The effect of thyroxine treatment in neonatal life on heat production in adult male and female rats

	Sex	Number of rats	Body weight (g)	Heat production/h kJ	kJ/m^2	J/g
Control	M	10	232.09± 9.51	9.44±0.47	17.74±0.80	40.91±1.94
	F	11	168.76± 4.50[f]	8.64±0.49	20.40±1.22[g]	51.41±3.10[f]
Neonatal thyrotoxicosis	M	8	212.75± 8.47	7.90±0.16[ad]	15.81±0.40[ce]	37.40±1.21[e]
	F	6	131.80±14.11[bef]	5.70±0.49[adf]	16.57±1.51[ce]	44.80±4.35
Neonatal caloric deprivation	M	6	223.53± 6.86	9.63±0.52	18.63±1.14	43.30±2.71
	F	7	167.63± 5.49[f]	8.26±0.27[g]	19.71±0.68	49.47±1.87[g]

[a] $p<0.001$–0.005
[b] $p<0.01$ –0.02
[c] $p<0.025$–0.05
} Comparison between control and neonatal thyrotoxicosis.

[d] $p<0.001$–0.005
[e] $p<0.025$–0.05
} Comparison between neonatal caloric deprivation and neonatal thyrotoxicosis.

[f] $p<0.001$–0.005
[g] $p<0.025$–0.05
} Comparison between males and females.

to use 40 ml oxygen. A correction was made for the temperature rise during the measurement. The volume of oxygen consumed was converted to standard condition and the result expressed in terms of international energy unit, joule (J), on the basis of per square meter of surface area and body weight. The square meter of surface area of the animals was calculated from the formula: (Animal weight$^{0.73}\times 10$) : 1000. Statistical evaluation of the data was done with Student's t-test.

Results. The results are summarized in the table. There was no statistically significant differences of body weights in male rats between control, neonatal thyrotoxicosis, and neonatal calorie deprivation. However, the b.wt of female rats treated with thyroxine at birth was smaller as compared with controls ($p < 0.02$) and neonatal rats undergoing caloric deprivation ($p < 0.025$). There was a significant sex difference of b.wt irrespective of treatments, with greater in the male than in the female ($p < 0.001$). The oxygen consumption was significantly reduced in rats made thyrotoxic with large doses of thyroxine during the neonatal period as compared with the control and the neonatal caloric deprivation.

Discussion. The administration of large doses of thyroxine into rats during the first few days of life produces many abnormalities in adults[1,2,5]. These usually include impaired body, pituitary and thyroid growth, diminished pituitary and serum thyrotropin concentrations, and a diminished serum thyroxine. Although the hypothalamic thyrotropin-releasing hormone is increased, its concentration in the circulating blood was found to be significantly reduced, suggesting that thyroid hypofunction secondary to decreased thyroid-stimulating hormone secretion may be the consequence of an impaired hypothalamic secretion of thyrotropin-releasing hormone[2]. This influence of the thyroid gland secretions can be measured readily by determining the rate of oxygen uptake in the animals. The present experiments clearly indicate a reduction of oxygen consumption in rats with neonatal thyrotoxicosis as compared with the controls.

Since in rats neonatal thyrotoxicosis is associated with early weight loss, it might be predicted that caloric deficiency or some factor related thereto, rather than excess of thyroid hormone, is responsible for the abnormalities seen in these rats later in the life. However, Azizi et al.[1] reported that food deprivation during the neonatal period sufficient to produce early growth curves comparable to those seen in thyroxine-treated pups failed to produce subsequent abnormalities in either thyroid-stimulating hormone secretion or thyroid ^{131}I metabolism. In addition, the present investigation shows that there was no difference in oxygen uptake between neonatal calorically-deprived rats and normal control ones (table). On the other hand, the amount of oxygen utilized in rats with neonatal thyrotoxicosis was significantly decreased as compared with calorically-deprived rats.

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DISPUTANDUM

A simple theoretical criterion of chemical carcinogenicity?

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Summary. The simple theoretical criterion for chemical carcinogenicity based on the 'average quasi-valence number' is discussed and shown to be inappropriate as a reliable indicator of carcinogenicity of any organic compound.

V. Veljković and D.I. Lalović[1] claim that the 'average quasi-valence number Z*' of an organic compound is a 'simple theoretical criterion for chemical carcinogenicity'. They define

$$Z^* = \left(\sum_i^m N_i Z_i\right) \Big/ \left(\sum_i^m N_i\right) \qquad (1)$$

where N_i is the number of atoms of the i-th type in the given organic compound, Z_i is the number of valence electrons in atom i, and m is the number of different elements in the molecule. For $Z^* > 3.20$, the compound will definitely be a 'noncarcinogen', since this condition is necessary and sufficient. On the other hand for $Z^* < 3.20$,

the compound will be a 'potential carcinogen'. This last condition is only necessary for carcinogenicity but not sufficient. This criterion is very simple to use and very attractive for many scientists impressed by the word 'theoretical'. It therefore seems worthwhile to examine the logical validity of this criterion and to investigate its usefulness on some examples.

