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Office of the Administrator
Science Advisory Board
Washington, DC 20460

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EPA

Report of the Clean Air Scientific Advisory Committee

Review of the U.S. Consumer Product Safety Commission's Health Effects and Exposure Assessment Documents on Nitrogen Dioxide

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 9, 1986

OFFICE OF
THE ADMINISTRATOR

Honorable Carol Dawson
Acting Chairman
U.S. Consumer Product Safety Commission
Washington, DC 20207

Dear Ms. Dawson:

The Clean Air Scientific Advisory Committee (CASAC) of the U.S. Environmental Protection Agency has completed its review of the health effects and exposure assessment documents on nitrogen dioxide provided by the U.S. Consumer Product Safety Commission. This review was conducted at the Commission's request in order to obtain independent outside scientific advice on the potential health hazards associated with exposure to 0.1 to 1.0 ppm nitrogen dioxide generated by unvented indoor combustion sources. We are pleased to transmit to you the enclosed report which represents the Committee's analysis and recommendations concerning the documents and the specific questions that you raised.

The Committee has concluded that: 1) repeated peak exposures at concentrations of 0.3 ppm of nitrogen dioxide may cause health effects in some individuals and there is a possibility that such effects may occur at concentrations as low as 0.1 ppm. We note, however, that both the epidemiological and chamber studies at or near this range of concentrations have produced inconsistent evidence regarding the health effects of such exposures; 2) the population groups that appear most sensitive to nitrogen dioxide exposure include children, chronic bronchitics, asthmatics, and individuals with emphysema; and 3) the most direct evidence regarding lung damage associated with nitrogen dioxide is obtained from animal studies - such studies conclude that a number of effects occur in a variety of animal species, many of which can be considered serious and irreversible. The relevance of these studies to human exposure at concentrations found indoors is uncertain.

The Committee also addressed the adequacy of the CPSC documents as a basis for assessing the risks of exposure to nitrogen dioxide emissions, and provided guidance regarding further efforts to assess the risks associated with indoor use of appliances producing nitrogen dioxide emissions. We found that the CPSC documents addressed the appropriate issues, but that they were repetitive and not well integrated. Perhaps this was reflective of their being prepared by various authors at different times for different purposes. We recommend that the CPSC utilize more fully the EPA Criteria Document and Staff Paper on Nitrogen Dioxide as primary resources in developing an assessment of the health risks of indoor combustion sources.

The Committee appreciates this unique opportunity to interact with the Commission and to provide scientific advice on an issue of current interest and great importance to us all.

Sincerely,

James H. Ware, Chairman
Review Panel on Nitrogen Dioxide
Science Advisory Board

Morton Lippmann, Chairman
Clean Air Scientific Advisory Committee
Science Advisory Board

cc: Lee Thomas
A. James Barnes
Don Ehreth
Craig Potter
Peter Preuss
Terry Yosie

A REVIEW OF THE CONSUMER PRODUCT SAFETY COMMISSION'S HEALTH EFFECTS AND EXPOSURE ASSESSMENT DOCUMENTS ON NITROGEN DIOXIDE

A Report by the Clean Air Scientific Advisory Committee of the U.S. Environmental Protection Agency

Science Advisory Board
U.S. Environmental Protection Agency
Washington, DC

May 1986

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U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee

Panel for the Review of Nitrogen Dioxide Health Effects and Exposure Assessment Documents for the Consumer Product Safety Commission

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1. EXECUTIVE SUMMARY

This is the report of the U.S. Environmental Protection Agency's (EPA) Congressionally established Clean Air Scientific Advisory Committee (CASAC) concerning its review of the Nitrogen Dioxide (NO_2) Health Effects and Exposure Assessment Documents of the U.S. Consumer Product Safety Commission (CPSC). Under the provisions of an interagency agreement between the two agencies, the CASAC reviewed the CPSC documents at a public meeting on September 26-27, 1985, in Bethesda, Maryland.

Following its review of the documents prepared by the CPSC, the CASAC reached the following major conclusions:

- Preliminary evidence from epidemiologic and related indoor air pollution monitoring studies suggest that repeated peak exposures at concentrations of 0.3 ppm of NO_2 may cause health effects in some individuals and raises the possibility that such effects may occur at concentrations as low as 0.1 ppm. However, the epidemiologic and controlled human exposure studies provide somewhat inconsistent evidence which makes it difficult to be more definitive.

- Population groups that appear to be most sensitive to NO_2 exposures include children, chronic bronchitics, asthmatics, and individuals with emphysema.

- Human epidemiologic studies suggest that exposure to NO_2 may lead to increased respiratory illness rates among children. However, the most direct evidence regarding lung damage associated with NO_2 is obtained from animal studies. Such studies conclude that a number of effects occur in a variety of animal species, many of which can be considered serious and irreversible.

- The work undertaken by the CPSC to quantify the indoor NO_2 concentrations produced by kerosene space heaters is innovative and important and provides information that is essential to assess human health risks from these and other appliances producing NO_2 emissions.

- The EPA Air Quality Criteria Document and Staff Paper for NO_2 provide peer reviewed information and assessments directly relevant to questions facing the CPSC. The CASAC recommends that CPSC use these documents more fully as a primary resource in developing an assessment of the health risks of indoor combustion sources.

- The documents submitted by CPSC for CASAC's review were prepared at different times by various authors, for different CPSC purposes; therefore, they were sometimes repetitive and not well integrated. Although the documents generally identified the appropriate issues, they were not sufficiently developed to provide a primary resource for risk assessment without further revision. However, in light of the availability of the EPA Nitrogen Dioxide Criteria Document and Staff Paper, such revision may not be needed.

