Dr. Mary S. Wolfe <wolfe@niehs.nih.gov>
Executive Secretary
Report on Carcinogens Subcommittee
Board of Scientific Counselors
National Toxicology Program
P.O. Box 12233, A3-07
Research Triangle Park, NC 27709

DEC 0 1 2000

Dear Dr. Wolfe:

Enclosed is a document Critique of Draft Report on Carcinogens Background Document for Talc: Asbestiform and Non-Asbestiform for distribution to the Subcommittee as background information for the oral presentation I wish to make at the May 13 - 15, 2001 meeting of the Subcommittee. I prepared the report at the request of Mineral Technologies, Inc. and it is being sent to you at their request.

I am pleased to have the opportunity to present material to the Subcommittee that I believe will assist them in considering the classification of talc, free of asbestiform fibers.

Sincerely,

Roger O. McClellan, DVM, DABT, DABVT
Advisor: Inhalation Toxicology and
Human Health Risk Analysis
1111 Cuatro Cerros SE
Albuquerque, NM 87123
E-Mail: roger.o.mcclellan@att.net
Telephone: (505) 296-7083
Fax: (505) 296-9573

Copies to:

Angie Sanders <Sanders5@niehs.nih.gov
Fred Squire < Fred.Squire@mineralstech.com
Garrett Gray < Garrett.Gray@mineralstech.com
Katie Yagerman < Katie.Yagerman@mineralstech.com
Mike Larson < Mike.Larson@mineralstech.com
Linda Loretz < loretzl@ctfa.org

Critique of "Draft Report on Carcinogens Background Document for Talc; Asbestiform and Non-Asbestiform"

Prepared by:
Roger O. McClellan, DVM, DABT, DABVT
Advisor: Inhalation Toxicology and
Human Health Risk Analysis
1111 Cuatro Cerros SE
Albuquerque, NM 87123
E-Mail: roger.o.mcclellan@att.net
Telephone: (505) 296-7083
Fax: (505) 296-9573

Prepared for:
Mineral Technologies, Inc.
405 Lexington Ave.
New York, New York 10174

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Summary

A rigorous scientific evaluation of the available epidemiological, animal toxicology and supporting data for talc free of asbestiform fibers does not support classification of this material as a "reasonably anticipated to be human carcinogen." The consideration of two very different materials—asbestiform talc and talc free of asbestiform fibers—in the same document has, in this reviewer's opinion, created a "halo effect" in which the classification of asbestiform talc (a known human carcinogen) has inappropriately influenced the classification of talc free of asbestiform fibers. Talc free of asbestiform fibers should not be listed in the 10th Report on Carcinogens.

Talc, hydrous magnesium silicate, is a distinctly different material than asbestiform talc which may contain a variable amount of asbestiform fibers. Since 1976, strict standards have been in place to ensure that talc used in pharmaceutical, food, and cosmetic products is free of asbestiform fibers. Thus, it is crucial that the carcinogenic potential of the two very different materials be considered independently.

The interpretation of epidemiological studies of talc is complicated by a myriad of factors, including the unknown degree to which some talc products produced prior to 1976 may have contained asbestiform fibers. The strongest epidemiological study (Gertig, et al, 2000), a prospective cohort study of nurses, did not show a significant increase in the relative risk of various cancer for ever use of talc on the perineum or on sanitary napkins and showed no increase in risk with increasing frequency of use of talc. Earlier studies yielded a mix of results with a few studies yielding weak statistically significant associations between ovarian cancer and talc use (unspecified as to presence or absence of asbestiform fibers) while a number of studies did not show a statistically significant association between talc use and ovarian cancer. The evidence does not reach the NTP threshold of a "causal interpretation is credible but that alternative explanations such as chance bias or confounding factors could not be adequately excluded" required for a determination of "limited evidence of carcinogenicity from studies in humans" and classification of a material as "reasonably anticipated to be a human carcinogen."

A single well-conducted study is available of rats and mice chronically exposed by inhalation to well-characterized talc free of asbestiform fibers. The talc used had been processed to maximize the number of small, readily respirable particles. The exposure concentrations (6 and 18 mg/m^3) were hundreds of times maximum credible human exposures for users of talc-containing consumer products. No excess of tumors of any type were observed in mice. Statistically significant increases in pheochromocytomas of the adrenal gland were reported for male and female F344/N rats. These tumors are usually observed in high incidence in old F344 rats (the males in this study were observed for 113 weeks and the females for 122 weeks) and have been observed in increased incidence in studies with chronic inhalation exposure. These increases are not considered to be compound-specific and are thought to have a threshold exposure-response relationship. An increase in lung tumors was observed in female rats but not male rats. This increase in lung tumors is not compound-specific and is similar to that observed in rats exposed to very high concentrations of small particles of a wide range of particles not otherwise classified (nuisance dusts) such as titanium dioxide and carbon black, lacking in direct genotoxic activity. The exposure response relationship for lung tumors resulting from this non-compound specific mechanism is thought to have a threshold exposure-response relationship.

