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July 9, 1968

Mr. K. M. Reese
American Chemical Society
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Dear Mr. Reese:

Your request of me in your letter of July 2 seems to be an entirely reasonable one, and is certainly one to which I am prepared to respond, with especial reference to the discussion on lead in the SECTION ON AIR of the REPORT ON ENVIRONMENTAL IMPROVEMENT. It would hardly be possible, at this time, for me to make a critical appraisal of the entire draft. It is difficult enough to determine how far to go in my critique of the portion which deals with lead.

The difficulty arises from the fact that the approach which is being made now to the issue of lead in the air and its effects on human health, in my view, is based upon a toxicological misconception, to begin with, and is accompanied by a greatly exaggerate feeling of ignorance of the matter. Some of the people who are talking loudly take a position not unlike that within which we found ourselves in the nineteen-twenties, when this question was first raised for investigation. All of a sudden the presence of lead in the air has been rediscovered, after a period of nearly forty years during which extensive investigations have revealed a very impressive body of information--incomplete to be sure, but certainly highly reassuring so far as present hazard to the public health is concerned. And instead of proceeding to seek out the further informati required to solve the problem for years to come, every effort is being made to review, with deeply critical attitude, the information at hand.

Let me begin with Patterson's totally unsupported notions of lead in the primordial environment of man and in man's tissues. Certainly less lead was available in the immediate environment of primitive man than that of modern man. We undertook in 1929-30, in an investigation of primitive, native Mexican Indians, to determine how much lead was to be found naturally in their environment and in their excreta. The analytical methods were not as sensitive then as now, but they were reliable and the results were reproducible, as excellent chemists were able to show. But for one technological (actually a handcraft of ancient origin) artefact, namely, some scanty supply of locally fabricated pottery with a lead glaze (fired at high temperature and so not readily dissolved), artificial sources of lead absorption were absent. It could readily be established that this source was of very minor importance. The clear evidence of the data on soil, vegetation, animal life (and of foods consumed in their natural state), demonstrated that the daily intake of lead by those people was of the order of about half of that of U.S. citizens. The mean rate of the excretion of lead in their urine, and the mean content of lead in their blood (as redetermined in 1937-38 when presently sensitive methods of analysis were available) turned out to be about two-thirds that of the adult citizen of the United States. Patterson simply dismissed these facts when he heaped inference on inference and concluded that primitive man had little or no exposure to lead.

Thus, one has difficulty in escaping the likelihood that the human animal was born into an environment containing lead, that this element was indeed a factor in his life, and that it has continued to be such, with some gradual increase and decrease through the centuries, as men made use of the metal, taken from below the surface of the earth, in an increasing number and varieties of ways.

The further evidence of the past thirty years or more demonstrates that the lead in the common human environment of the U.S., including that of cities and towns, has remained nearly stationary. This is evidenced by the levels of the concentrations of lead in the air, as well as by the lead content of the urine, blood and tissues (so far as is known) of groups of individuals, during that period of time. Lead in the environment, both that in food and beverages, and that in the air in certain areas of the U.S. that have been under observation for more than 20 years, has tended to decrea while the output of lead in the urine and the concentration of lead in the blood of groups of persons in the general population have undergone slight, perhaps insignificant, decrease.

The concept of the existence of a public hazard due to lead in the air was based by Patterson, and adopted to a greater or lesser extent by laymen, by a few clinicians who were familiar with the manifestations of lead poisoning, and by some persons with public responsibilities that bore heavily on their shoulders, upon the fact that lead has had a bad reputation as a "cumulative" poison for centuries, that sometimes it causes seriou illness and disability, and at times fatalities. In the minds of such persons, any quantity absorbed means some danger; if much is very dangerous, a little is somewhat dangerous. From the physiological viewpoint, this is nonsense, but from a biologically naive, apprehensive lay viewpoint, it is simple, self-evident and unassailable truth. The fundamental factor of the level of dosage, in relation to the toxicity of a chemical substance, does not enter into this concept to give it substance, and hence it is devoid of virtue. The toxicity of a chemical is a function of its concentration rather than of its intrinsic nature or composion, so that at different levels of concentration it may be useful, merely incidental, or toxic, even lethal. The importance of the biological principles stated above in the considerations of environmental health lies in the fact that modern technology, which is the economic basis of our society, has created and will continue to create a host of potential hazards, each of which must be recognized, appraised and brought under suitable control, so as to eliminate significant threats to human life and health. If this turns out to be impossible of achievement in the specific instance, the source of the hazard must, of course, be eliminated. In the case of lead, we have managed to establish criteria through which conditions of genuine safety in industry can be achieved. It is one of a limited number of substances which have been investigated sufficiently to that end. We have failed to eliminate industrial lead poisoning solely because it has not been possible to disseminate and apply the available "know how" throughout industry. As to the general environment, we have not completed the atmospheric specifications for public safety, but we have been able to define criteria for public safety in terms of the lead content of food and beverages under fixed conditions of atmospheric contamination. A basis for setting a standard for the ambient air is near at hand and can soon be promulgated. There is no occasion for alarm, however, for it is evident, for all practical purposes, that danger, if any, from this source, lies in the future. Moreover, methods of investigation have been developed to the point that makes possible the recognition of hazard before it can have exerted significant effects.