2. INTRODUCTION

A. Background

The Consumer Product Safety Commission (CPSC) has been concerned about exposure to nitrogen dioxide associated with the use of gas cooking stoves and a variety of home combustion heaters. Various studies, including several conducted for the CPSC, have shown that the levels of nitrogen dioxide exposure associated with the use of these appliances significantly exceed the national ambient air quality standard (NAAQS) as well as the short-term standard for nitrogen dioxide recommended by staff of the U.S. Enviromental Protection Agency (EPA).

On March 29, 1985, Commission Chairman Terrence Scanlon requested the assistance of the EPA's Congressionally established Clean Air Scientific Advisory Committee (CASAC) in conducting the CPSC's review of the potential health hazards associated with exposure to 0.1 to 1.0 plus parts per million (ppm) nitrogen dioxide generated by the unvented combustion sources used in the home (see Appendix C). In this request, the CPSC requested guidance on issues such as:

- the levels of nitrogen dioxide for which there are data indicating adverse health effects;
- the identity of subsets of the population more sensitive to nitrogen dioxide than others; and
- whether exposure to nitrogen dioxide leads to irreversible lung damage.

On May 1, 1985, EPA Administrator Lee M. Thomas agreed to this request, noting that the CASAC, which has reviewed the scientific basis of EPA's NAAQS for nitrogen dioxide, is well qualified to address the issues raised by the CPSC (see Appendix D). Staff of both agencies then developed an interagency agreement which was signed in August 1985.

Under the provisions of this interagency agreement, the CASAC reviewed the CPSC documents at a public meeting on September 26-27, 1985, in Bethesda, Maryland. At this meeting, the Committee heard presentations from CPSC staff on exposure assessment, controlled human exposure, animal toxicology and epidemiology relating to nitrogen dioxide, as well as comments from the interested public. The focus of this review was the September 1985 report of the Commission entitled Review of Nitrogen Dioxide: Health Effects and Exposure from Consumer Products, a six-part document discussing health effects of nitrogen dioxide and presenting information on kerosene heaters and unvented gas space heaters.

B. Report Format

This report has been divided into an Executive Summary, Introduction, three major Sections and an Appendix. Of the three major sections, Section 3 discusses the similarities between the assessment needs of the EPA and

the CPSC as well as the CASAC's view of its role in the CPSC review, and, in particular, the Committee's views regarding use of information generated by the EPA to simplify CPSC's assessment process. Section 4 contains the conclusions and recommendations of the Committee concerning Chairman Scanlon's three questions. Section 5 addresses additional issues that go beyond the information requested by Chairman Scanlon. Appendix A addresses in more detailed fashion some of the CASAC's comments on the documents supplied by the CPSC. Appendix B is a copy of the October 18, 1985 CASAC report to EPA detailing its findings and recommendations concerning EPA's National Ambient Air Quality Standard for nitrogen dioxide. Appendix C contains Chairman Scanlon's March 29, 1985 letter requesting the review. Appendix D presents Administrator Thomas' May 1, 1985 response to the request. Appendix E contains full citations to the literature referenced in this report.

3. COMMENTS ON THE GOALS OF THE REVIEW

During the course of its meetings on September 26-27, the CASAC sought to clarify the goals of the review. The Committee concluded that it had three tasks:

- To comment on the three questions posed by Chairman Scanlon regarding the health effects of NO_2.
- To assess the adequacy of the documents prepared by CPSC staff as a basis for assessing the risks of exposure to NO_2 emissions.
- To provide guidance to CPSC regarding further efforts to assess the risks associated with indoor use of space heaters and other appliances producing NO_2 emissions.

The questions posed by Chairman Scanlon in his letter to the EPA are both difficult and highly relevant to CPSC concerns about the potential health effects of kerosene space heaters. Fortunately, the EPA Criteria Document and Staff Paper on NO_2 provide peer-reviewed information directly relevant to these questions. We encourage CPSC staff to use these documents as a primary resource in future efforts to assess the health risks of indoor combustion sources.

The second and third tasks are similiar to those that the CASAC ordinarily performs in advising EPA on the adequacy of air quality criteria documents and staff papers. Given the availability of these EPA documents, we believe that further CPSC efforts should focus on quantification of the peak and average NO_2 concentrations produced in residences by unvented combustion sources and on systematic reevaluation of the evidence summarized in the EPA Criteria Document and Staff Paper with a focus on the higher indoor NO_2 concentrations produced by unvented combustion sources relative to the typical ambient concentrations of NO_2 implicitly addressed in the EPA documents.

4. MAJOR CONCLUSIONS AND RECOMMENDATIONS ON ISSUES POSED BY CPSC

In its evaluation of the materials provided by the CPSC, the CASAC drew a distinction between the material on exposure assessment and the documents reviewing the health effects literature. The Committee noted that CPSC staff and contractors have undertaken important and innovative work to quantify the indoor NO_2 concentrations produced by different, but typical uses of kerosene space heaters. The documents summarizing this work provide new and important information directly relevant to CPSC concerns. This information is central to assessing the health risk of indoor use of these and other applicances producing NO_2 emissions. Moreover, this material is unlikely to be assembled by other government or private groups. Thus, the CASAC urges the CPSC to continue this work and to further investigate the implications of these data for the impact of space heaters and other indoor sources on the population distribution of exposures to NO_2. Specifically, further efforts by CPSC staff to assess the health risks associated with indoor use of kerosene space heaters and other sources of nitrogen dioxide emissions should focus on efforts to quantify the nitrogen dioxide concentrations produced by these sources. We urge the CPSC to avoid duplication of EPA's effort to develop a comprehensive review of the literature on health effects of NO_2.

The following paragraphs respond to the questions posed by CPSC Chairman Scanlon.

- For what levels of nitrogen dioxide are there data indicating adverse health effects?

