Concerning a Model of Carcinogenesis *

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Several questions are raised concerning the Popp model of carcinogenesis by polycyclic hydrocarbons.

There have been numerous efforts aimed at correlating some physico-chemical property of the polycyclic aromatic hydrocarbons with carcinogenic potency [1–9]. Recently, Popp has published several papers in this and other journals proposing a model of chemical carcinogenesis in which a resonance effect between the hydrocarbon and a bioreceptor plays a key role [10–14]. His model is based on a self consistent field molecular orbital study of the π-electron systems of 3,4-benzpyrene (3,4BP), which is a strong carcinogen, and 1,2-benzpyrene (1,2BP), which is completely noncarcinogenic. Popp's method was to examine those molecular properties which have significantly different values for the two hydrocarbons, and to regard these characteristics as perhaps being crucial to the carcinogenic mechanism. The model is an interesting one, so it seems worthwhile to see how well the hypothesis applies to more than just these two members of the polycyclic hydrocarbon family.

Mentioned [12] as significant differences between 3,4BP and 1,2BP, and hence of potential biological significance, are the following: 1. 3,4BP has a lower ionization potential than 1,2BP; 2. the p and α singlet excited states of the π-electron system lie lower in energy for 3,4BP than for 1,2BP; and 3. there is a large difference in free valence for a particular carbon in 3,4BP relative to the free valence in 1,2BP for an equivalent position, in a sense made precise in Popp's article.

Let us consider how these points hold up when they are applied to a larger family of similar compounds. First, with respect to ionization potential, the Pullmans have demonstrated [15] that there is little or no correlation between ionization potential and carcinogenic activity for the polycyclic hydrocarbons. It suffices for our purpose to note that the experimentally determined ionization potentials for the noncarcinogens naphthacene, pentacene, and perylene all have ionization potentials which are lower than that of 3,4BP [15]. Second, with regard to the excited state energies, the noncarcinogenic five ring compound pentacene has both α and p singlet excited state energies lower than 3,4BP, as determined experimentally from ultraviolet spectra [16]. Third, the "free valence" as calculated by Popp does not conform to the standard definition for free valence. Popp defines and calculates [12] the free valence of a carbon in terms of a sum of bond orders between the carbon and *all* other carbons in the molecule. In the standard definition for free valence [17, 18] the summation is *only* over those carbon centers which are adjacent to the carbon in question. When the usual definition of free valence as a measure of chemical reactivity is used, then Popp's SCF bond orders lead to values which show an unremarkable difference between 3,4BP and 1,2BP for the center which he singles out. Popp is almost certainly correct in maintaining that there are several necessary conditions that must be met by a polycyclic hydrocarbon in order for it to be carcinogenic, as proposed, for example, in the very successful theory of the Pullmans [1]. The Popp model may well reflect some of the truth, but the difficulty here suggested in the form of a noncarcinogen meeting the criteria which are satisfied by 3,4BP, is a problem that should be faced.

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* *c.f.* Note on page 454.

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