substances. Another cause of this non-susceptibility may reside in the egg nucleus, since the fish egg completes the maturation divisions after the spermatozoon has entered the egg. However, in 2 experiments with Crenilabrus pavo, we observed that about one-fourth of the pretreated eggs gave rise to embryos with disturbances of the skeleton. When, on the other hand, the spermatozoa are pretreated (2 min in 10^{-4}–10^{-5} M thalidomide) the results were very clear, and in agreement with those previously obtained with sea urchin larvae[6]. After pretreatment of the sperm, the differentiation of the notochord becomes disturbed. Also the general development of the larva is clearly affected and the development of the various larval organs is delayed or suppressed. A very evident effect of pretreatment of the spermatozoon is the defective differentiation of the distal part of the notochord (cf. figures 1, control, and 2, thalidomide).

B. Treatment with thalidomide after fertilization. A treatment for only 3 h, started at various intervals after fertilization, brought about severe disturbances of the development of the notochord and the resorption of the yolk sac was likewise affected. There was, moreover, an accumulation of pigment; figures 3a (control) and 3b (10^{-5} M thalidomide for 3 h) show the effect of thalidomide on the differentiation of the embryo. Cleavage was influenced negatively and hatching became delayed, which indicates that not only the mesoderm is affected by the drug. Though the treated embryos hatch into free-swimming larvae, the lethality is high and no adult animals are likely to be formed.

Discussion. It is a remarkable fact that the response to treatment with thalidomide during embryonal life of warm-blooded animals displays a rich variation, which is evidently correlated with the particular strain of animals used in the experiments[2–4]. We introduced gametes and embryos from sea urchins as a material for testing toxicity on the cellular and embryonal level[6,7].

The present experiments with marine fishes corroborate the results from our previous work on echinoderms. The species of fishes used are very different and they live and reproduce under very different environmental conditions. The response to thalidomide was uniform, and not species-related, and the main morphogenetic effects were concentrated to the differentiation of the mesoderm. The full effect was obtained already by pretreating the spermatozoon for only 2 min in a 10^{-5} M solution of thalidomide. Since the spermatozoon mainly consists of a nucleus, it is warranted to conclude that thalidomide interacts with the genome, and particularly with the genes which govern the differentiation of the skeleton.

7 B. E. Hagström and S. Lönning, Experientia *32*, 744 (1976).

Simple theoretical criterion of chemical carcinogenicity

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Summary. The correlation between the average quasi-valence number and carcinogenicity of organic compounds has been established and discussed.

In our recent work[1], we have established the correlation between the pseudoatomic potential[2] and carcinogenicity. The complex form of the pseudoatomic potential, employed in the previous work, contained Coulomb interaction and Pauli repulsion components, and it was rather difficult for calculation by non-specialists.

Since in this potential the average quasi-valence number Z*, defined as:

$$Z^* = \frac{\sum_{i=1}^{m} N_i Z_i}{\sum_{i=1}^{m} N_i} \qquad (1)$$

where N_i is the number of atoms of the i-th type in the given molecule, Z_i is the number of valence electrons in the atom of the i-th type[3], and m is the number of chemical elements in the molecule, plays a very important role[4,5], we decided to look for the possible existence of a correlation between the average quasi-valence number and carcinogenicity of chemical substances.

Calculated values of the average quasi-valence number for about 400 organic compounds of known carcinogenic activity strongly correlate with their carcinogenic properties. In the table, we present data for the analyzed compounds biologically tested in mammals. On the basis of available biological results, we have concluded that potential carcinogens have Z* values below 3.20, while noncarcinogens are characterized by Z* above 3.20. The borderline value of 3.20 has been chosen on the basis of empirical biological data. The Lyon (International Agency for Research on Cancer) criterion for carcinogenicity has been used in this work.

The classification of about 400 organic compounds[6] into 2 categories: potential carcinogens and noncarcinogens is connected with an error of about 8%. Corresponding error for compounds tested in mammals and reported in Lyon's monographs is only 5%.