The CASAC has concurred with EPA's recommendation to retain the current Annual Primary National Ambient Air Quality Standard of 0.053 ppm (Appendix B). Evidence suggests that this average annual concentration should provide adequate protection against the adverse health effects associated with long-term exposure and protect to a lesser degree against short-term effects related to peaking of outdoor concentrations. Among the adverse effects related to chronic exposure in animals are a reduction in resistance to respiratory infection, accelerated aging of the lung manifested as a loss of elastic recoil, fibrotic and emphysematous-like structural changes in the lung, and impairment of function.

The lowest concentration(s) associated with acute adverse health effects can be expressed in a range of estimates. Preliminary epidemiologic findings and related indoor air pollution monitoring studies assessing the variation of NO_2 levels in gas stove homes suggest that repeated peaks in the range of 0.15 to 0.30 ppm may be of concern for children (USEPA, 1982). The limited number of controlled laboratory studies on human subjects, both healthy and with underlying lung disease, have produced conflicting results. For example, increased bronchial reactivity to a provocative aerosol has been reported after exposure to 0.1 ppm NO_2 in asthmatics (Orehek et al., 1976). This finding was not confirmed in a second study at the same concentration involving asthmatics and healthy subjects (Hazucha et al., 1983), while a third study found a "...variable effect..." on bronchial reactivity (Ahmed et al., 1982). The effect

of 0.2 ppm NO_2 on bronchial reactivity in asthmatics has been equivocal (Kleinman et al., 1983). Although both bronchoconstriction (Bauer et al., 1984; Rogers et al., 1985) and increased airway reactivity (Bauer et al., 1984) were found in response to 0.3 ppm NO_2, another study could find little or no effects at 4.0 ppm (Linn et al., in press). Therefore, the data base remains too sparse and the between-studies variance too great to project definitive dose-response relationships and complicates the task of identifying "safe levels" for the general population. Moreover, the mechanisms underlying these effects, and consequently their potential for contributing to chronic lung damage, are unknown. Such information may be vital in judging which effects are adverse, but much of this latest generation of studies has not yet appeared in the peer reviewed literature. Nonetheless, this preliminary evidence suggests that repeated peak exposures at concentrations of 0.3 ppm of NO_2 may cause health effects in some individuals and raises the possibility that such effects may occur at concentrations as low as 0.1 ppm, encouraging a cautionary approach in matters of policy.

As discussed in Appendix A, both the epidemiologic studies of children exposed to gas stove emissions and the controlled exposure studies of adults exposed to NO_2 have reported inconsistent findings regarding the health effects of these exposures. Such large uncertainties in clinical and epidemiological data are troubling to policy makers but are a reality in interpreting the currently available evidence on the health effects of NO_2.

- Which subsets of the population are most sensitive to nitrogen dioxide?

The EPA Staff Paper on NO_2 states that:

> ...the groups that appear to be most sensitive to exposures to NO_2 include children, chronic bronchitics, asthmatics, and individuals with emphysema....Health effects data from epidemiological studies in gas stove homes suggest that young children are at increased risk of respiratory symptoms and infection from exposures to elevated concentrations of NO_2....Other groups at risk to NO_2 exposures are asthmatics and bronchitics. Human clinical study data have provided evidence that some of these individuals suffer mild symptomatic effects (nasal discharge, headaches, dizziness, and labored breathing) after light to moderate exercise during an exposure to 0.5 ppm NO_2 for two hours.[1]

CASAC concurs with this statement.

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[1] Review of the National Ambient Air Quality Standards for Nitrogen Oxides: Assessment of the Scientific and Technical Information. U.S. EPA, Office of Air Quality Planning and Standards, Research Triangle Park, NC, EPA 450/5-82-002, Page 41, August 1982.

- Does exposure to nitrogen dioxide lead to irreversible lung damage?

As noted in Appendix A, controlled exposure studies provide little information about this question. Human epidemiologic studies suggest that exposure to nitrogen dioxide may lead to increased respiratory illness rates among children. Although a history of respiratory illness in childhood may be predictive of respiratory disorders in adult life, relatively little is known about this relationship at the present time. Thus, the most direct evidence regarding lung damage resulting from exposure to nitrogen dioxide is obtained from animal studies. These studies are reviewed in EPA's Criteria Document and Staff Paper. The Staff Paper provides the following summary of this complex and extensive data base:

> In critically assessing animal studies involving short-term exposure to NO_2, it is obvious that numerous effects have been observed for a variety of animal species (dogs, rabbits, guinea pigs, monkeys, rats, and mice). There is presently no reliable way to relate human and animal dose-response data. Many of the effects associated with short-term exposures appear to result not from a single exposure, but from multiple exposures in the range of 0.2 ppm to 0.5 ppm for several hours. Of particular interest is that exposure of animals to concentrations slightly above those currently being experienced in the ambient air appears to cause a decrease in resistance to bacterial infection.... this same type of effect has also been reported to occur in humans.
>
> ... effects which have been associated with animals exposed to NO_2 over relatively long periods (1 day to several years) ... include: (1) significantly increased susceptibility to infection resulting in increased mortality for continuous and intermittent exposure to $\geq$ 0.5 ppm NO_2; (2) decreased immunological response resulting in increased respiratory infection for exposures of 0.5-1.0 ppm NO_2, continuous and intermittent; (3) increased lung protein content suggesting edema and cell death for 3-6 week exposures to 0.5 or 1.0 ppm NO_2 in Vitamin C deficient animals; (4) hematological disturbances (e.g. increased cholinesterase lysozyme levels) suggestive of liver and heart damage at 0.5 ppm NO_2 for 1 week; (5) increased RBC 2,3-diphosphoglycerate, indicating tissue deoxygenation after 1 week exposure to 0.36 ppm NO_2; (6) emphysematous alterations resulting from a six month exposure to 0.1 ppm NO_2 with daily spikes of 1.0 ppm NO_2 or 68 months exposure to 0.64 ppm NO_2 and 0.25 ppm NO followed by a 2 year period in clean air.