The mechanisms of induction of the lung tumors and pheochromocytomas in the rats are not relevant to human cancer induction at credible levels of human exposure to talc. Thus, the evidence from experimental animal studies fails to reach the NTP threshold for "sufficient evidence of carcinogenicity from studies in experimental animals" required for classification of a material as reasonably anticipated to be a human carcinogen.

Talc, free of asbestiform fibers, does not "belong to a well-defined structurally-related class of substances whose numbers are listed in a previous Report on Carcinogens," nor is there convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans. Information on asbestiform talc is not relevant to assessing the hazards of talc free of asbestiform fibers. The supporting evidence does not reach the NTP threshold for classification of a material as "reasonably anticipated to be a human carcinogen."

In summary, the weight of the evidence from epidemiological, animal toxicology and supporting studies on talc free of asbestiform fibers indicates that this form of talc does not pose a carcinogenic hazard to humans and should not be listed in the 10th Report on Carcinogens.

Introduction

The National Toxicology Program (NTP) Report on Carcinogens (RoC) is a key part of a national strategy for reducing cancer risks to the U.S. population. The RoC lists those agents, substances, mixture or exposure circumstances that are either "known" or "reasonably anticipated" to cause cancer in humans and to which a significant number of people in the United States are exposed. The classifications of "human carcinogen" or "reasonably anticipated to be human carcinogens" are statements of the cancer hazard potential of an agent, substance, mixture or exposure circumstances. This is the first step in the risk analysis process which for quantitation of risk requires information on the potency of the agent for causing cancer and exposure profile of the population.

It has sometimes been argued that the RoC does not really involve risk assessment, implying somehow that the RoC classifications of a substance and a listing in the report are not really significant. This is clearly not the case. The mere listing (or lack of listing) of an agent can have tremendous impact. A wide range of public and private organizations and, ultimately, members of the public make decisions based on whether agents are or are not listed. This includes decisions on the regulation of agents, their production and use in the manufacture of other products, and their sale. The labeling of a product or a constituent of product as a "*human carcinogen*" or "*reasonably anticipated to be a human carcinogen*" leads to decisions to not purchase or use the product in favor of the purchase or use of other non-classified or unlisted materials.

Indeed, past concern for the health hazards of talc that may have contained asbestiform fibers led the industry to voluntarily set a standard for talc free of asbestiform fibers. This standard put in place in 1976 ensures that talc use in cosmetics, food, and pharmaceutical products is free of asbestiform fibers. Thus, it is important that the cancer-causing potential of talc free of asbestiform fibers be appropriately evaluated and not confused with materials recognized as having human cancer-causing potential.

TALC, FREE OF ASBESTIFORM FIBERS

Talc (CAS number 14807-96-6) (Asbestiform and Non-Asbestiform) has been nominated for listing in their 10th Report on Carcinogens. It should be noted that CAS number 14807-96-6 refers to pure talc and should be used with the term "asbestiform." This nomination will be considered at a public meeting of the NTP Board of Scientific Counselors' Report on Carcinogens (RoC) Subcommittee on December 13, 14, and 15, 2000. The nomination is supported by a "Draft Report on Carcinogens Background Document for Talc Asbestiform and Non-Asbestiform."

The draft document reviews relevant background information on these two very different classes of Talc. The draft report also includes the conclusions of the "Result of NIEHS Report on Carcinogens Review Group (RG1) Review" and "Result of NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2) Review." Both review groups concluded that talc containing asbestiform fibers is *known to be a human carcinogen.* The classification for Talc containing asbestiform fibers is "based on" sufficient evidence of carcinogenicity from human epidemiological studies." The report also notes that "these studies are supported by the prior listing of asbestos as a known human carcinogen in the Report on Carcinogens (1980).

Both groups classified talc free of asbestiform fibers as "*reasonably anticipated to be a human carcinogen.*" The classification for talc not containing asbestiform fibers is based on (a) consistent evidence from human epidemiological studies, which showed an increase in ovarian cancer in women who used cosmetic talc on the genital area, and (b) evidence of carcinogenicity from a study on experimental animals.

