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JOSHUA LEDERBERG
PRESIDENT

February 5, 1980

Dr. Leon Goldberg
President
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Dear Dr. Goldberg:

Thank you for sending me the January 16th statement on the formaldehyde study. As you know there is little doubt that formaldehyde is a bacterial mutagen and in fact I had some small interest in this question myself around 1951. It occurred to me at that time that the important variable governing the chronic toxicity of formaldehyde in animals would probably be the body distribution of active material given the variety of reactions that it would be likely to undergo in transit, especially the formation of Schiff bases and methylol derivatives.

In that connection I was particularly intrigued by the possible difference in species response of rats versus mice. I wonder if this might not be an excellent test case to pursue mechanistic analyses of species differences (which I hardly need persuade you are an essential part of the rationale for extrapolation to human risk!) I am not aware of any premonitory information; but one in this case might look for differences in the chemical activity of nasal secretions as between the two species that might account for the difference in response. (Of course there could be one at the cellular level which would be much more difficult to determine). Since there would be a fairly ready bioassay for genotoxic activity it would probably not be too difficult to do at least a preliminary study on the complexes found in rat versus mouse tissue. Of course one also has to take into account the irritant and inductive effects of the formaldehyde itself in eliciting these hypothetically different secretions.

Probably less likely to be relevant in the present circumstance is the remarkable synergism between aldehydes and peroxides that was observed by Dickey et al in 1949. There is a hint there also of a spontaneous reaction between formaldehyde and molecular oxygen: I know this can go to formate at some measurable rate but I just do not know of any studies on the accumulation of peroxide intermediates. It is unlikely that the occurrence of peroxide is going to be a species differential; but of course the much larger question of enzymatic catalysis of the conversion of formaldehyde to still more active reagents is, I have to presume, both open and plausible.

I hope the more detailed footnotes do not obscure the primary challenge that is presented by the species difference in response.

Yours sincerely,

Joshua Lederberg

Encls.

See CIIT
(Chemical Industry Institute
of Toxicology)