A critical assessment of the available animal toxicological data for long-term exposure to NO_2 reveals that many of the above effects occur in a variety of animal species, and that many of the effects can be considered serious and irreversible. For example, the emphysematous alterations in dogs associated with long-term exposure to NO_2 are of major concern since the occurrence of this type of effect in humans would clearly be adverse.

While most of the chronic studies were conducted at exposures considerably higher than those encountered in the ambient air, it should be noted that one study did observe emphysematous alterations in mice when exposed to NO_2 levels about twice the current annual standard. However, in this study, the chronic exposure was supplemented with daily spikes of 1.0 ppm and it is not possible to determine if the cause of the effect was chronic exposure, short-term spikes or a combination of these two.

Currently there is no means available to extrapolate the results of the animal studies (either short-term or chronic) directly to humans. Nevertheless, the animal toxicology studies do indicate that NO_2 exposure causes serious biological damage to a number of animals. These studies clearly raise a "warning flag" for potential effects in humans.[2]

Thus, while the animal studies do provide evidence that both short-term and long-term exposure to nitrogen dioxide can lead to irreversible health effects in a variety of animal species, it is difficult at the present time to determine whether these effects are of concern at concentrations associated with use of kerosene heaters, gas stoves, or other indoor sources of NO_2.

5. ADDITIONAL ISSUES

The documents summarizing the evidence regarding the health effects of NO_2 exposure correctly identify many of the important issues and studies, but the Committee believes that the materials have some important deficiencies. In particular, we note that the various documents have not been integrated, and we also have numerous questions about the studies chosen for emphasis and about the interpretation of some of the evidence. An informal compilation of CASAC's comments regarding the CPSC's review of the health effects literature is included as Appendix A.

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[2] Review of the National Ambient Air Quality Standards for Nitrogen Oxides: Assessment of the Scientific and Technical Information. U.S. EPA, Office of Air Quality Planning and Standards, Research Triangle Park, NC, EPA 450/5-82-002, Pages 10-11, August 1982.

The EPA's experience in preparing Criteria Documents and Staff Papers for the periodic assessment of criteria pollutants has shown that preparation of such reviews is enormously difficult and time consuming. Moreover, EPA staff routinely submit several revisions of each of these documents to CASAC in their efforts to develop a consensus on the relevant literature and its implications. In our view, the CPSC materials are comparable to the first draft of such integrated documents. From that perspective, the documents could provide a basis for developing an integrated review of the relevant literature. Given the effort involved in developing an integrated risk assessment, however, the Committee urges CPSC not to duplicate the resource-consuming effort required of the EPA in its periodic assessment of the health effects of NO_2. Rather, CPSC should make extensive use of the EPA Criteria Document and Staff Paper on Nitrogen Dioxide in its assessment of the health risks associated with indoor sources of nitrogen dioxide. In particular, the CPSC should utilize EPA's Staff Paper to the extent practicable. Every effort should be made to avoid duplication of reviews of the health effects literature carried out by EPA and reviewed by CASAC under the requirements of the Clean Air Act.

APPENDIX A

Document Review - More Detailed Comments

DOCUMENT REVIEW

The CPSC provided the following six documents to the Committee as background for the review:

- Update on Health Effects Associated with NO_2
- Health Effects of Nitrogen Dioxide
- Status Report on Kerosene Heaters (includes update: Health Effects of NO_2; Nitrogen Dioxide Health Assessment 1984)
- Status Report: Pollutants Generated by Unvented Gas Space Heaters
- Kerosene Heater Emissions: Estimation of Exposure
- Indoor Air Quality Kerosene Heater Testing Documentation

A. Overall Comments

Because these documents were prepared at different times by various authors for different CPSC purposes, they were sometimes repetitive and not well integrated. An introduction for the documents presented by CPSC delineating the purpose of the review would have been helpful. In addition, the CASAC's decision not to recommend a short term standard for ambient NO_2 concentrations in its review for EPA should not be interpreted as implying that no adverse effects are associated with the higher concentrations produced by indoor sources. Thus, an introduction discussing the potentially high NO_2 concentrations caused by space heaters and other sources and the need to re-evaluate the health effects literature with these concentrations in mind would have provided a sharper focus for the assessment.

The CPSC should consider organizing the material according to major topics and issues. This has already - and commendably - been done in part, i.e., Biochemistry, Pulmonary Functional Effects, and Extra Pulmonary Effects. In dealing with any category of effects, emphasis should be given to what is known about the mechanisms of the effect - this being a particularly valuable contribution of animal and *in vitro* toxicology - and whether similar mechanisms have been demonstrated or are plausible in humans. An important way of organizing and classifying effects is by duration, i.e., acute and chronic. Virtually the only explicit information available on the chronic effects of NO_2 (short of industrial accidents affecting individual workers) results from animal studies.

The CPSC should attempt to define the actual exposure levels of the indoor environment and to focus the discussion of health effects on those levels, insofar as possible. This effort should include any information on the frequency of occurance of such levels as well as the relationship between pollutant level and averaging time. Such an approach would help distinguish this document from the EPA documents which were concerned with outdoor effects.

There is a tendancy in the CPSC documents to overstate findings which may actually be more attributable to chance and which are not really statistically significant. Normal variation is a reasonable expectation,

but more caution is needed in interpreting statistical significance. The Committee was advised by the CPSC that their normal practice is to state when a finding is not statistically significant and may have been attributable to change and that caveats have been added when necessary.