This critique considers the scientific evidence on the carcinogenic potential of talc not containing asbestiform fibers. I conclude that the weight of the evidence from epidemiological, experimental animal toxicology and supporting studies indicates that this form of talc does not pose a carcinogenic risk to humans. Thus, talc free of asbestiform fibers should not be listed in the 10th Report on Carcinogens.

In the sections that follow, the evidence supporting this conclusion will be reviewed against the NTP decision criteria for classifying an agent, substance, mixture, or exposure circumstances as "*reasonably anticipated to be a human carcinogen.*"

The criteria are:

> There is limited evidence of carcinogenicity from studies in humans, which indicates that *causal interpretation is credible* but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or
>
> There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence or carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Characterization of Talc Free of Asbestiform Fibers

Talc is hydrous magnesium silicate ($Mg_3 Si_4O_{10} [OH]_2$, mol wt 379.26, CASRN 14807-96-6). This CAS number refers to pure talc free of asbestiform fibers. Deposits of talc around the world are heterogeneous as to their purity and the extent to which other minerals are present, including asbestiform varieties. The serpentine group contaminant may be chrysotile and the amphibole group contaminants may be amosite, crocidolite, asbestiform tremolite/actinolite, and asbestiform anthophyllite. Recognizing that several types of asbestiform fibers are *known human carcinogens*, it is apparent that talc contaminated with asbestiform fibers will have very different biological activity than pure talc free of asbestiform fibers.

Unfortunately, in the past, many biological investigations that have been concerned with studying the association between various health endpoints and exposure to talc have not involved well-characterized materials and the extent to which asbestiform fibers, if any, were present is unknown. This deficiency in characterization is reflected in the published literature. This point is made in the NTP document and in the review of some papers. However, in some cases the uncertainties in material characterizations need to be more clearly documented. I suggest the document be carefully reviewed to ensure that all characterizations of talc and contaminants are accurately described or clearly identified as unknown.

In my professional opinion, it would be most appropriate to create two documents; one addressing talc containing asbestiform fibers and a second document containing information on pure talc free of asbestiform fibers. This would help ensure that the cancer-causing potential of these two very different classes of material is appropriately addressed based on the relevant scientific information.

Epidemiological Evidence

The International Agency for Research on Cancer (IARC, 1987) evaluated talc for its carcinogenic hazard. The IARC panel very wisely considered the two different classes of material: (a) talc containing asbestiform fibers and (b) talc that does not contain asbestiform fibers. The panel concluded that the epidemiological evidence was sufficient to classify talc containing asbestiform fibers as *carcinogenic to humans*. In contrast, the panel concluded that talc that does not contain asbestiform fibers was *not classified as to its carcenogenicity* to humans, because evidence for carcinogenicity was inadequate.

The results of recent studies of cancer risks associated with occupational exposure to talc and asbestiform fibers are largely consistent with the data reviewed by IARC in 1987. There are no studies reviewed in the NTP report which show an excess of lung cancer in individuals exposed to talc free of asbestiform fibers.

The NTP contains a section (3.2.1) that reviews studies evaluating the association between ovarian cancer and genital exposure to talc. The NTP report briefly reviews 16 case-control studies and one recently reported cohort study. The results of the case-control studies are very heterogeneous. Of 41 different analyses performed relative to ovarian cancer and various indirect indices of exposure to talc, 15 yielded statistically significant positive associations, two were of borderline significance with the confidence interval for the odds ratio including 1.0 and 24 were not statistically significant.

All of the case-control epidemiological studies have serious issues of bias, including confounding, recall bias, non-response bias, and interview bias. In addition, the interpretation is complicated by the long latent period for ovarian cancer and the high likelihood that a major portion of the talc exposure occurred during a time period when the presence of asbestiform fiber contamination of the talc could not be excluded. Since 1976, the industry has had a voluntary standard for producing talc free of asbestiform fibers for use in cosmetics, food and pharmaceutical products.

