Correlation between the carcinogenicity of organic substances and their spectral characteristics

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Summary. A correlation between the carcinogenicity of organic substances and their UV-absorption characteristics has been established. It is found that chemical carcinogens have absorption maxima in the wavelength region of 206–248 nm. On the basis of revealed correlation, a mechanism of chemical carcinogenesis is proposed.

We have established recently an empirical correlation between the average quasi-valence number of organic substances and their carcinogenic properties[1]. On the basis of the IARC data[2], we found that noncarcinogens have the average quasi-valence numbers (Z*) higher than 3.20, while potential carcinogens have Z* lower then 3.20. Most of the exceptions, which comprise about 8% of some 400 analyzed substances, have Z* in the interval: 3.20±0.3.

One of the serious shortcomings of our findings lay in the fact that we could not fully explain the cause of the correlation established. For this reason we turned our attention to the mechanism of carcinogenesis.

Analyzing known facts about the induction of carcinomas by highly different agents, such as UV-radiation, chemicals and viruses, we come to the conclusion that the hypothesis according to which an oncogenic information ('cancer' DNA) is present in the cell prior to action of any carcinogenic agent[3], seems most probable.

We assumed that the 'cancer' DNA is a part of normal cell's DNA, but that it is inactive[4]. In well differentiated cells of higher organisms, it is, by our assumption, a superfluous part of DNA firmaly blocked. This part played some role at certain stages of evolution, or could still play a limited role during the early stages of embryonal growth. Consequently, we supposed that the most important step in the process of carcinogenesis is deblocking of 'cancer' DNA. We also assumed that the mechanism of deblocking is independent of the nature of carcinogenic agent. However, since the UV-radiation is a purely physical agent, characterized only by 1 parameter - energy, its deblocking action must be due to this parameter. From the foregoing assumptions, it follows that deblocking action of other carcinogenic agents, chemical substances, for example, must also be due to some characteristic energy features of chemical carcinogens. Since the UV-radiation which is most effective in inducing cancer lies in the region of 233–278 nm[5], we have analyzed the UV-absorption spectra of chemical carcinogens in order to see whether they have peaks in this spectral region, and whether they differ in this respect from noncarcinogens. The results of the analysis are given in tables 1–3. As one can see, there is a strong correlation between the UV-spectral characteristics and carcinogenic properties of organic substances listed in the tables. On the basis of available data, we can formulate the following conclusion: organic carcinogens have absorption peak(s) in spectral

Table 1. Correlation between spectral caracteristics and carcinogenic properties of some aromatic hydrocarbons

Substance	λ_1 (nm)	λ_2 (nm)	λ_3 (nm)	λ_4 (nm)	Carcinogenicity
3,4-Benzophenanthrene[1]	218	281	303	353	+
Phenanthrene[2]	219	251	292	330	+
Naphthalene	220	274	297		+
Chrysene[1]	223	267	306	360	+
1,2,5,6-Dibenzanthracene[3]	223	299	394	402	+
Antanthrene[4]	231	310	433		+
Pyrene[1]	241	272	333	362	+
Anthracene[2]		251	355		−
Perylene[3]		253	338	435	−
Triphenilene[1]		257	273	333	−
Pentaphene[3]		258	314	345	−
Naphtacene		274	472		−
1,2-Benzopenthacene[4]		291	332	552	−
Penthacene[3]		303	427	581	−
Coronene		305	342	427	−
Ovalene			348	457	−

Structural isomers are indicated by the numbers above corresponding names of substances.

Table 2. Correlation between spectral caracteristics and carcinogenic properties of some organic substances

Substance	λ (nm)	Carcinogenicity
Thioglycolic acid	200	−
Glycolic acid	200	−
Acetylsalicylic acid	202	−
Serine	203	−
Propionic acid	204	−
Acetamide	205	−
Propiolactone	209	+
2-Nitrophenol	209	+
Butyrolactone	209	+
Fluoroanthrene	209	+
Phenol	210	+
3,4-Benzopyrene	210	+
Naphtylamine	212	+
Azoxymethane	217	+
Furanes	208–220	+
Phenanthrene	219	+
Tetrachlorethane	221	+
2-Aminophenol	224	+
3,17-Dihydroxy-16-hydroxy-imino-androst-5-ene	224	+
Steroids	225	+
Hydrazine	227	+
Acridine	249	−
Menadione (vitamin K)	249	−
Mycomycin	256	−
Uracil	263	−
Ascorbic acid (vitamin C)	264	−
Barbituric acid	256	−
Riboflavine	445	−
β-Carotine	452	−

In the measurements we used common solvents (Scott[6]).

Table 3. Correlation between spectral caracteristics and carcinogenic properties of steroid hormones

Substance	λ (nm)	Carcinogenicity
Estradiol	225	+
Testosterone	238	+
Mestranol	242	+
Progesterone	240	+
Medroxyprogesterone acetate	240	+
Dimethysterone	240	+
Norethysterone	240	+

Data concerning these hormones are taken from IARC Monographs, vol. 6[2].

regions of 206-248 nm. The boundaries of this energy region are purely empirical. There are several exceptions to this rule in the vicinity of the border wavelengths.