The foregoing statement of the present position seems to me to be an essential basis for additional comments on the report of your Committee. If it appears to be a somewhat sweeping statement, I ask you to remember that I've been engaged for some forty years, with the help of some highly competent people, in obtaining information that would enable me to fulfill my professional responsibilities in this matter both to the industries involved and to the people of this and other countries. One cannot bear such responsibility on the basis of inferences and half-baked information.

Specific Comments:

1. On page 124, second paragraph, the "estimate" of the natural lead content of the atmosphere as made by Patterson is pure inference. It should not be dignified in a truly scientific publication without some indication of skepticism. The statement and the reference tend to give it a degree of authority that is false.

2. In the same paragraph, the statement about the "large gaps" in our knowledge of the behavior of lead over-emphasizes our ignorance. The latter is real, insofar as mechanism of action is concerned, but the descriptive pattern of the behavior of lead in the organism is well delineated. Furthermore, it is important to recognize the great bulk of the negative information that is available as to the effects of lead in the concentrations which occur in the environment and in the structures of plants and animals, including man. Many of us, as investigators, view with regret the popular view of the insignificance of negative information, and of the ominous characteristics of what may be imagined, as against what has not been found. Few current investigators are aware of the fact that several periodic surveys of the American population (that is, of course, of sizeable groups in the population considered to be the most likely victims of environmental lead), have failed signally to turn up any evidence of any harmful effect of lead in the general environment. This work was begun so long ago that present investigators have had little awareness of it. One would think that the Three Cities Survey was the only survey that had been carried out. Still fewer hygienic authorities or even investigators, outside of occupational medical circles, are aware of the fact that our group in the Kettering Laboratory has had large numbers of workmen in the lead trades under systematic observation over periods of many years, in such a manner as to enable us to differentiate between hazardous and non-hazardous conditions of exposure to, and absorption of, lead. It is agreed, of course, that these observations do not apply strictly to all segments of the general population, but the important point is that it is possible clearly to differentiate safe from dangerous levels of absorption of lead, and that the threshold point is sharply defined. The fact of further importance is that the quantitative differentiation between dangerous levels of lead absorption, and those which characterize the persons who are subjected only to lead in the common or general environment is not slight, as has been suggested ignorantly, but rather is readily perceptible, provided appropriate analytical information is obtained.

3. I must refrain from commenting on the top paragraph on page 125. I am not at all enthusiastic about some of the efforts of research undertaken under the several categories referred to, but I hope for the best. The two things which I want to see done in a definitive manner, in addition to what we are engaged in now (the determinati of the upper limit of physiological tolerance for lead in the air, when combined with the current levels of lead intake and absorption associated with our food and beverages are as follows:

A. The determination of the body burden of deceased persons of all ages who can certainly be said to have been subjected only to common general environmental types of exposure to lead throughout their lifetimes or large segments of their lifetimes;

B. The determination of the clearance of particulate lead compounds of minute dimensions, i.e., under 0.25 or 0.30 microns in diameter, from the lung. The figure which I gave for the pulmonary retention of lead sesquioxide (particles of mean diameter of 0.05 micron ranging up to the largest particles at 0.18 micron) of 35 to 45 percent has been taken to mean that this proportion of inhaled lead is absorbed in the lung.