To begin with, equation (1) depends solely on the molecular formula. Therefore all different isomers must have the same carcinogenic potential, which is not true. The number of the valence electrons of the halogens is arbitrarily set from 7 to 1 without further motivation. The reason is obvious, since otherwise compounds like CCl_4, $CHCl_3$ etc. would be declared as definite noncarcinogens, which contradicts experience. The problem of carcinogenic metabolites is elegantly circumvented by stating that it is sufficient to inspect only the parent compound, since Z* of any possible metabolite will not deviate by more than 10% from that of the parent, which is hardly to be believed.

Table 1. 'Potential cancerogens'

Compound	Formula	Z*
Hydrogen	H_2	1.00
Water	H_2O	2.67
Methane	CH_4	1.60
Ethane	C_2H_6	1.75
Pentose	$C_5H_{10}O_5$	3.00
Hexose	$C_6H_{12}O_6$	3.00
Palmitinic acid	$C_{16}H_{32}O_2$	2.16
Linolic acid	$C_{18}H_{32}O_2$	2.23
Stearinic acid	$C_{18}H_{36}O_2$	2.14
Arachidonic acid	$C_{20}H_{32}O_2$	2.30
Bilirubin	$C_{33}H_{36}N_4O_6$	2.83
Chlorophyll A	$C_{55}H_{72}MgN_4O_5$	2.51
Estradiol	$C_{18}H_{24}O_2$	2.45
Testosterone	$C_{19}H_{28}O_2$	2.37
Progesterone	$C_{21}H_{30}O_2$	2.38
N-Nitrosodiethylamine	$C_4H_{10}N_2O$	2.47
4-Nitrobiphenyl	$C_{12}H_9NO_2$	3.08
1.2-Benz-pyrene	$C_{20}H_{12}$	2.88
1.2-Benz-anthracen	$C_{18}H_{12}$	2.80

Table 2. Cancerogens[2] classified as 'definite noncancerogen'

Compound	Formula	Z*
Dimethylsulfate	$C_2H_6O_4S$	3.38
Thiouracil	$C_4H_4N_2O_2S$	3.69
N-(Carbamoylmethyl)-2-diazacetamide	$C_4H_6N_4O_2$	3.38
Guanine-3-oxide	$C_5H_5N_5O_2$	3.65
2-(5-Nitrofurane-2-yl)-1.3.4-thiadiazole-5-amine	$C_6H_4N_4O_3S$	4.00
3-Hydroxyanthranilic acid	$C_7H_7NO_3$	3.22
N-Nitroso-N-phenylurea	$C_7H_7N_3O_2$	3.26
4,4'-Dinitrobiphenyl	$C_{12}H_8N_2O_4$	3.46
Aflatoxine B_1	$C_{17}H_{12}O_6$	3.31

Moreover, there are some serious logical shortcomings. Although the limit has the exact value of 3.20, remarkably enough, the distance of Z* from this limit is of no importance; otherwise compounds like H_2 and CH_4 should be very strong potential carcinogens (table 1). Testing equation (1) for some examples reveals that the majority of organic compounds is classified as potential carcinogens, an absurdity. Nevertheless, $Z^* < 3.20$ being a necessary but not a sufficient criterion for classifying a compound as a potential carcinogen, one should fairly declare it not classifyable in this case, the statement being empty. The classification 'definite noncarcinogen', for which $Z^* > 3.20$ is necessary and sufficient, is very unreliable, too. There are numerous counterexamples in the literature[2], e.g. in almost every one of the cited groups of examples in the book of U. Wölcke (table 2). According to the literal meaning of equation (1), a chemical compound will more probably be a 'definite noncarcinogen' the more heteroatoms with electron lone pairs it has, or the more unsaturated it is. Converting a carcinogen into a harmless noncarcinogen, e.g. by introducing nitro- or nitroso-groups into it, does not seem to be a realistic procedure. For all these reasons, the average quasi-valence number is entirely unsuited as a criterion for the carcinogenicity of organic compounds.

After submitting this paper, 2 related papers came to my attention. Lyle and Lyle[3] likewise critically examine the average quasi-valence number. In the other paper, Veljković and Lalović[4] show dissatisfaction with it as well. Therefore they propose[4], as an additional necessary criterion for carcinogenicity, the existence of at least 1 UV-absorption peak in the 'purely empirical' range of 206–248 nm. Instead of elaborating on this known approach[5], they produce an experimentally correct classification for 52 substances by omitting data (e.g.: anthracene: 217, 221, 246 nm; perylene: 227 nm; triphenilene: >225 nm: $\varepsilon > 10000$; pentaphene: 247 nm; naphthacene: 215, 220, 228, 239 nm; coronene: 215, 228 nm; acetylsalicylic acid: 225 nm; acridine: >225: $\varepsilon > 10000$; ascorbic acid: 247 nm; riboflavine: 222 nm)[6], by interpreting non-measured data as non-existing (e.g.: pentacene, ovalene, β-carotine)[6] or by simply giving false data (e.g.: mestranol: the given value 242 nm[4] is a minimum with $\varepsilon \sim 0$, the peaks are 278, 287 nm[6] and a shoulder at 220 nm). It would seem difficult in praxi to predict the carcinogenicity of organic molecules by this improved method at a better chance than 1:1. There are far better theoretical[7] and experimental[2] clues to the carcinogenicity of chemical compounds in the literature.

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