From table 1, one can see how the above rule solves the problem of structural isomerism, which cannot be taken into account by the criterion based on the average quasi-valence number.

The other, more important benefit from the established correlation could be connected with the mechanism of carcinogenesis. The discovery of correlation gives support to the basic assumption made on the mechanism of carcinogenesis. It proves the similarity of action for different carcinogenic agents. Additional facts in favour of postulated mechanism are found in table 3, where relevant spectral data and carcinogenic properties of some steroid hormones are given. Most of the listed hormones are carcinogenic, in agreement with the rule stated above. On the other hand, it is well known that hormones play an important role in differentiation, in process of deblocking the relevant part of DNA. Such a deblocking represents decisive step in carcinogenesis, as envisaged by the proposed mechanism.

By combining findings from this paper with those of preceding work[1], we can state the following rule: if the organic substance has the average quasi-valence number less than 3.20, and if its spectrum shows absorption peak(s) in the wavelength region of 206-248 nm, it should be considered (with high probability) as carcinogenic. The organic substance which does not satisfy the above requirements should be noncarcinogenic.

On the basis of the analyzed organic substances considered in IARC Monographs[2], we found that the above rule is fulfilled in 91% of the cases. While our finding could be used for preselection of organic substances with respect to carcinogenicity, its main importance is, however, related to the mechanism of carcinogenesis.

The 'island' of chemical carcinogenicity, encompassed by the average quasi-valence number and the UV-spectral requirement, could be taken as a guide for the further studies of the basic cancer mechanism.

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4 Similar hypothesis already exists, see B.J. Culliton, Science *177*, 44 (1972).
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Quantitative aspects of structural changes in chorioallantoic placenta of the rat during its development[1]

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Summary. Volume analysis of chorioallantoic placenta of the rat from day 12 through day 22 of fetal development shows quantitatively the changes in volume density of fetal and maternal parts, and changes of volume fractions of structural components along with the increase of absolute volume of the placenta.

The placenta differs from other organs in its origin. It develops from maternal and fetal tissue into an intergral morphologically differentiated organ. Considerable changes in the quantitative relation between the parts of maternal and fetal origin have been observed in the course of complex developmental processes of chorioallantoic placenta of the rat. The structure of that placenta is also subjected to various changes, and characteristic histomorphological features arise in both parts of the placenta during its development[2]. The kinetic of these developmental processes is also manifested by constant changes in quantitative relations of these structural components[3]. The quantitative changes of maternal and fetal parts, as well as those of their individual structural components, were investigated by volumetric analysis[4] in the chorioallantoic placenta of the rat from the initial stage of its development until parturition.

Material and methods. Placentae of Wistar rats were taken on each day from the 12th to the 22nd day of embryonic development. They were fixed in Gendre's solution and embedded in paraffin. The 7 µm thick serial sections were stained with hematoxylin eosin and Masson's trichrome stain. In addition PAS reaction and PAS reaction with the diastasis test were made.

Weibel's multipurpose test system was used for point counting volumetry[5,6]. For each day of embryonic development, the relative volume density of the following components was determined: a) maternal and fetal parts, b) their integral parts: decidua basalis and its blood vessels, labyrinth, basophil, giant and glycogen cells, and spaces arising from cytolysis of glycogen cells. By the same method the absolute volume of placenta was determined on days 13, 16, 19 and 22 of embryonic development. Statistical evaluation of the data included calculation of arithmetic means of results obtained for each component by day of observation, and the SE.

Results and discussion. The results of volumetric analysis display numerically the constant changes in the quantitative relations of integral parts of the placenta from the beginning of its formation to parturition. In the initial developmental stage, the chorioallantoic placenta consists almost entirely of maternal tissue ($V_{Vm}0.94,\pm0.02$) with a minimum volume participation of fetal tissue ($V_{Vf}0.0$), (figure 1). In the following days, this relation rapidly changes in favour of the fetal part, so that on the 14th day the fetal part ($V_{Vf}0.53,\pm0.03$) exceeds the maternal ($V_{Vm}0.47,\pm0.03$). The ratio between fetal and maternal elements continues to change in the same direction. From the 16th day of embryonic development until parturition, the relation between fetal and maternal parts does not show any essential changes. The volume density of the fetal part then amounts to $V_{Vf}0.96,\pm0.03$. These data indicate that, at the end of embryonic development, the relation between structural elements of maternal and fetal origin is inversely proportional to the relation of these elements in the beginning of placental development.

The volume analysis of structural elements of maternal origin shows (figure 2) that, in the initial stage of placental development, the decidua basalis has the greatest share ($V_{Vd}0.79,\pm0.02$) and the decidual blood vessels the smaller