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

December 17, 1984

OFFICE OF
THE ADMINISTRATOR

Hon. William D. Ruckelshaus
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

The Environmental Health Committee of EPA's Science Advisory Board has completed its review of the Health Assessment Document for Manganese, prepared by the Office of Health and Environmental Assessment (OHEA) in EPA's Office of Research and Development [EPA-600/8-83-013; June, 1983; External Review Draft]. The draft document was prepared for Agency-wide use to place health effects associated with this pollutant in perspective. It will serve specifically as a scientific basis for regulatory decisions by the Office of Air and Radiation.

The Committee referred the task of preparing its report to its Metals' Subcommittee. The latter panel met for this purpose on October 23, 1984, and its report is attached to this letter. The Committee fully concurs with the Subcommittee's evaluation.

The Committee agrees with the major conclusions in the draft health assessment document. Specifically, it concurs with the position that manganese is associated with two health effects in humans. These include:

(1) Pulmonary symptoms, defined as either an inflammatory response at high manganese exposures or an increased susceptibility to pulmonary diseases with low, chronic manganese exposures.

(2) Neurological signs and symptoms characterized by both psychiatric and movement disorders.

The Committee questions the document's conclusion, however, that pulmonary effects occur at lower exposures than do neurologic effects.

In addition, the Committee finds evidence that manganese may be a mammalian mutagen, according to the criteria established by the National Academy of Sciences. Although manganese is an essential trace element, the literature does not indicate whether or not inhaled manganese contributes to nutritional needs.

At the time of its review the Committee suggested that OHEA staff obtain more detailed technical comments from individual members. Following this consultation, the Committee agreed to prepare a formal report of its scientific review of the document. In addition to these consultations, the revisions to which OHEA staff agreed to make on November 10, 1983 include:

(1) to reorganize the review of neurotoxic effects with a more critical viewpoint, and to insure that the document is consistent with the current neuroscience data and literature.

(2) to focus attention on the few studies in which both pulmonary and neurotoxic effects were examined.

(3) to provide diagrams of nervous system structures and processes deemed to be the sites of manganese neurotoxicity.

(4) to define better the biologic nature of the nervous system effects of manganese (so-called manganism), which was treated inconsistently in the text.

(5) to incorporate the information from several papers not referenced in the document, as suggested by the Committee. These papers are described in the enclosed technical comments.

(6) to provide additional information in those tables summarizing health effects. The new information would set out:
   (a) the nature of the effect, in brief descriptive terms.
   (b) the minimum level of exposure that led to the observation of statistically significant health effects, if effects were observed.
   (c) the maximum level of exposure that produced no significant effects, if any levels of exposure did not elict health effects.

Additional technical comments are reported in the attached paper. A separate set of comments from individual Committee members have previously been transmitted to OHEA. We appreciate the opportunity to provide our scientific advice on this issue and request that the Agency formally respond to our letter. We stand ready to provide any further review that is requested.

Sincerely,

Herschel E. Griffin, M.D.
Chair, Environmental Health Committee

Norton Nelson, Ph.D.
Chair, Executive Committee

cc: Alvin L. Alm (A-101)
Joseph A. Cannon (ANR-443)
Bernard D. Goldstein (RD-672)
John A. Moore (TS-788)
Jack E. Ravan (WH-556)
Milton Russell (PM-219)
Lee M. Thomas (WH-562A)

TECHNICAL COMMENTS BY THE METALS' SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE ON THE DRAFT HEALTH ASSESSMENT DOCUMENT FOR MANGANESE

The Metals' Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board has completed its review of a draft Health Assessment Document for Manganese [EPA-600/8-83/013; June 1983; External Review Draft] which was prepared by the Office of Health and Environmental Assessment (OHEA) in the Office of Research and Development. The Committee charged its Metals' Subcommittee with the task of summarizing its major technical comments and preparing this report. The Committee concurs with the Subcommittee's technical comments.

The Committee agrees with the position in the draft document that manganese can elicit pulmonary and neurologic effects in humans. The Committee questions the Agency's finding, however, that pulmonary effects occur at lower exposure levels than do neurologic effects.

The document relies too heavily on a Japanese epidemiologic study of pulmonary effects in children living near a fermomanganese processing plant. Due to confounding factors, such as the proximity of home site to the plant, other pollutants in the exhaust, passive smoking, or socioeconomic status, variables other than exposure to manganese could explain the results. The manganese exposure levels at which effects are recorded in the Japanese study appear inconsistent with the levels at which pulmonary effects were recorded in other experiments. For such reasons, the study does not provide a sufficiently strong scientific basis to support the conclusions in the document. The pulmonary effects noted in these children might also be due to other compounds in the emissions.

The Committee finds that manganese is a possible mammalian mutagen according to the criteria established by the National Academy of Sciences.

Although manganese is an essential trace element, it is not clear from the literature whether inhaled manganese is available as a nutrient. Inhaled manganese may by-pass those processes by which manganese becomes available for nutrition. Data are available in humans and dogs regarding lung retention of manganese. The Agency should use these data to estimate deposition and absorption.