A major prospective cohort study based on the Nurse's Health Study centered at Harvard University was reported by Gertig et al (2000). A major strength of this study was the ascertainment in 1982 of the use of baby powder, talcum, and deodorizing powder and the ascertainment of ovarian cancers diagnosed by 1996. Any exposure of these individuals to talc products after 1976 should have been to talc free of asbestiform fibers. However, it is not possible to exclude exposure to talc containing fibers prior to 1976. The relative risk for ovarian cancer and ever use of talc on the perineum was 1.1 (0.9 - 1.4) and for use on sanitary napkins was 0.9 (0.6 - 1.3). And significantly there was no increase in risk with increasing frequency of use. Gertig et al also examined associations for several histologic subtypes; all serous, 1.3 (0.9 - 1.7); serous invasive 1.4 (1.0 - 1.9); endometrial, 0.9 (0.5 - 1.9); and mucinous, 0.9 (0.5 - 1.7). These results from a well-designed and well-conducted study do not meet the threshold for limited evidence of carcinogenicity and are reassuring. The Nurse's Health Study is on-going and updates of analyses relative to ovarian cancer and talc use can be expected. The size of the population (over 78,000 available for analysis) and recognition that the individuals are now 54 -

79 years of age (a time period when ovarian cancer incidence increases) should allow the opportunity for more detailed analyses.

The present epidemiological evidence on talc free of asbestiform fibers does not reach the NTP threshold definition, which is—"There is limited evidence of carcinogenicity from studies in humans; which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not be excluded." Thus, based on epidemiological evidence, there is no basis for listing talc free of asbestiform fibers as "*reasonably anticipated to be a human carcinogen.*"

Laboratory Animal Evidence

The IARC panel in 1987 reviewed all of the available evidence from laboratory animal studies with talc free of asbestiform fibers and concluded that it did not provide evidence of carcinogenicity. Since the review, the NTP (1993) sponsored, at the Lovelace organization in Albuquerque, NM a long-term inhalation exposure study with F344/N rats and B6 C3 F1 mice exposed to well-characterized aerosols of talc particles. The talc was free of asbestiform fibers and was specially prepared to yield small, readily respirable particles, thereby maximizing the potential for deposition in the respiratory tract of rats and mice.

The mass median aerodynamic diameters were in the range of 2.7 to 3.6 _m with geometric standard deviations of about 2.0. The particles present in cosmetics, food and pharmaceutical products are typically larger in size, thereby having lower probability of being respired, deposited and retained in the respiratory tract of laboratory animals or humans. I am quite familiar with these studies, since I was President/Director of the Lovelace Inhalation Toxicology Research Institute when the studies were initiated and the in-life portion of the research conducted.

The Lovelace studies have generally been acknowledged as being well-conducted. Unfortunately, to minimize the cost the studies in both rats and mice used only two exposure levels (6 and 18 mg/m^3) and control groups. In retrospect, it would have been preferable to have had at least the lowest exposure level. Both talc levels are very high and resulted in substantial lung burdens.

The low solubility of the talc resulted in long-term retention that was probably further enhanced by persistent pulmonary inflammation. The absence of a lower exposure level group makes it impossible to know how the lung burdens would have increased in the absence of pulmonary pathology and make it impossible to quantitate the impact of the talc-induced pathology on the kinetics of talc retention. Based on the severe pathology present in the 18 mg/m^3 exposed ratio, it is clear that this level exceeded the maximum tolerated dose that is appropriate for an inhalation study. (Lewis et al, 1989.) This increased the potential for development of effects that are not compound related.

Beyond extensive pulmonary pathology, the NTP report (1993) made note of an increased incidence of pulmonary tumors in the female rats at 10 mg/m^3 and an increased incidence of

pheochromocytomas in both male and female rats at 18 mg/m^3. No excess of any type of tumors was observed in either male or female mice.

The excess of lung tumors in the female rats clearly related to the excessively high exposure concentration (18 mg/m^3). This is a non-specific effect of a type observed in rats with a number of "particles not otherwise classified" (PNOC) or "particles not otherwise regulated" (PNOA) (previously these were referred to as "nuisance dusts"). Examples are titanium dioxide, volcanic ash, and carbon black.

The mechanism of development of lung tumors by chronic exposure to high levels of PNOC materials lacking in the capacity to directly interact with DNA has been elucidated by Driscoll and Oberdorster (Driscoll, et al). The key steps are development of large lung burdens of particles, persistent inflammation and mutations in lung cells leading to lung tumors late in life. These phenomena are considered to have threshold exposure-response relations. Most importantly, the rat lung tumors observed at high levels of exposure to PNOC materials are not thought to be relevant for characterizing human cancer hazards. (Oberdoerster, 1995; Goodman, 1995; Zazenski et al, 1995; McClellan, 1996).