In connection with the above average quasi-valence number criterion, one should notice the following:

a) The criterion is based on the use of molecular formula and it is insensitive to the effects of isomerisms.

b) Investigations of the primary molecular form alterations due to metabolic processus have shown that the average quasi-valence number of original molecule is not changed by more than 10%. This explains some of the

1 V. Veljković and D. I. Lalović, Cancer Biochem. Biophys. *1*, 295 (1976).

2 V. Veljković and D. I. Lalović, Phys. Lett. *45A*, 59 (1973).

3 In case of halogen elements instead of Z = 7, Z = 1 should be taken.

4 V. Veljković, Phys. Lett. *45A*, 41 (1973).

5 V. Veljković and D. I. Lalović, Phys. Rev. *11*, 4242 (1975).

6 In the table we included all those substances for which we found well established biological data obtained from mammalian systems.

Correlation between the quasi-valence number and carcinogenicity of the organic chemical compounds

Compound	Molecular formula	Z*	Carcinogenicity[7,8]
Carbon tetrachloride	CCl_4	1.60	+
Chloroform	$CHCl_3$	1.60	+
Tetramethyllead	$Pb(CH_3)_4$	1.88	+
Tetraethyllead	$Pb(C_2H_5)_4$	1.93	+
Vinyl chloride	C_2H_5Cl	2.00	+
1,2-Diethylhydrazine	$C_4H_{12}N_2$	2.11	+
Polychlorinated biphenyls	$C_{12}Cl_{10}$	2.12	+
1,1-Dimethylhydrazine	$C_2H_8N_2$	2.17	+
Bis(chlormethyl)ether	$C_2H_4Cl_2O$	2.22	+
Chlormethyl methyl ether	C_2H_5ClO	2.22	+
N-Nitroso-di-n-butylamine	$C_8H_{18}N_2O$	2.28	+
Hydrazine	N_2H_4	2.33	+
Mirex	$C_{10}Cl_{12}$	2.36	+
Heptachlor	$C_{10}H_5Cl_7$	2.36	+
Aldrin	$C_{12}H_8Cl_6$	2.38	+
N-Nitrosodiethylamine	$C_4H_{10}N_2O$	2.47	+
Aramite®	$C_{12}H_{23}ClO_4S$	2.49	+
Benzene	C_6H_6	2.50	+
DDT	$C_{14}H_9Cl_5$	2.50	+
DDD (TDE)	$C_{14}H_{10}Cl_4$	2.50	+
Dichlorbenzene	$C_6H_4Cl_2$	2.50	+
Dieldrin	$C_{12}H_8Cl_6O$	2.52	+
Auramine	$C_{17}H_{21}N_3$	2.54	+
3,3'-Dimethylbenzidine	$C_{14}H_{16}N_2$	2.56	+
Methoxychlor	$C_{16}H_{15}Cl_3O_2$	2.61	+
Dihydrosafrole	$C_{10}H_{10}O_2$	2.67	+
4,4'-Methylenedianiline	$C_{13}H_{14}N_2$	2.67	+
4-Aminobiphenyl	$C_{12}H_{11}N$	2.67	+
Aminoazotoluene	$C_{14}H_{15}N_3$	2.69	+
Benzidine	$C_{12}H_{12}N_2$	2.69	+
Dimethylaminoazobenzene	$C_{14}H_{15}N_3$	2.69	+
Naphtylamine	$C_{10}H_9N$	2.70	+
Chrysoidine	$C_{12}H_{13}ClN_4$	2.73	+
N-Nitrosodimethylamine	$C_2H_6N_2O$	2.73	+
3,3'-Dimethoxybenzidine	$C_{14}H_{16}N_2O_2$	2.76	+
Urethane	$C_3H_7NO_2$	2.77	+
Benzanthracene	$C_{18}H_{12}$	2.80	+
Chlorobenzilate	$C_{16}H_{14}Cl_2O_3$	2.80	+
Yellow OB	$C_{17}H_{15}N_3$	2.80	+
Diacetylaminoazotoluene	$C_{18}H_{19}N_3O_2$	2.81	+
Sudan II	$C_{18}H_{16}N_2O$	2.81	+
Safrole	$C_{10}H_{10}O_2$	2.82	+
Azobenzene	$C_{12}H_{10}N_2$	2.83	+
Ethylenethiourea	$C_3H_6N_2S$	2.83	+
Sudan red 7B	$C_{24}H_{21}N_5$	2.84	+
Dibenzanthracene	$C_{22}H_{14}$	2.84	+
Aminoazobenzene	$C_{12}H_{11}N_3$	2.85	+
Propylthiouracil	$C_7H_{10}N_2OS$	2.86	+
