiologic Studies

Three epidemiologic studies (56,70,71) indicated that chronic effects on the pulmonary system as well as hematologic changes may be observed in workers exposed to oxides of nitrogen at and below the current federal limits. However, each of these studies contained errors or omissions in at least one of the following categories: (1) inadequate characterization of exposure concentration or duration of exposure, (2) exposure to gases in addition to the oxides of nitrogen which may induce similar toxic effects, and (3) inconsistent or conflicting results on the toxic effects observed. Therefore, carefully controlled cross-sectional studies which adequately characterize the environment and control for exposures to airborne contaminants other than the oxides of nitrogen should be conducted.

Workers exposed to oxides of nitrogen should be compared with normative data obtained from appropriate control subjects on measures of the pulmonary system including ventilatory mechanics and spirometry as well as hematologic indices, such as the percentage by volume of methemoglobin. Attempts should also be made to determine the risk of acute and chronic obstructive pulmonary disease as a function of concentration and time of exposure to oxides of nitrogen.

### Chronic Studies in Animals

Although a number of animal studies indicated chronic changes in respiration, [129,144] cellular morphology of the pulmonary system, [71,99,129,132,133,134,146,147,154,157] reproduction, [142] immune

responses, [116,117,155,156,158] and weight gain [127] resulting from long-term exposure to oxides of nitrogen, most of these studies used continuous exposures which are atypical of the occupational setting. Furthermore, some studies have indicated a regression or a reversal of toxic effects either during exposure [95,130,131] or during the postexposure recovery period. [91,92,94,95] Such data suggest the possibility of adaptation to inhalation of oxides of nitrogen or regeneration and repair of pulmonary tissues during times in which the subject is away from the exposure environment. Therefore, future studies investigating the chronic effects of long-term exposure to oxides of nitrogen in animals should utilize exposure schedules similar to those observed in industry, ie, 6-10 hours/day, 5 days/week. Dose-effect relationships should be generated on dependent variables, such as respiration rate, pulmonary mechanics, morphologic changes of pulmonary tissue, incidence of chronic obstructive diseases of the pulmonary system, methemoglobin levels, and autoimmune responses at concentrations corresponding to 1/10-2 times the recommended limits. Particular emphasis should be placed on collecting data on exposures to nitric oxide since the data base concerned with the toxicity of this oxide of nitrogen is minimal at this time.

#### Reproduction

Shalamberidze and Tsereteli [142] observed significant changes in estrus, litter size, and fetal weights in rats exposed to nitrogen dioxide at 1.3 ppm for 12 hours/day over a 3-month period. No effects were noted in animals exposed for the same time at 0.07 ppm. Further research is needed to define the limits of exposure at which these changes take place

in the rat and in other animal species. If it can be demonstrated that low-level exposure to oxides of nitrogen consistently results in changes in the reproductive system of various animal species, then special restrictions on exposure of female workers to oxides of nitrogen must be implemented.

#### Mutagenicity

Nitrous acid has been shown to have a potent mutagenic effect on lower forms of life, such as tobacco mosaic virus [165] and Escherichia coli. [166] Although nitric oxide and nitrogen dioxide may combine with water to form nitrous acid under certain conditions, evidence of mutagenesis by exposure to these oxides of nitrogen per se have not been found in the literature. Therefore, studies of the possible mutagenicity of nitric oxide and nitrogen dioxide, including microbial screens, should be conducted.

#### Carcinogenicity

The results of three studies [160,161,162] reviewed in this document suggest that either continuous or intermittent exposure to oxides of nitrogen at fairly high concentrations does not result in a significant increase in neoplastic changes in mice, hamsters, and rats. NIOSH has been informed of a number of studies which are currently in progress, the results of which are yet incomplete or inconclusive. Thus, although available evidence suggests no direct cause-and-effect relationship between inhalation of oxides of nitrogen and the development of neoplasms, NIOSH believes that results of on-going research and future research in this area

must be obtained before a final conclusion is made.

Of particular concern is the possible effect of oxides of nitrogen in combination with other occupational contaminants, such as hydrocarbons, fibrous dusts, and organic solvents. Preliminary evidence [163] suggests a possible synergism between nitrogen dioxide and benzo(a)pyrene in producing squamous cell carcinomas in rats where the concentration of nitrogen dioxide used in this study was 25 times greater than the recommended ceiling limit. Recently, there has been an increasing concern about the in vivo or airborne formation of N-nitroso compounds from oxides of nitrogen and primary or secondary amines. The results of several animal studies indicate that inhalation of some secondary nitrosamines at high concentrations can result in acute liver damage and severe hematologic changes, [182] whereas long-term exposure at lower concentrations produces carcinomas in the trachea and lungs. [184,185] Although secondary nitrosamines have been shown to form from precursors in the gastrointestinal tract, [178] similar data have not been found on in vivo formation in the pulmonary system. Furthermore, no animal data or epidemiologic data have been found which can link cancer to nitrosamine exposure at concentrations observed in occupational environments. It is evident that research must be initiated to answer these important questions concerned with exposure to nitrosamines and that a concentrated effort must be directed toward determining the possible additive, synergistic, or inhibitory effects of oxides of nitrogen in combination with hydrocarbons, fibrous dusts, and organic solvents on neoplastic dose-response relationships.

### VIII. REFERENCES

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