Indirect evidence indicates that the proportion absorbed is nearer 10 percent, and that the balance is cleared to the alimentary tract or outside of the body, but almost everybody goes right along saying that 35 to 50 percent of finely divided particles that are inhaled are absorbed. We expect soon to be able to give a definitive answer to this crucial question.

4. I consider the report and the action of the Department of Commerce in the matter of lead in gasoline to be extremely foolish and irresponsible. Again, without anything by way of a reason for action other than an uninformed apprehension, they have proposed steps that represent a radical departure from more responsible and better informed thought on this subject. I am sure that you would not say this, nor would I, under any other conditions than those that might be furnished by a strictly professional or official inquiry. However, I would not give their view the type of prominence that would normally flow from a responsible official utterance or action. This one is based on a very scanty familiarity with the problem at issue.

5. The first paragraph on page 126 states a controversial issue fairly. I think you should know, however, that the evidence on which the conclusion has been based that the relationship between lead in the air and lead in the blood (within the range of values that obtain in the general urban atmosphere) is predictable, is on extremely thin ice. Our experimental subjects exposed to 10 micrograms of lead per cubic meter of air (despite Goldsmith's mathematics) have failed to respond by developing higher concentrations of lead in the urine and blood beyond the limits of variability displayed in control observations. Similar experiments at 20 micrograms have not as yet yielded certainly significant responses on the part of subjects who have spent approximately half of their time (per week) under conditions of respiratory exposure. If this is the case, how in the world can one attribute changes in the concentration of lead in the blood (in the third decimal place) to slight variations in the concentration of lead in the ambient air? I do not suggest that you use or even trust (at this time) these undocumented statements. I merely suggest that the conclusions derived from the type of systematic observations which we are carrying out are hardly in the same category as those arrived at by "epidemiological" and mathematical manipulations of incomplete data. As we have shown, the variability of the lead in the alimentary tract is by far the largest variable in the human intake and absorption of lead under ordinary conditions of life, and when this factor is unknown in an individual or group, one cannot, by statistical slight-of-hand, make definitive decisions as to the causation of variation in the lead content of the blood or urine.

6. This brings us to the second paragraph on page 126, in which there are two incorrect statements of fact.

A. ("The naturally occuring lead - - - etc. contributes only a minor part of human consumption.") This is not true. The best evidence is that from a third to a half of our intake of lead in food and beverages is of natural origin. If one is prepared to look imaginatively into the primordial state of the earth and of man and to accept hypotheses that have no tangible support, he may, but to set this against such evidence as is available is hardly acceptable conduct. If one accepts the likelihood that something of the order of 0.1 to 0.2 mg. of lead per day in our food and beverages is derived from nature, the absorption of 10 percent (or thereabouts) per day adds up to 10 to 20 micrograms per day.

B. ("Some studies have shown that 25 to 50 percent of inhaled lead is absorbed, although - - -.") This is also untrue. What has been shown is that some 35 to 45 (perhaps, but not, certainly, as much as 50) percent of a specific dispersion of

articles of inhaled lead, ranging up to 0.2 micron in diameter, is retained in the respiratory system. The ultimate fate of this is unknown, but the indirect evidence is that much of that retained in the lung is cleared therefrom and winds up in the alimentary tract. All of the available physiological information indicates that much less than 25 to 50 percent, perhaps as little as 10 percent, of that inhaled is actually absorbed in the lung.

7. On page 127, first partial paragraph, the statement as to the "estimates based on geochemical evidence," must be objected to on the grounds that there is no such "evidence." The statement that "guestimates" based on multiple inferential hypotheses, would be more in keeping with the facts. Even the most recent observations (which require critical examination) on the skeleton of primitive people in Peru found quantities in the skeletal tissues ranging, according to reports, from 5 to 110 parts of lead per million parts of bone. This would add up to something of the order of 60 to 1320 milligrams of lead in the entire skeleton, if these were fresh bones. I have no way of knowing in what condition these bones were found, but I would guess that they had been reduced to something resembling the residual mineral in the bone in the course of time. This would change the basis of calculation to yield a smaller quantity. In any case, it is a far cry from 2 milligrams, and is not greatly dissimilar from our findings at the present time. The question of primitive man, in this respect, is still open, and because of the nature of the question is unlikely to be answered with a proper degree of certainty. Schroeder's suggestion concerning skeletons in the catacombs might well be followed up, but a very careful examination of the premises and of the history of the accumulation of skeletons there would have to be made if valid results are to be obtained.

