ETHYL CORPORATION

INTER-OFFICE

To R. K. Scales — Address Detroit

From George Roush, Jr., M. D. — Address New Orleans

Subject — Date October 28, 1968

As you have requested, I have reviewed Dr. Kehoe's report entitled "Report of the Progress of an Investigation to Develop a Standard for the Tolerable Concentration of Lead in the Ambient Air", dated October 17, 1968. I will state first my conclusions concerning the report, and then I will deal with specific details of the report.

I will summarize what I think are the conclusions to be drawn, both for new concepts as presented, as well as any changes in viewpoint of Dr. Kehoe:

1. Dr. Kehoe states that this study is applicable to only healthy individuals.
2. He states that the body burden of lead in man does increase with age, reflecting his exposure, and he does not once mention the word equilibrium in this report.
3. 20 µg of lead per cu m of air would result in a potentially hazardous exposure for the general population.
4. 10 µg of lead per cu.m of air was not tested over a sufficiently large portion of the day to determine whether it would produce an effect in man; that is, a rise in the urinary lead excretion.
5. His data would indicate that 42 hours per week of exposure at 20 µg per cu.m of air will produce an effect on the urine excretion, and when the remaining hours of the week with exposure of 1 ug per cu.m. of air is breathed, this would produce an equivalent exposure to an average exposure of 5 to 6 µg per cu m of air.
6. Since we are searching for the highest level of exposure that does not increase the urinary lead, Kehoe calls our attention to the fact that 21 hours per week exposure was without effect. This is equal to an average exposure of 3 to 4 µg per cu m.

I will now turn to a review of the details of Dr. Kehoe's report.

In the Introduction:

The point is made that Kehoe is studying reasonably healthy, normal individuals, and the problem of relating this study to the health of the infirm is left unanswered. (The Three City Study did look at chronic diseases, and the statement is made "neither the ranges of individual values nor the means of lead concentrations in the blood in the grouped cases are remarkable").

For the first time, to my knowledge, Dr. Kehoe says that, at this low level of exposure, accumulation does occur (in the past, Kehoe said that there was no accumulation after 30). In several contexts, Dr. Kehoe refers to accumulation - on this occasion just mentioned, again on Page 2, when he mentions selective absorption into the skeleton, and then on Page 7, when he states that the fall in blood lead again is due to the selective absorption of lead into the skeleton.

Dr. Kehoe calls the accumulation that occurs insignificant, but, insignificant in potential for producing harmful effect. I believe that Dr. Kehoe is looking for the earliest measure of accumulation, a measure of exposure, and far below any level that could produce a health effect.

On Page 2, he says that we can't define the exposure of man in any precise terms, and correctly so. I believe that the exposure of man lies some place between his exposure at ambient levels plus his exposure at times when the levels are increased i. e., on or near the roadways.

Further on Page 2, when he talks of lead being selectively ~~being~~ taken up by bone, there is no mention of an equilibrium state as he had expressed on numerous occasions in the past. He does state, again correctly so, that blood is a poor reflector of the body burden of lead, but it is a rough approximation of the body burden. The true correlation between the two is not known. This fact does create problems when we are trying to evaluate the effect of ambient lead on man when we measure blood leads.

On Page 2 and Page 3, Dr. Kehoe discusses the movement of lead from soft tissues into bone where it is relatively unavailable and that this constitutes a safety factor. This implies further that there is an accumulation, but also that we are using up a safety factor at levels found in ambient air.

Also on Page 3, he states that in the recent past, porphyrins and delta amino levulenic acid abnormalities have become apparent. The effect of lead on porphyrin metabolism has been known in the early '50's, if not in the '40's.

On Page 4, Dr. Kehoe states that a study of blood and urine content of lead can insure freedom from lead intoxication. I believe that this represents a poor choice of words, since all agree that the problem is not frank lead poisoning, but rather freedom from all biologic effects of lead - which Kehoe undoubtedly meant.

Also on Page 4, he states that his criterion of health is based on: 1. A criterion that has stood the test of time (certainly defensible); and, 2. Is correct in principle. He does not need to defend his study on this basis. He is only testing, to determine the first evidence that there is a rise in urine or blood lead as a reflection of exposure - long before there is effect on porphyrins, ALA, or any other biologic effect.

In the Experiment:

Turning to Dr. Kehoe's discussion of the Experiment, on Page 6, Dr. Kehoe said that in 1967 his subject was excreting an increased amount of lead (and therefore even at this level of exposure he was responding with an increase in urinary lead). I will calculate as Goldsmith probably will do:

42 hours per week = 6 hours per day.