For animal toxicology studies, the CASAC recognizes that one of the major problems, beyond the issue of whether or not the animal's health is adversely affected, is how to extrapolate animal data to humans. Relative dosing is one of the major issues in these extrapolations. This document need not exhaustively review dosimetry, but giving some perspective relative to the problems with animal studies would be helpful.

B. Exposure

Nitrogen dioxide is produced by a variety of combustion sources within the home, including space heaters and gas stoves. Although the CPSC document carefully describes a limited number of studies concerning emissions from certain space heater devices, additional discussion is needed of the relative NO_2 contribution of these devices compared to gas stoves.

The current protocols used by the CPSC to characterize emissions from space heaters are carefully conceived and well executed. Their approach focuses on the contributions to steady state levels represented by a 4 to 6-hour average concentration. The extrapolation of this information on steady state levels in confined spaces to actual homes is obviously more difficult. To the extent that additional information on the potential for shorter term (one-hour) peaks and their spatial distribution within the home can be generated from current data, this information would be very useful.

The chamber studies and modeling work carried out by CPSC and its contractors have been informative. In particular, these studies have identified a range of steady state concentrations associated with continuous operation of space heaters in chambers, and have characterized the relative emission rates of white and blue flame heaters, as well as the reductions in emissions achieved by catalytic converters and dual chamber designs. Such modeling activities are insufficient, however, to characterize distribution and temporal pattern of concentrations experienced by persons using space heaters in their homes. Factors that could affect the distribution of exposure include model preferences, age of heating units, mode of operation, and home characteristics. Given the potential health and regulatory significance of issues concerning kerosene space heaters, additional direct measurements of indoor concentrations are urgently needed. Such data should ideally be gathered in the context of a well designed sampling frame, with attention to temporal and home-to-home variability and to such covariates as wind speed and indoor and outdoor temperature. Given the paucity of direct measurement data available, a well-defined set of measurements in 50 to 100 homes, for example, would be of great value. If the CPSC is unable to undertake such a study,

interested scientific and industry groups should be encouraged to collect NO_2 measurements in homes using kerosene heaters. To the extent that long-term exposures of NO_2 are relevant to health, the present passive collector technology can be directly applied to this large home to home survey. If short-term (less than 6-hour) peak concentrations are more relevant, then the passive sampler technology must be supplemented with continuous NO_2 analyzers.

C. Animal Studies

The section on in vitro and animal toxicology is concise, and, for the most part, clearly stated. However, at times it is too selective and superficial in its attempt to reduce some complex problems to simple judgments.

If the CPSC chooses to rewrite the document, it should consider organizing the material more effectively. Effects might be organized under Pulmonary (biochemical, functional, immunological, resistance to infection, morphological) and Extra-pulmonary. Wherever possible, the document should distinguish between acute, subacute and chronic effects. Virtually the only empirical information available on the subacute and chronic effects of NO_2 (short of occupational accidents) comes from animal studies and, thus, this information is particularly important.

A topic not treated anywhere in the document is the uptake of NO_2 within the respiratory system, an issue which has implications for regional dose and for identifying target tissues. NO_2 uptake has been measured in some animal species; it has also been modeled in a preliminary way for the human lung. A critical issue in any attempt to extrapolate from animals to humans is the extent to which, for a specified ambient concentration, both total dose (corrected for differences in size) and regional dose are comparable across species.

An important issue that warrants separate, integrated treatment is a discussion of factors influencing susceptibility. These might include age, sex, nutritional status, and any animal models of underlying lung disease or extrapulmonary disease that may have been tested. This is another area of research in which animal toxicology can contribute significantly to insight into human risk. Whatever information is available on mechanisms of effect should also be added.

Summary tables for all three sections (animal, clinical, epidemiological) providing details on selected critical studies are useful and could be organized to show effects as functions of increasing concentrations (separate tables for acute and chronic exposures). Such tables could also include whatever information is available on the reversibility of effects.

The animal toxicology discussion includes a variety of biochemical changes that occur in response to single or repeated exposures to NO_2. In general, these changes are reversible; even dead epithelial cells may be replaced through regenerative processes. However, some of the changes may

become part of a process that culminates in irreversible tissue damage and deformity. This process may be sustained if the exposure to NO_2 is sufficiently protracted or severe, if other forms of environmental stress are also present, or if the defensive and reparative responses of the body are compromised. The studies of Gillespie and co-workers suggest that the evolution of changes that are "emphysematous-like" in character may continue even after cessation of exposure to NO_2; however, this work has defects in experimental design and should be redesigned. How reversible the effect of NO_2 may be following protracted exposure must be determined empirically by allowing the animals to survive after ending the exposure; data of this sort are presently scarce.

D. Controlled Human Exposure

This section of the CPSC Report gives a useful review of the key scientific literature. The Committee identified no substantial errors or omissions in this material. Nevertheless, a reader wishing to compare and contrast the various studies needs a tabular summary similar to Tables 2 and 6 in the EPA Staff Paper on Nitrogen Dioxide (USEPA, 1982).

Committee members offered many suggestions for changes in content, emphasis, or language. The specific comments below highlight some issues about responsiveness of population sub-groups, interpretation of pulmonary function measurements, and interpretation of conflicting results from different controlled human exposure studies.

Specific Suggestions:

Comments in the CPSC document that imply definitive knowledge about the relative NO_2 responsiveness of population sub-groups who have lung disease should be revised (see pages 19 and 20)[3]. Because available results are conflicting, they should be cautiously interpreted and statements about them referenced whenever possible.

The discussion of confounding issues that arise in the interpretation of pulmonary function measurements (see page 20)[3] should be changed to indicate: 1) that intra-subject variability in clinical studies is mitigated by using repeated measures with subjects serving as their own control, 2) that with due care, subjects with decreased lung function reserve from respiratory disease can and are being studied to collect evidence about how their responsiveness to NO_2 exposure varies with disease severity, and 3) that the use of the term "significance" has statistical support; if not, another word should be used.