The Committee has various comments on the exposure sections of the draft document. A scientific explanation is needed on the choice of variables in the exposure equation given in terms of mg/day; neither is mg/day a concentration. No evidence is presented to support the concept that breathing rate determines uptake. The deposition fraction is not constant among different species. Also, body surface area is not a good basis for converting inhalation doses between species. Since lung retention can be calculated from the studies by Morrow et. al., (see reference below) the Agency can calculate lung accumulation. From this information, an equilibrium lung concentration can be estimated from ambient concentrations and particle sizes. The Committee recommends that the document provide air concentrations, rather than total uptake per time period, to the extent that the available data exist. The discussion of exposure also needs to address the effect of particle size upon uptake by inhalation. Finally, it is not clear that the term "C_A" that is used in the test is an air concentration. An explanation for this term and its use should be presented.

Human equivalent intake rate ("HEI" in the text) is equal to the amount of manganese inhaled by the experimental animal per day, corrected by a factor supposedly reflecting body surface area. Apparently, this factor is introduced to correct for differences in the fraction of manganese deposited in the respiratory tract between animals and humans. No scientific justifications are presented for the assumptions (see page A-2) that particulate matter is absorbed and retained proportional to the breathing rate, and that the retained fraction is the same for all species.

In calculating health effects associated with manganese exposures, there are two relevant dose factors. These include: 1) the dose to the lung which is determined by deposition and clearance of the inhaled manganese, and 2) the dose to the central nervous system which is based upon transfer rates from the lung. Because of unknown differences in the sensitivity of inhaled manganese between rodents and humans, the extrapolation of effects to the human lung from rat inhalation studies is speculative. Likewise, the calculation of dose to the central nervous system in the absence of data on the metabolism of inhaled manganese and the transfer rates from the lung to the central nervous system lacks scientific support.

Since it can be assumed that deposition in the lung and subsequent clearance and metabolism of manganese in primates will best resemble these processes in humans, the most relevant data is that reported in studies of nonhuman primates. Differences in particle sizes (experimental study versus ambient air) and in the chemical species of manganese have to be considered in making such comparisons. If manganese dioxide (as used in some primate studies) occurs in ambient air, for example, the dose (D) in micrograms, deposited per day in monkeys, could be estimated from the following formula:

$$D = f \cdot C \cdot V_{min} \cdot 1440,$$

where f= fractional deposition (dependent on aerodynamic particle size, in the alveolar region).

C = concentration of inhaled manganese (in micrograms per liter).

V_{min} = minute Ventilation (in liters per minute).

1440 = minutes in one day

Knowing the half-time for clearance of manganese dioxide from the lung ($T_{1/2}$ = 62 days; Morrow, 1964) one can calculate the accumulated amount (A_t) of manganese in the lung according to:

$$A_t = \frac{D}{b}(1 - e^{-bt})$$

where $b = \frac{\ln 2}{T_{1/2}} = 0.011$,

and for continuous chronic exposure at a given concentration this expression becomes:

$A_h = \frac{D}{}$ (equilibrium value in lung).

For pulmonary effects, assuming that the concentration of manganese in the lung is the same in monkeys and humans, it is possible to calculate the accumulated amount for human lungs. With the equilibrium value (A_q) of manganese in human lungs, one can further attempt to estimate an ambient exposure concentration of manganese, taking into account different fractional deposition values for the particle sizes occurring in the ambient air.

This discussion is only a general outline of an attempt to arrive at an human equivalent exposure level. Many questions, however, remain unanswered and need further evaluation, including the use of results from nonprimate species (especially rodents), manganese compounds of different chemical form, transfer rates to the brain for inhaled manganese, and aleveolar compared to pulmonary dose.

The reproductive effects section is unclear and needs better organization. The Committee suggests that all information about male (versus female) exposures should be integrated into one section. Studies that lead to negative conclusions need to be addressed with more consistency. Also, the reader will be confused by evaluations of some studies that wander from reporting apparent positive results to a finding that effects were absent. The possibility of indirect effects of manganese stemming from endocrine mechanisms should be addressed.

The Committee's review of the document has highlighted one deficiency in the literature which could be remedied through research. This pertains to the correspondence in time of pulmonary and neurologic end points in response to inhaled manganese. Further research on this issue would hopefully resolve the questionable conclusion (see page 4 of the Agency's issue paper for manganese) that pulmonary effects occur at lower exposures than do neurotoxic effects.

Some additional key literature citations which the Agency should reference include:

(1) P.E. Morrow, F.R. Gibb and K. Gazioglu, "The Clearance of Dust From the Lower Respiratory of Tract of Man: An Experimental Study," in Inhaled Particles and Vapors II, C.N. Davies, ed., (1965), pp. 351-358.

(2) P.E. Morrow, F.R. Gibb and L. Johnson, "Clearance of Insoluble Dust From the Lower Respiratory Tract," Health Physics, 10 (1964), 543-555.

In addition, Dr. Weiss provided OHEA with a reference to a paper by Van Bogaert & Dallemagne that represents the first study of manganese inhalation with primates.

The Appendix to the document, which discusses various issues related to Acceptable Daily Intake (ADI) levels for manganese, should be revised or deleted. OHEA may wish to follow-up with individual Committee members to review their concerns over the conversion of ADI's using various routes of administration as well as other issues.