6/24 x 20 m^3 (respired) /day x 20 $\mu g/m^3$ = 100 μg inhaled in the chamber.
18/24 x 20 m^3/day x 1 ug/m^3 = 15 μg inhaled during the remaining day.
115 μg represents the total lead inhaled per day.

Therefore, if Dr. Kehoe's experiment is correct, 115 μg per day produces a response, and if the 115 ug were inhaled at a constant level over the entire 24 hours, then 115/24 = 5 to 6 μg per m^3 would be the concentration which would produce a response, an increase in urinary lead.

Further, in this same paragraph on Page 6, Dr. Kehoe states that 21 hours of exposure per week didn't produce a response. Using the same method of calculation as above:

21 hours per week = 3 hours per day and 1/8 x 20 x 20 = 50 μg.

7/8 x 20 x 1 = 17.5 ug, and 67.5 μg per day = the total lead inhaled/day that did not produce a rise in urinary lead. Again, 67.5 μg/20 m^3 = 3-4 $\mu g/m^3$ would be the concentration which could be inhaled without effecting the urinary excretion of lead. Since Dr. Kehoe says that 31.5 hours/week produced a dubious change, this level of exposure would be intermediate between 3 to 4 $\mu g/m^3$ and 5 to 6 $\mu g/m^3$.

On Page 7, Dr. Kehoe really extends his extrapolation. He states that if his experiment had been continued for 4 1/2 years, then the blood lead would have begun to rise. (Again, giving evidence of an increase in body burden). He also adds that the effect observed on blood, that is, a fall in the concentration of lead is evidence of threshold of detection, and (without stating so in so many words), he says, this is a threshold of increasing body burden - even though the concentration of lead is falling. This obviously is only his interpretation of this phenomenon.

In the Discussion (on Page 8), he states that is evident that 20 µg will not be tolerated by the human population, and he goes further to state that if this exposure were to continue through a lifetime, it can hardly fail to be potentially hazardous. This is quite an extrapolation from an 18 month experiment in one man that produced a rise in urine lead from . 025 to . 0425 mg/day.

Concerning Dr. Kehoe's statement that even a 73 hour exposure is not sufficient to insure that 10 µg/m³ is a safe ambient standard is indeed a re-assessment of his data. However, reviewing his paper of 1966 entitled "Criteria for Human Safety from Contamination of the Ambient Atmosphere with Lead", an exposure of 42 hours of exposure at 10 µg/m³ produced a change in urine excretion. Then . 31 x 20 m³/day x 10 µg/m³ = .62 µg, and . 69 x 20 x 1 = 13. 8; a total of 75. 8 µg/day is then calculated as the amount that will produce an increase.

This use of two sets of data suggests that the actual amount which will produce a chang is the same for the 10 or 20 µg exposure level. That is, the concentration x time for both of these exposures is about equal.

I believe that my use of Dr. Kehoe's data is reasonable and a logical conclusion, using this data, is that about 5 µg does raise the excretion of lead in the urine. The Albany-Birmingham study of API-LIA should substantiate Dr. Kehoe's conclusions (this study will expose 6 prisoners to 10 to 20 µg/m³ for 22 hours per day for up to 4 months, but only after a similar study had been completed in animals.)

How do we relate Dr. Kehoe's findings, in this experimental setting, to the practical problem of lead in air? Dr. Kehoe's study was designed to study the physiological handling of lead in the range in which it is found in the ambient air. The Six City survey has been designed to evaluate the influence of lead in air on blood lead - it is interesting that those concerned with this study have agreed that the sampling tool should be lead in blood because of the extreme variability of lead in urine, whereas, the blood better reflects the body burden. This study will then tell us whether the concentration of lead in air, and here we know that this is the actual lead to which man is exposed, has produced an effect on the body burden.

The next point to be made is that, if the level of exposure (the lead in air) does produce a measurable response, then the next problem will be to decide what is the maximum acceptable response; that is, without hazard. Dr. Kehoe has not attempted to answer this question, but rather, by inference, he believes that the level that produces a change in urinary lead excretion should be the air quality standard. I believe the answer is best obtained by looking at populations which have significantly higher levels of exposure, either naturally or as a result of occupational exposure, and of course, occupational exposures are usually highest. LIA has formulated definite plans to do exactly this.

When the Albany-Birmingham, Six City, and the study of occupational populations are completed, we will be in a better position to decide on the air quality criteria for lead.

If there are questions concerning this review, I am sure that I shall hear them.

George Roush, Jr., M. D.

GR/n
cc: Dr. G. F. Kirby