As pointed out in the CPSC document (see page 21),[3] results of the presently available studies on NO_2 effects are inconsistent. The CPSC should expand its discussion of the reasons for such inconsistency to include

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[3] Page references are to the CPSC Report Update on Health Effects Associated with Nitrogen Dioxide, 1985 by Lori Saltzman

other factors that are also likely (if not more likely) for this development - such as differences in exposure methods as well as differences in subject populations. For example, the "positive" studies have probably involved more sensitive asthmatics than the "negative" studies, but judging this will be very difficult until detailed results have been released and critically reviewed.

From short-term (1-hour) controlled studies of adults, one could estimate the lowest-observable-effect level to be below 0.2 ppm at one extreme, or above 4.0 ppm at the other extreme depending on the response being tested. This large discrepancy between different findings is troubling to scientists as well as to policymakers. With ozone and sulfur dioxide, the discrepancies between different studies and different laboratories are much smaller. However, two recent reports (Bauer et al., 1984; Rogers et al., 1985) have observed changes in lung function in exercising asthmatics exposed to 0.3 ppm NO_2. Despite the failure of other studies to demonstrate such changes, these levels may provoke responses in some asthmatic individuals. There is no good explanation for the widely divergent results on NO_2.

The controlled human studies which have suggested unfavorable effects at low concentrations (0.2 - 0.3 ppm or even lower) all have employed adult asthmatics. Asthmatics thus are the best candidates for the "more sensitive" designation. However, other studies have concluded that many mild asthmatics experience a detectable effect at concentrations an order of magnitude higher. This has led to the suggestion (not explicitly tested as yet) that NO_2 sensitivity is correlated with an index of severity of asthma, perhaps the degree of airway obstruction or baseline airway hyperreactivity.

The demonstration of unfavorable short-term reversible effects is sometimes thought to imply a possible risk of long-term irreversible effects, but any direct relationship between short-and long-term effects remains unclear. As indicated above, even short-term effects have not been demonstrated unequivocally for NO_2.

E. Epidemiology

The most relevant studies for the CPSC's needs are the British and U.S. studies of the health status of children and adults living in homes where gas is used for cooking or heating. The CPSC review document is an accurate evaluation of these studies. The Staff Paper (USEPA, 1982) represents a more extensive evaluation of all NO_2-related epidemiologic studies, with conclusions that are consistent with the CPSC evaluation. In brief, the extensive information available is suggestive but not conclusive that unvented gas combustion devices in homes are associated with slight excesses of respiratory illnesses, especially in children. The inconsistent findings among investigators and among different studies by the same investigators, some of which are comparisons of cross-sectional

and longitudinal observations, suggest that the many confounding factors which inevitably occur have not been adequately accounted for (and, in some instances possibly "over-corrected").

It is evident that use of gas for cooking or heating is not a risk factor of great magnitude in comparison with a factor such as cigarette smoking. It is also not certain that NO_2 is the causal factor for whatever risk may be associated with gas stoves or heaters. Unfortunately the majority of epidemiologic studies include no information on NO_2, and among those that do have actual measurements, the number of homes and characterization of concentrations are very limited. This suggests that better quantification of exposure is a major need in future studies.

The epidemiological studies provide some information relevant to the three questions posed by the CPSC. Regarding the concentrations at which adverse health effects are seen, these studies suggest that repeated exposures to peak NO_2 concentrations in the range of 0.15 to 0.30 ppm may be associated with increased risks of respiratory illness in children. No relevant epidemiologic research has been directed at other particularly susceptible groups such as asthmatics, bronchitics, heart disease patients, or the elderly. Epidemiological studies to-date have not addressed the question of the reversibility of effects.

APPENDIX B

Nitrogen Dioxide Closure Letter of the Clean Air Scientific Advisory Committee - October 18, 1984

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ANTHONY J. LANZA RESEARCH LABORATORIES AT UNIVERSITY VALLEY
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MAIL AND TELEPHONE ADDRESS: 550 FIRST AVENUE, NEW YORK, N.Y. 10016

October 18, 1984

Honorable William Ruckelshaus
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Ruckelshaus:

On July 19-20, 1984, the Clean Air Scientific Advisory Committee (CASAC) met to consider the Agency's proposal regarding revisions to the National Ambient Air Quality Standards (NAAQS) for Nitrogen Dioxide. Included in this proposal is the reaffirmation of the existing annual average standards for nitrogen dioxide at 0.053 ppm (100 ug/m^3), and solicitation of public comments on both the need to set a separate short-term standard and the need to use an alternative form of the standard (statistical instead of deterministic). The Committee has prepared this closure letter to advise you of its major conclusions and recommendations concerning the scientific and technical aspects of these and other issues associated with the Agency's proposal for the revision of the NAAQS for nitrogen dioxide.

Through previous closure letters dated June 19, 1981 and July 6, 1982, respectively, the CASAC advised that the revised Air Quality Criteria Document for Nitrogen Oxides was scientifically adequate for standard setting and that the Office of Air Quality Planning and Standards (OAQPS) Staff Paper represented a balanced and thorough interpretation of the scientific evidence contained in the criteria document. The Committee has reviewed relevant research which has been published since those documents were prepared, and concludes that the scientific conclusions reached in those documents are still satisfactory.