Benzofluoranthene	$C_{10}H_{12}$	2.88	+
7H-Dibenzocarbazole	$C_{20}H_{13}N$	2.88	+
Oil orange SS	$C_{17}H_{14}N_2O$	2.88	+
Sudan brown RR	$C_{16}H_{14}N_4$	2.88	+
Acetamide	C_2H_5NO	2.89	+
Dibenzopyrene	$C_{24}H_{14}$	2.90	+
C. I. Disperse Yellow 3	$C_{15}H_{15}N_3O_2$	2.91	+
Dibenzacridine	$C_{21}H_{13}N$	2.92	+
4-Hydroxyazobenzene	$C_{12}H_{10}N_2O$	2.94	+
Citrus red No. 2	$C_{18}H_{16}N_2O_3$	2.97	+
Thiourea	CH_4N_2S	3.00	+
Cycasin	$C_8H_{16}N_2O_7$	3.03	+
Methylazoxymethanol	$C_4H_8N_2O_3$	3.06	+
Nitrosoethylurea	$C_3H_7N_3O_2$	3.07	+
4-Nitrobiphenyl	$C_{12}H_9NO_2$	3.08	+
Streptozotocin	$C_8H_{15}N_3O_7$	3.15	+
Methyl methanesulphonate	$C_2H_6O_3S$	3.17	+
Dicetene	$C_4H_4O_2$	3.20	—
Adenosin	$C_{10}H_{13}N_5O_4$	3.20	—
Salicyclic acid	$C_7H_6O_3$	3.26	—
Quintezene	$C_6Cl_5NO_2$	3.28	—
Piperonyl	$C_8H_6O_3$	3.29	—
Orange I	$C_{16}H_{11}N_2NaO_4S$	3.31	—
Dimethylsulphate	$C_2H_6O_4S$	3.38	—
Alizarin	$C_{14}H_8O_4$	3.38	—
Ammonium urate acid	$C_5H_7N_5O_3$	3.50	—
5-Nitro-2-furaldehide semicarbazone	$C_6H_6N_4O_4$	3.50	—
Carmoisine	$C_{20}H_{12}N_2Na_4O_7S_2$	3.51	—
Evens blue	$C_{34}H_{26}N_6Na_4O_{14}S_4$	3.51	—
2-(2-Furyl)-3-(5-nitro-furyl)acrylamide	$C_{11}H_8N_2O_5$	3.54	—
6-Mercaptopurine	$C_5H_4N_4S$	3.57	—
Sunset yellow FCF	$C_{16}H_{10}N_2Na_2O_7S_2$	3.59	—
Amido-G-acid	$C_{14}H_8O_4$		—
Amarath	$C_{20}H_{11}Na_3N_2O_{11}S_3$	3.71	—
Alizarin orange	$C_{14}H_7NO_6$	3.71	—
Xantin	$C_5H_4N_4O_2$	3.73	—
1-/(Nitrofurfurylidine)-amino/hydantion	$C_8H_6N_4O_5$	3.83	—
5-Nitro-2-furamidoxime	$C_5H_5N_3O_4$	3.76	—
Alloxantin	$C_8H_4N_4O_8$	4.08	—
Alloxan	$C_4H_2N_2O_4$	4.17	—

errors in theoretical prediction of noncarcinogenicity in case of chemical compounds having Z* close to the borderline value of 3.20.

c) In case of noncarcinogenecity the quasi-valence number is necessary and sufficient criterion. For carcinogenic activity it is necessary but not sufficient. For this reason, we classify all substances in potential carcinogenes and noncarcinogenes.

On the basis of results obtained we conclude that the average quasi-valence number of organic compounds can be used for theoretical prediction of potential carcinogenicity of organic compounds.

Very simple calculation of the average quasi-valence number (the ratio of the sum of all atomic valence electrons and the number of atoms in the given molecule) allows one to check and use the above correlation.

The established correlation could be of practical benefit in selection and use of organic compounds, as well as shedding some new light on the mechanism of carcinogenesis.

Interesting relationships between other biological activities of organic compounds and their average quasi-valence numbers have also been found and will be discussed elsewere.

7 IARC Monographs, Evaluation of Carcinogenic Risk, vol. 1–8. Lyon 1972–1975.

8 Ann. N.Y. Acad. Sci. *163*, 589 (1969).