8. In the only complete paragraph on page 127 is the statement that, "Some people who are exposed occupationally, such as traffic policemen and parking garage employees, have run as high as 0.06 milligram per 100 grams of whole blood." Taken by itself, this sentence is definitely misleading, for two reasons. First, the term "occupational" as employed in our discussions, has been used hitherto to apply to industrial exposure to lead, in order to differentiate it from conditions that exist in the non-industrial or general environment. Admittedly, the term as used is generally descriptive of the work of these groups, but it is an entirely unconventional usage and is therefore misleading. It is something I failed to note and correct in editing the text of this report. The difficulty lies in the fact that our selection of these groups in this and in previous surveys was intended to determine the status of persons who sustained the maximum of exposure to lead derived from the exhausts of automobiles, without any other unusual type of exposure to lead. By contrast, the garage mechanics, whose exposure to the exhaust of automobiles was also high, are subjected to other types of exposure. Many of the men do car body work, involving exposure to paint and solder. Many of them remove carbon from engines by methods which disperse lead (and carbon) in the air. A few of them repair storage batteries. Almost all of them wear filthy clothing and are themselves filthy with oil and grease and grime from automobiles and floors. This has been designated as "occupational" exposure to lead in differentiation from respiratory exposure limited to exhaust fumes. I admit that this is bad semantics, but it simply followed the habitual or conventional practice of identifying "occupational" exposure with industrial employment. As you will agree, I believe, the garage mechanic is in a different situation than the traffic policeman. We investigated a large number of these on several occasions, because we were concerned lest their exposure to exhaust fumes added to their other types of exposure to lead would sum up into a hazardous situation. Actually, however, it has not done so, but has merely induced a statistically significant excretory response (as well as a slightly elevated concentration of lead in the blood) which is far below the threshold of danger. By contrast, neither the traffic policemen nor the parking garage employees can be

differentiated from people in the other groups in our survey by a statistically valid elevation of the lead in either urine or blood. The mean values in the urine are indeed somewhat higher but the numbers of persons involved in the groups, when set against the individual variability of the results, do not yield any statistically significant differentiation.

To one other point here, I must object. Much was made, by some of those who engaged for the first time in this type of investigation, of the fact that 12 of the results obtained within the entire set of analytical results in the blood of individuals were at, or above, the level of 0.06 mg. per 100 grams of whole blood (one was at 0.07). It was even suggested that this represented the situation of a certain segment of the population, and that this was very near the threshold of danger (i.e., the level of 0.08 mg. per 100 grams of whole blood). I was astonished that anyone could take this position, but I took the responsibility for having every result above 0.05 mg. checke This was done in Cincinnati by ourselves, and in California by the State Department o Health. Every single result so checked turned out to be of the order of 0.03 or less This was exactly what our previous experience had led me to expect, in view of the possibilities that exist for slight contamination of samples in the process of their collection and analysis, and the intrinsic analytical error. The latter for our "dithizone" method is of the order of $\pm$ 10 percent, and while it is usually lower, it is occasionally higher in routine procedures. Obviously, this error is magnified appreciably by the calculation to 100 grams of whole blood. Sometimes the sample is under 10 grams (or milliliters)in routine sampling, and the factor of calculation is disproportionately high. By sheer chance, alone, a certain number of high results tends to creep into a large series of analyses, so that, when we are investigating a supposedly "normal" group of persons, we analyse duplicate specimens of blood. By such means we have found that the occasional result above 0.05 mg. per 100 grams of whole blood of the so-called normal persons is almost always the result of an unusual error. I, therefore, was not concerned about 11 of the 12 high results listed in the Three Cities Survey. I was, however, genuinely concerned about an 0.07 which occurre in one among a group of men employed in an airplane manufacturing plant in Californi since this is too close for comfort to the threshold value of 0.08. It was said tha none of these men had been exposed to lead at their work, but I've had much too much experience with allegedly lead-free occupations to take this seriously without detai investigation. Fortunately, this result, too, turned out to be a misfire.