The CASAC has concluded that the existing annual average primary standard for nitrogen dioxide adequately protects against adverse health effects associated with long-term exposure and provides some measure of protection against short-term health effects. Therefore, the Committee concurs with the Agency's recommendation to retain the current annual average primary standard of 0.053 ppm. The Committee further concludes that, while short-term effects from nitrogen dioxide are documented in the scientific literature, the available information was insufficient

to provide an adequate scientific basis for establishing any specific short-term standard, or for determining an acceptable number of exceedances, a concentration limit, and an averaging time for such a standard. Indeed, the scientific basis for setting a separate short-term standard appears to be less firm than it was at the time of the Committee's previous review. We recommend that the Agency vigorously pursue a research program designed to address and resolve the issues related to short-term effects of nitrogen dioxide.

The Committee reaffirms its conclusion from two years ago that a secondary standard set at a level equivalent to the annual primary standard would offer sufficient protection against the identified welfare effects of nitrogen dioxide.

Members of the Committee who held a view on the issue of the form of the standard favored retaining the present deterministic form rather than adopting a statistical form for the annual standard.

A more extended analysis of the factors leading to the Committee's recommendations is contained in the enclosed report. Thank you for the opportunity to present the Committee's views on this important public health issue.

Sincerely,

Morton Lippmann

Morton Lippmann, Ph.D.
Chairman, Clean Air Scientific
Advisory Committee

Enclosure

cc: Mr. Alvin Alm
Mr. Joseph Cannon
Dr. Bernard Goldstein
Dr. Terry Yosie

CASAC Findings and Recommendations on the Scientific Basis for a Revised NAAQS for Nitrogen Dioxide

Options Presented by the Agency

Agency staff presented for CASAC review and comment three options that the Agency could pursue in concluding its current review of the NAAQS for nitrogen dioxide. These are as follows:

1. Reaffirm the annual standard at the current level and propose a short-term standard, or

2. Reaffirm the annual standard at the current level and conclude that a short-term standard is not needed, or

3. Reaffirm the annual standard at the current level, defer a decision on a short-term standard, and perform high priority research on short-term effects of nitrogen dioxide.

Based on the Committee's review of the scientific issues associated with the reaffirmation of the annual standard and the possible short-term standard as discussed below, the Committee believes: 1) that there is an insufficient scientific basis for action on option 1; and, 2) that options 2 and 3 are functionally equivalent, i.e. a vigorous program of research into the short-term effects of nitrogen dioxide is needed and can be accomplished under either option.

Scientific Issues in Revising the Standards

In CASAC's closure letter of July 6, 1982, the Committee discussed its review of the nitrogen oxides staff paper, noting that no single study provided the scientific basis for a decision on revising the primary standard for nitrogen dioxide. Rather, it could be based on a "weight of evidence" approach, using animal studies, controlled human exposure studies and epidemiology studies to provide both quantitative (i.e. exposure/effect) and qualitative (mechanistic) support for such a decision. Since that time new studies have been completed and, along with previously discussed studies, form the basis for the Committee's conclusions and recommendations concerning the critical issues associated with reaffirming the annual standard and evaluating a short-term standard for nitrogen dioxide.

1. Animal Toxicology Studies.

The results from recent animal studies provide further substantiation of the effects of nitrogen dioxide exposure on immune functions and increased susceptibility to infection. Some of these studies also examine patterns of exposure to nitrogen dioxide that are closer simulations of what may be actually occurring in, for example, gas stove homes. An example of this

is superimposing repeated short-term higher levels of exposure to nitrogen dioxide (e.g. 0.4 to 5.0 ppm, or more) on relatively low background levels of nitrogen dioxide, such as found in gas stove homes.

2. Controlled Human Exposure Studies.

The more recent controlled human exposure studies (mostly unpublished) present rather mixed and often contradictory results concerning respiratory effects in asthmatic and normal subjects exposed to concentrations in the range of 0.1 to 4.0 ppm nitrogen dioxide. Kagawa and Tsuru (1979) reported results possibly suggestive of short-term nitrogen dioxide effects on pulmonary function in normal subjects without combined provocative challenge by other agents (such as carbachol). Although they reported no significant differences for mean pulmonary function changes for a group of six subjects exposed to 0.15 ppm nitrogen dioxide, there were small significant decreases in airway conductance in three of the six subjects. However, the smallness of these decrements and questions regarding the statistical analyses used suggest caution in accepting the reported findings as demonstrating nitrogen dioxide effects on pulmonary function at 0.15 ppm. More recently, Bauer et al. (1984 - abstract) exposed asthmatics to 0.3 ppm nitrogen dioxide and observed effects on both pulmonary function after exercise and airway reactivity following cold air challenge.

3. Epidemiological Studies.

The most recent epidemiological studies indicate less conclusive findings of an association between nitrogen dioxide and respiratory effects than previously reported. The first report of the Harvard Six Cities Study, published several years ago, noted one positive result -- an association between both lung function changes and respiratory illnesses in children under age two and exposure to gas stoves -- among a number of associated variables. More recent analyses, published in Ferris et al. (1983) and Ware et al. (1984) made adjustment for the socio-economic status of the children under age two and reported that the association between their living in homes with gas stoves and their incidence of respiratory illness is no longer statistically significant. From these results, as well as those reported by other investigators studying people living in homes with gas stoves, CASAC concludes that the scientific evidence supporting an association between living in homes with gas stoves and increases in respiratory illnesses and symptoms is insufficient to support specific limits for either short-term or long-term standards for nitrogen dioxide.

Annual Standards

1. Primary Standard.

The CASAC reviewed the results of animal, controlled human exposure, and epidemiological studies to determine if such evidence provided a scientific basis for retention of the annual standard and scientific support

for establishment of a short-term standard. The most serious effects associated with nitrogen dioxide exposures that are reported in the scientific literature result from animal studies conducted at concentrations well above those permitted by the current annual standard. Although there are large uncertainties in extrapolating these results directly to humans, the seriousness of these effects coupled with the biological similarities between animals and humans suggests that there is risk to human health from long-term exposure to nitrogen dioxide. This set of factors, widely accepted within the scientific community, leads the Committee to conclude that there is a continuing need for a long-term nitrogen dioxide standard.