The NTP report cites a study by Pickrell et al (1989) noting that clearance rates from human lungs are slower than from rats, raising the possibility of similar pathologic responses in rats and humans exposed to talc. It is noteworthy that the observations of Pickrell et al were based on rats exposed to talc for only 20 days. From such short-term observations, it is not possible to confidently estimate the long-term clearance of inhaled materials, leading Pickrell et al to underestimate the rate of clearance from the lungs of the rats. The data of Pickrell et al and the qualitative observation of talc particles and talc "bodies" isolated from human bronchiolar lavage fluid many years after exposure and talc is a weak argument for the relevance of the rat lung tumor findings to human hazard under any kind of credible human exposure to talc.

The NTP (1993) report cites the Lovelace inhalation bioassay as providing evidence for carcinogenicity of non-asbestiform talc in male and female rats based on increased incidences of benign and malignant pheochromocytomas of the adrenal gland. Tumors of this type are very common in aged F344 N rats (Boorman et al,1990 and NTP Data Base 2000). The tumors rarely occur before one year and the incidence increases with age. In the Lovelace study, surviving male rats were killed after 113 weeks of exposure to talc and the female rats at 122 weeks. These relatively late "kill times" compared to the 104 weeks for a typical two-year bioassay provided additional time for the development of pheochromocytomas at a time when the spontaneous incidence is rapidly increasing.

The frequency with which the complex of adrenal medulla lesions (from hyperplasia to frank malignancy) occurs complicates the interpretation of the true carcinogenic hazard of materials. This topic has been reviewed by Tischler and DeLellis, 1988; Tischler and Coupland, 1994; Tischler, 1996; and Boorman et al, 1990. A further complication relates to consistency in the careful handling of the tissue and in sectioning of the gland. It is well recognized that a variety of neural, hormonal or growth factor stimuli can influence the progression from hyperplasia to benign to malignant tumors. This could include the stress associated with individual housing of rats continuously in wire-bottomed cages and the added stress of the substantial pulmonary

pathology at the 18 mg/m^3 exposure level. Similar increases in pheochromocytomas have been observed in other inhalation studies with particulate materials such as cobalt sulfate, nickel oxide and nickel subsulfide (NTP Data Base, 2000). It is plausible that the influence of fibroblast growth factor from the severely inflamed and fibrosing lung could have served as a proliferative stimuli to the chromaffin cells of the adrenal gland. The development of pheochromocytomas appears to be not related to any direct effect of the talc and is very likely a non-specific effect. Further, the effect is observed only at an exposure level in excess of a maximum tolerated dose (Lewis, et al, 1989). It is not expected that this mechanism would be operative in humans at credible levels of human exposure to talc.

The scientific evidence from the NTP/Lovelace study of inhaled talc free of asbestiform fibers does not meet the NTP threshold criteria for classifying this agent as *reasonably anticipated to be a human carcinogen*. (See criteria reviewed in the introduction.) Although there is an increased incidence of tumors at multiple tissue sites (lung and adrenal gland) in a single species, it is clear that the tumor effect is mediated by mechanisms that are unlikely to be operative in humans exposed at maximum credible concentrations and durations.

Supporting Evidence

Talc free of asbestiform fibers has been evaluated for genotoxicity using assays to measure mutagenic and clastogenic activity. The results as reported by IARC, 1987; NTP 1993 and 2000 have been uniformly negative. These negative findings lend support to the interpretation of the excess lung tumors in the female rats as being high exposure level findings not relevant to characterizing human cancer hazard for credible levels of human exposure.

Conclusions

The NTP (2000) report concludes "Ingested or inhaled non-asbestiform talc particles are unlikely to be absorbed into the systemic circulation and distributed to other parts of the body." This is a noteworthy conclusion that I endorse. The statement is relevant to evaluating the human significance of the pheochromocytomas of the adrenal gland. Obviously, if talc is not absorbed and distributed via the circulatory system, this effect in the adrenal glands must have occurred via an indirect mechanism. I submit that the indirect mechanism has a threshold exposure-response relationship similar to that observed for the development of lung tumors via non-specific mechanisms not related to the specific material inhaled.

The conclusion concerning a lack of absorption and systemic circulation for non-asbestiform talc is also highly relevant to evaluating the potential cancer hazards of talc ingested in food or pharmaceutical products. It is appropriate to conclude that purposeful addition of talc free of asbestiform fibers to either food or pharmaceutical products does not pose a human cancer risk.