I have gone into this matter at some length in addressing a chemist (or a representa of chemists), for the reason that much of the present discussion of slight differenc in analytical results under various circumstances and in various hands is entirely unrealistic. It is not apparent in the report of the Three Cities Survey, but it is true nevertheless that there was a slight but fairly consistent difference in the results obtained by the three groups of analysts. The USPHS method yields systemati lower results than those which we obtain under the same circumstances. Moreover, considering the analytical error, small as it is, it is foolish to express individua results on the blood in any terms other than to the nearest integer in the second decimal place, or perhaps to the nearest naught or five in the third decimal place. Mean values can, of course, be extended to the third decimal just as they turn out, but an astonishing number of people accept a single result on one individual as bein precise. Actually in practice, the variability due to physiological factors plus analytical deviation is found, in a large series of analyses on the blood of the sam individual under seemingly identical conditions from day to day, to be represented i

a frequency distribution that is very similar to that of single results on a large series of similarly situated individuals. It is knowledge of this type, gained by long experience with the phenomena involved in this problem, that tends to separate out the wheat from the chaff, and gives balance to judgment. It is because this has not been the attitude of mind toward the voluminous data of this field that I have taken the trouble to deal with some of the details of the matter. I hope you will not have been bored with them, or conclude that I've been "gilding the lily."

(9) I have said enough to indicate my position in relation to detailed discussions in this field of investigation, and I think I should desist. I hesitate to do so, however, without some mention of the problem of infants and children. The question of the significance of lead in the ambient air has been badly confused with the relatively high incidence and severity of lead poisoning among children between the ages of 1 and 3 (or perhaps 4) years of age in a number of cities in the U.S.A. The two situations have no relationship whatever to each other. There are other reasons for confused thinking in this part of the problem. If I were in your position, I would delete all discussion of this matter. Let me say, however, with reference to the least concentration of lead in the blood at which intoxication is found to occur, that I have never seen, nor have I had reported to me in connection with our own analytical services, a single case of lead poisoning in a child, at the onset of the illness, in whom the concentration of lead in the blood was lower than 0.08 mg. per 100 grams of whole blood. Cincinnati and Baltimore were the first cities in the United States in which this matter was investigated with considerable care. (Boston was involved early also, but did not follow the relationship of intoxication to lead in the blood.) We collaborated with our colleagues in the Children's Hospital and in the Cincinnati General Hospital from the early nineteen-thirties in systematic investigations. We had fewer cases than those in Baltimore, but the same situation existed, if only to a less extensive degree, geographically, in the two cities. The problem in children is characterized by a very large dosage of lead (by mouth), over relatively short periods of time (as compared with the exposure of adults in lead-using industries). Many cases of elevated lead concentrations in the blood have been seen over the years, and many of them have had no presenting symptoms of illness, but most of those that had become ill of characheristic lead poisoning within a few days before their admission to the hospital, had concentrations of lead greatly in excess of 0.08 mg. per 100 grams. None had less, so that we came gradually to recognize the fact in relation to children, as we had in adults in industry, that this was a threshold value. Here too, the value 0.08 could be 0.07 or 0.09, so that we carried out duplicate analyses in almost every instance as a check on the analytical deviation. Accordingly, I am fairly certain that those (Moncrief et al. - London, and other investigators) who have reported lower concentration in lead poisoning in children have not attended sufficiently to the precision of the analytical work, or have not ascertained the interval of time between the onset of the illness under consideration, and the performance of the analyses. (The concentration of lead in the blood of children diminishes rapidly, somewhat in direct proportion to the brevity of the period of exposure, following the termination of the exposure, so that delayed analyses yield lower results than those obtained in direct temporal relationship to the period of exposure.)

I advise you also against discussion of certain aspects of the biochemical information about lead. The quantitative aspects of this matter, in relation to enzyme systems and, particularly, to interference with the synthesis of hemoglobin in the body, are highly important, and the available information is of great physiological interest. Unfortunately, however, the clinical methods that have been employed in the determination of delta-amino-laevulinic acid in the urine and of the porphyrins in urine and blood,