The results from recent studies showing some evidence of detectable health effects due to short-term nitrogen dioxide exposures do not provide sufficient evidence to develop a concentration level, an averaging time, or a number of exceedences for a short-term standard. For example, the gas stove studies were originally used in support of the rationale for a short-term standard; however, recent reassessments by the authors of these studies led them to reduce the level of statistical significance of their reported results. Moreover, the results of the recent clinical studies have been inconsistent. As a result, the overall scientific support for a short-term standard is more equivocal than previously thought. If the CASAC were to make a recommendation favoring a short-term standard, the Committee would also have to take into account the need to determine the number of allowable exceedances, the establishment of a concentration level, and the identification of an averaging time. At the present time, the Committee is unable to make such recommendations due to the absence of a sufficient body of information on such factors.

2. Secondary Standard.

The CASAC has not identified any further information to change its conclusion from two years ago that a secondary standard set equivalent to the annual primary standard would offer sufficient protection against the identified welfare effects of exposures to nitrogen dioxide. Although the issue of visibility impairment was raised, several members noted that, given the present state of knowledge, it is difficult to identify the degree to which nitrogen dioxide concentrations may contribute to this phenomenon. The Agency indicated that further work on this complex, multi-pollutant issue has been assigned a high priority in relation to the task force on visibility and that the issue will be addressed further at subsequent CASAC meetings. The Committee is looking forward to reviewing the results of the Agency's progress on this important issue.

Form of the Standard

The Committee did not reach a consensus on the desirability of changing the form of the standard from the present deterministic form to a statistical form which uses the available arithmetic averages from

the last three-years to determine compliance. Although most members of the Committee took no position, one member suggested that there is a stronger argument for a statistical approach to short-term standards than for annual standards. Two others favored the retention of the current deterministic form for the annual standard.

Research Efforts

The CASAC was encouraged to learn that the Agency is currently pursuing research which addresses some of the issues raised in our December 30, 1983 report to you on Research Needed to Support the Development of NAAQS. We look forward to continued reports from the Agency on the progress of this important research. The Committee feels compelled to reiterate that without an adequately funded research program aimed at assessing the significance of the health effects associated with short-term nitrogen dioxide exposures, the Agency cannot make scientifically informed decisions concerning the need for a short-term standard, its concentration level, averaging time or an acceptable number of exceedances.

Summary of CASAC Recommendations

For the reasons stated, the Committee recommends that you reaffirm the annual standard at the current level, and that you defer a decision on the short-term standard while pursuing an aggressive research program on short-term effects of nitrogen dioxide.

APPENDIX C

Letter from CPSC Commissioner Scanlon
March 29, 1985

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207

The Chairman

March 29, 1985

Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

Dear Mr. Thomas:

I am requesting the assistance of the Environmental Protection Agency's Clean Air Science Advisory Committee (CASAC) in our review of the potential health hazards associated with exposure to 0.1 to 1.0 plus ppm nitrogen dioxide generated by the unvented combustion sources used in the home.

The Commission has been concerned about consumer exposure to nitrogen dioxide associated with the use of gas cooking stoves and a variety of combustion home heaters. Various studies, including several conducted for the CPSC, have shown that the levels of nitrogen dioxide exposure associated with the use of these appliances significantly exceed the ambient air standard as well as the short term standard previously recommended by the EPA staff.

Various gas stove and combustion heater industry representatives have indicated a willingness to modify their product in order to reduce consumer exposure to nitrogen dioxide but there remains some disagreement as to what the target level should be. In an effort to expedite this process, I believe that the CASAC, since it has recently reviewed the data on NO_2, could give the Commission guidance on questions such as:

-the levels of nitrogen dioxide for which there are data indicating adverse health effects;
-the identity of subsets of the population more sensitive to nitrogen dioxide than others; and
-whether exposure to nitrogen dioxide leads to irreversible lung damage.

Please advise me as to the feasibility of obtaining such assistance, and, if it is feasible, the process for obtaining CASAC review. Thank you for your assistance in this matter.

Sincerely yours,

Terrence Scanlon

Terrence Scanlon
Chairman

APPENDIX D

Letter from EPA Administrator Lee Thomas
May 1, 1985

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 1 1985

THE ADMINISTRATOR

Honorable Terrence Scanlon
Chairman
U. S. Consumer Product Safety
Commission
Washington, D. C. 20207

Dear Mr. Scanlon:

Thank you for your March 29 letter in which you request the assistance of EPA's Clean Air Scientific Advisory Committee (CASAC) in evaluating consumer exposures to nitrogen dioxide associated with the use of gas cooking stoves and a variety of combustion home heaters. The Committee, which has reviewed the scientific basis of EPA's National Ambient Air Quality Standard for Nitrogen Dioxide, is well qualified to address the issues identified in your letter, and I support your request to solicit its scientific advice. I know that the CASAC Chairman, Dr. Morton Lippmann of New York University, would also be willing to assemble his panel to undertake this review.

I suggest that your staff coordinate the preparation for the CASAC meeting with Dr. Terry F. Yosie, Director of EPA's Science Advisory Board, (382-4126) and Mr. Bruce Jordan of EPA's Office of Air Quality Planning and Standards (919) 541-5655. Two specific requests that I have of the Commission staff is to work closely with Dr. Yosie and Mr. Jordan in preparing the scientific materials to submit to CASAC, and to provide budgetary support to defray the cost of the meeting. I estimate that the costs of the review will approximate $15,000 - $20,000.

Thank you for your interest in working with the Agency on this important public health issue.

Sincerely,

Lee M. Thomas
Administrator

APPENDIX E

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