

**ITEM NO.:** 7  
**DATE:** May 26, 2000  
**CONTRACT NO.:** 97-329

## **STAFF EVALUATION OF A DRAFT RESEARCH FINAL REPORT**

**TITLE:** The Health Impact of Nitric Oxide: Effects on Lung Function, Cellular and Biochemical Processes in Healthy Humans

**CONTRACTOR:** University of California, San Francisco

**PRINCIPAL INVESTIGATOR:** Stephen C. Lazarus, M.D.

**AMOUNT:** \$32,880

**DURATION:** 23 Months

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For further information, you may contact Mr. Dane Westerdahl at (916) 323-1522.

### **I. SUMMARY**

This project is a review of published literature on nitric oxide (NO). The project was undertaken to determine whether there are sufficient data to suggest that ambient concentrations of NO have the potential to cause or modify human disease. In addition, it provided some sample data on ambient concentrations of NO in a "typical" indoor laboratory/hospital setting.

### **II. TECHNICAL SUMMARY**

#### **Objective**

The specific objective of this project was to review the basic scientific, clinical, and epidemiologic literature relating to NO; assess the effects of ambient levels of NO on humans; and evaluate the potential for ambient NO to cause human disease.

The proposal addressed the following specific questions:

- Are ambient concentrations of NO harmful?
- Is there an association between increased exposure to NO and respiratory illness (e.g., infections, asthma, chronic bronchitis, and chronic obstructive pulmonary disease [COPD] exacerbations)?
- Which of the following targets of inhaled NO are important markers of NO effects, and which should be examined in studies of the health effects of NO: Pulmonary function, neutrophils, eosinophils, macrophages, platelets, nerves, cardiac function, hemoglobin (methemoglobin)?
- Does inhaled ambient NO induce or modulate endogenous production of NO?
- Does ambient NO increase in a typical hospital based laboratory setting?
- Are there significant or otherwise important differences between instruments available for monitoring ambient levels of NO and clinical/medical grade instruments?

## **Background**

NO is produced during combustion and is commonly found in urban atmospheres, as well as in indoor environments throughout California. Although NO normally converts readily to nitrogen dioxide (NO<sub>2</sub>), significant concentrations are still found in ambient urban air near combustion sources, and especially near major highways. Recent epidemiologic studies suggest a link between NO<sub>2</sub> exposure and childhood respiratory infection, lung cell damage, croup, asthma, bronchitis, and adverse changes in immune system functions. But NO<sub>2</sub>, under controlled exposure conditions, has not been shown to be especially harmful. This raises the possibility that observed epidemiologic effects may, in fact, be due to the precursor, NO. Additional research has also indicated that NO is produced endogenously by a variety of cell types, including smooth muscle cells, airway epithelial cells, platelets, nerves, macrophages and other immune system cells. It has also shown that NO can regulate the function of many cells, including (but not limited to) immune system cells, platelets, and nerves.

## **Project Summary**

The project was designed primarily as a literature survey and critical summary of what is currently known about NO, with the purpose of enabling staff to determine whether there is a need for continued experimental research on possible health effects from NO exposure.

The contractors reviewed selected literature on NO, which was published between 1993 and 1999. They also developed a bibliography of other published literature from the same time period that was not reviewed. The review covers indoor NO concentrations, epidemiology, cellular and molecular effects, and the role of NO in inflammation and immune responses. The report presents some limited data indicating that the NO concentration in an indoor laboratory (i.e., the investigator's) was typically less than 6 parts per billion (ppb), although on a few occasions, it was as high as 15 ppb.

The epidemiologic studies reviewed, suggest that NO may have been involved in at least some of the excess hospitalizations, medical visits, and deaths observed in areas with elevated concentrations of nitrogen oxides, although possible mechanisms remain unknown. On the other hand, concentrations of NO as high as tens of ppm have been given to healthy volunteers and patients with COPD, without altering various measures of pulmonary function. However, some investigators have expressed the concern that pulmonary function tests may not be sufficiently sensitive to detect the deleterious effects of NO inhalation, or alternately, that NO may impact other organs. Published research has indicated that NO is produced endogenously and that it is involved in vasodilation, regulation and activation of many cell types, including (but not limited to) cells involved in immune reactions, and inflammatory responses. It is unclear whether there is an interaction between endogenous and ambient NO.

## **III. STAFF COMMENTS**

The staff finds that, although this is a potentially useful review, it is difficult to sort out the main points. Overall, staff was disappointed in the product. The report would be improved considerably if it were organized according to the six questions presented in

both the original project description and Objective section above. By doing this, the report would be focused on the critical questions that will drive development of future research directions. The literature, in some cases, should also be more carefully selected so that the results presented relate more clearly to the six questions.

The report should more fully synthesize the results of multiple studies, when describing the results presented, so that there is a clear statement of what is known and what is not known, with reference to each of the same six questions.

The information on the NO concentrations in the investigator's laboratory is useful. The discussion on monitoring methods, the limitations of various methods, and the correlation between different methods should be expanded.

The contractor should add a clear discussion of recommendations for future research directions. An Executive Summary and Abstract should also be added.

#### **IV. STAFF RECOMMENDATIONS**

Staff recommends that the Research Screening Committee accept this draft final report, subject to inclusion of appropriate revisions and additions in response to the staff comments, and any changes and additions specified by the Committee.