The NTP (2000) report goes on to conclude "the current data indicates that inhaled non-asbestiform talc is unlikely to pose a cancer risk to humans under exposure conditions that do not impair clearance mechanisms or raise chronic lung disease." I endorse the first portion of the conclusion. However, I do not think it is necessary to caveat the conclusion. The rat is exquisitely sensitive to develop lung tumors when insulted with high level exposures to "particles

not otherwise classified" (i.e. nuisance dusts). This was evident from the results of the Lovelace studies in which mice exposed for 104 weeks had significant chronic active inflammation in the lungs yet failed to develop lung tumors. The findings in the female rats exposed to 18 mg/_^{3} are similar to those observed with other PNOC, i.e. nuisance dusts such as titanium dioxide, carbon black and volcanic ash.

Recommendation

I recommend that the present draft report be revised as two separate documents. One report should deal with the mixture—talc and asbestiform fibers. It would appear based on the considerable literature on several forms of asbestos being classified as "human carcinogens" that the mixture will be classified as a "*known to be human carcinogen.*" The second report should cover talc free of asbestiform fibers. As outlined above, the scientific evidence is compelling for not classifying this material as "*reasonably anticipated to be a human carcinogen.*" Presentation of this scientific evidence for talc free of asbestiform fibers in a separate report will help ensure that a "halo effect" from consideration of asbestiform fibers does not influence decisions on the lack of carcinogenic potential for talc free of asbestiform fibers. It is not appropriate to list talc free of asbestiform fibers in the R on C.

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About the Reviewer

Roger O. McClellan, D.V.M. is an internationally recognized authority on the human health risks of airborne materials. He is currently an advisor to public and private organizations on human risk analysis and inhalation toxicology issues. He is President Emeritus of the Chemical Industry Institute of Toxicology, having served as President of the Institute from September 1988 through July 1999. As President, he provided leadership for one of the world's foremost research programs directed to developing an improved understanding of the mechanisms by which chemicals may cause adverse health effects. The program pioneered in the application of mechanistic information to reduce uncertainty in assessing human health risks of exposure to chemicals.

Prior to the appointment as President of CHT, Dr. McClellan was Director of the Inhalation Toxicoloty Research Institute, and President and Chief Executive Officer of the Lovelace Biomedical and Environmental Research Institute in Albuquerque, New Mexico. During his 22 years with the Lovelace organization, he provided leadership for development of one of the world's leading research programs concerned with the toxic effects of airborne materials. Prior to joining the Lovelace organization, he was a scientist with the Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, DC (1965-1966) and Hanford Laboratories, General Electric Company, Richland, WA (1959-1964). he received his Doctor of Veterinary Medicine degree from Washington State University in 1960.

Dr. McClellan has served in an advisory role to numerous public and private organizations. He is past Chairman of the Clean Air Scientific Advisory Committee, Member of the Executive Committee, Science Advisory Board, U.S. Environmental Protection Agency, Member National Council on Radiation Protection and Measurements; Member, Advisory Council for Center for Risk Management, Resources for the Future: a founding Member, Health Research Committee, Health Effects Institute; and service on National Academy of Sciences/National Research Counsel Committees on Toxicology (Past Chairman), Risk Assessment for Hazardous Air Pollutants, Health Risks of Exposure to Radon, Research Priorities for Airborne Particulate Matter, as well as the Committee on Environmental Justice of the Institute of Medicine. He also serves as Adjunct Professor at Duke University, University of North Carolina at Chapel Hill, North Carolina State University, and University of New Mexico. In addition, he frequently speaks on risk assessment and air pollution issues at other institutions and meetings in the United States and abroad. He is active in the affairs of a number of professional organizations, including past service as President of the Society of Toxicology and the American Association for Aerosol Research. He serves in an editorial role for a number of journals, including service as editor of *CRC Critical Reviews in Toxicology*. He is a diplomate of the American Board of Toxicology and the American Board of Veterinary Toxicology.

Dr. McClellan's contributions have been recognized by receipt of a number of honors, including election to membership in the Institute of Medicine of the National Academy of Sciences. He is a Fellow of the Society of Risk Analysis, the Health Physics Society, the International Aerosol Research Assembly, and the American Association for the Advancement of Science. He has a long-standing interest in environmental and occupational health issues, especially those involving risk assessment and air pollution, and in the management of

multidisciplinary research organizations. He is a strong advocate of risk-based decision-making and the need to integrate data from epidemiological, controlled clinical, laboratory animal and cell studies to assess human health risks of exposure to toxic materials.