specifically Coproporphyrin III, have not always been applied with sufficient precision, nor has the timing of the collection of samples of urine and their preservation been handled with such uniformity as to yield satisfactory information. There is no doubt that the measurement of these (and perhaps other) intermediate products of the metabolism of hemoglobin constitute important diagnostic procedures in relation to lead poisoning, but the real questions, of great importance in preventive medicine, are (1) whether these non-specific indicators of a metabolic disturbance are, in fact, the precursors of more serious forms of lead intoxication, when lead is the causative agent, and (2) whether they develop gradually with increase in the lead content of the body, or only precipitously at a certain critical point of absorption. If, for example, one or the other or both of these intermediate metabolites, which resul from inhibition of the rate of the synthesis of hemoglobin, appear in significant quantities before any other evidence of lead poisoning can be found, their determination, periodically, can be used to detect the imminence of lead poisoning, which then can be avoided (in industry, for example) by the termination of the exposure of the individual. If, however, these metabolic changes coincide in time with the onset of more severe types of illness, their detection is useless, for practical purposes, as a preventive procedure. (It has been shown that the determination of the lead content of the blood is indeed a specific and dependable means of prevention, but it would be advantageous to have a simpler and cheaper means of achieving the same result, if such a one could be developed to a comparable degree of precision.) We are examining these matters at present and are convinced that there is a sudden and sharp increase in the intermediate porphyrins, coincidental with an increase to a critical point in the lead content of the body. I regard this as a toxic effect of lead, when it can be established with reasonable certainty that lead is responsible for it,-that is, when there is no evidence of congenital porphyria, and no indication of any other type of intoxication that is known to be capable of inducing the phenomenon. Those who are "looking under the bed" for hitherto undiscovered, insidious effects of lead, that have escaped the "crude" observations of a host of clinicians through the centuries, who talk about "sub-clinical" lead intoxication as though there were some reason to suspect that the present period is unique in history, from the aspect of the exposure of the general population to lead, do not seem to realize that what they mean but do not say is that there may well be forms of lead poisoning which physicians through the centuries have failed utterly to recognize, and even yet do not have the wit and skill to detect. It is possible, of course, that this is true, just as it is possible that a large number and variety of agents of disease are capable of doing damage which, at present, is unrecognized. But how likely is this to be the case at this particular time, in view of the efforts at detection (research) that are being made at present. I am as skeptical as anyone can be as to the completeness of our knowledge of the agents and mechanisms for the production of disease. But I do not lie awake at nights brooding about them. I simply work, as effectively as I am capable of working, at the elucidation of these matters, in the recognition of the fact that much human life has been preserved in the face of many difficulties, and that it can certainly be preserved even more effectively in the future, despite the introduction of many man-made hazards, by the steady extension of medical and biological knowledge. I am not placid about this, but rather am often excited, but I do not live in a state of continuous apprehension about my own health and that of others, although, I am chronically distressed by the public and governmental apathy toward the very real hazards to which the industrial population (and to a lesser extent, other people who do the world's work) are being subjected.

Sincerely yours,

Robert A. Kehoe, M.D.
Professor Emeritus of

RAK:wp

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STEPHEN T. QUIGLEY
Director

July 2, 1968

Dr. Robert A. Kehoe, M.D.
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Dear Dr. Kehoe, M.D.

I should much appreciate having your comments on the enclosed draft of the section on air of the American Chemical Society report on environmental improvement. This study, as you may be aware, is being done under the aegis of the ACS Committee on Chemistry and Public Affairs, and eventually it will be published by the Society as a public service document. In addition to air, the report will cover water, solid wastes, and pesticides, barring unexpected changes in format.

Please note that the enclosed draft is still being processed by the task force of experts that the ACS has assembled to oversee the study. Thus it does not necessarily represent their final views on balance, fact, or opinion.

The primary purpose of this review is to get your critical comments on the factual and other aspects of this draft and to update those sections that require it. The sections that appear to be most pertinent to your organization are noted on the cover page of the draft by the page number on which they start. However, should you care to comment on other parts of the draft, your views would be welcomed. In some cases you will see questions in parentheses in the draft or noted in the margins. Whatever answers you can supply will be appreciated.

Because of the length and complexity of the draft and certain imponderables in its scheduling, I have not set a firm deadline for the receipt of comments to be incorporated in the draft. However, it would be helpful if I could hear from you within perhaps three weeks after you receive the material.

Thanks very much for your help.

Sincerely,

K. M. Reese

K. M. Reese
for the ACS Committee on Chemistry
and Public Affairs, Subcommittee on
Environmental Improvement.

KMR:js

Enclosure