

April 15, 1949

Dr. J. P. Holt, Research Director,
Standard Oil Company (New Jersey),
30 Rockefeller Plaza,
New York 20, New York.

Dear Doctor Holt:

Doctor Kehoe has asked me to reply to your letter of March 24, 1949, which raises the question of the proper duration of long-time experiments in which animals are forced to inhale toxic substances. I am quite in agreement with your statement that an experiment of six months would be sufficient to give the necessary information. Indeed, it has been our usual practice to continue such costly experiments no longer than six months, and I am unable to recall at the moment any instance in which an experiment of longer duration has been published by any other laboratory. It is, of course, possible that some chronic effect might be revealed by a longer experiment, but to perform such experiments would tie up the limited facilities available for such experimentation and preclude the securing of any information in regard to a wide variety of other substances used in industry about which we are almost totally ignorant. Had we the time I should like to repeat certain of the life-time feeding experiments which we have carried out in the past with various substances, and killing off the rats at six months, in order to determine whether we could have learned as much at the end of this briefer period as we did at about two years.

In citing the figure of \$4,000 to \$5,000. in my letter of October 8th, I had in mind an experiment of approximately six months duration, rather than one or two years, since that is our usual practice. In my

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letter of March 7, 1949, I indicated that only \$897.00 remained for work on phenylethanolamine. Since this has probably been reduced somewhat by the pathologic observations, which have been completed, it is obvious that not enough remains to cover the cost of an experiment carried on for six months. Fortunately, we have secured in the past inhalation work with TTC-7, information that may be useful as a guide to the choice of concentrations to be tested in a series of briefer experiments with a mist of TTC-7C.

Our forthcoming report will state that no histologic evidence of damage attributable to N-phenylethanolamine was encountered in the tissues of animals of several species that had been exposed to air bearing 0.024 milligrams per liter (4.3 p.p.m.). This concentration represents approximate saturation of the air with the vapor. To attain it required heating the liquid to 145°C. Exposure to this concentration gave rise to Heinz bodies in the blood of cats and, on two days, toward the middle of the experiment, when by overheating the well, the concentrations exceeded saturation, nearly all of the erythrocytes in the blood of one of the cats contained Heinz bodies. Notwithstanding this, at the end of the experiment there was no histologic evidence of visceral damage. The results of this experiment appear to indicate that dipping, or brushing, of rust preventive solutions would give rise to no intoxication attributable to the N-phenylethanolamine, assuming that contact with the skin is avoided.

I think it might be reasonable to anticipate that mists of the rust preventive solution containing 2 per cent of N-phenylethanolamine would not give rise to intoxication by the amine if the total concentration of the amine in air bearing such mists did not exceed 4 p.p.m. This assumes that fairly complete absorption of the amine vapor from the lungs occurred in our past

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experiment, and that the amine might be equally well absorbed from the mist regardless of its droplet size. From the fact that absorption occurs through the skin, we should not assume that none would occur from droplets too large to reach the alveoli. A few experiments might be set up in which various amounts of mist are sprayed into a chamber in the absence of animals, and the total concentrations of amine in the air determined. If we find that a heavy mist of the preventive solution with 2 per cent amine contaminates the air to an extent greater than 4 p.p.m., then we could carry on a few brief animal experiments to determine if such exposures are any worse than to 4 p.p.m. of vapor, using Heinz bodies, methemoglobin and red cell counts as criteria of absorption. These results might be correlated with those obtained in past experiments in which daily cutaneous applications were made over nearly six months. Based on the results of such preliminary observations, we might then wish to repeat exposures at some desirable concentration so long as the available funds permit. It is obvious that this approach, while it would tell us something of the hazard from the amine in the form of a mist, would be inadequate to answer the question of the extent to which other constituents of the rust-preventive solution might be deleterious.

Very truly yours,

Francis F. Heyroth, M.D.

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cc: Dr. R. A. Kehoe

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