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Relationship Between Specific Molecular Connectivity Indices and Teratogenicity, Carcinogenicity, and Mutagenicity of Carbamate Pesticides

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Molecular connectivity which is based on molecular topology and is an index of extent of molecular branching, is an important predictive tool in toxicology (Kier and Hall 1977; Rose and Jurs 1982; Sabljic and Protic 1982; Sabljic 1983). In the previous paper (Murakami and Fukami 1985) we introduced a concept of zero-order specific molecular connectivity which was obtained by dividing the zero-order molecular connectivity index (Sabljic 1983) with the number of non-hydrogen atoms in a molecule, and we calculated these values of representative pesticides and related compounds. It was found that carbaryl or Sevin, a broad spectrum carbamate insecticide with anticholinesterase activity, has very low zero-order specific molecular connectivity as compared with other pesticides.

In this report we calculate the zero-order specific molecular connectivity values of various carbamate pesticides. Furthermore, we derive the second-order specific molecular connectivity index which is obtained by dividing the second-order molecular connectivity index (Kier and Hall 1977) with the number of molecular fragments consisting of three adjacent and consecutive non-hydrogen atoms, and calculate these indices of the carbamates. The relationships between these indices and mutagenicity, carcinogenicity and teratogenicity of the pesticides as reported in the literature are examined.

MATERIALS AND METHODS

The zero-order molecular connectivity index, ${}^{0}\chi$, was calculated in the following fashion (Sabljic 1983). Each non-hydrogen atom in a molecule is described by its delta value, δ, which is equal to the number of adjacent non-hydrogen atoms. The index is then calculated for each compound according to the expression:

$$^{0}\chi = \sum_{j=1}^{n} (\delta_j)^{-0.5}$$

where "n" is the number of non-hydrogen atoms in a molecule. The zero-order specific molecular connectivity index is expressed as $^{0}\chi/n$.

The second-order molecular connectivity index, $^{2}\chi$, refers to molecular fragments consisting of three adjacent and consecutive non-hydrogen atoms (i,j and k)(Kier and Hall 1977). The value of c_{ijk} is computed as the reciprocal square root of the product of the delta values, $(\delta_i \delta_j \delta_k)^{-0.5}$. These c_{ijk} values are then summed by considering all molecular fragments in the molecule. The summarizing expression becomes

$$^{2}\chi = \sum c_{ijk} = \sum_{s} (\delta_i \delta_j \delta_k)_s^{-0.5}$$

where "s" is the number of molecular fragments consisting of three adjacent and consecutive non-hydrogen atoms in a molecule. The second-order specific molecular connectivity index is expressed as $^{2}\chi/s$.

RESULTS AND DISCUSSION

In Table 1 the zero- and second-order molecular connectivity indices and their corresponding specific indices of 12 carbamate pesticides are arranged in order of increasing the second-order specific molecular connectivity indices. Table 1 also provides an overview of the current status of mutagenicity, carcinogenicity and teratogenicity testing of the carbamate pesticides compiled by Woo (1983). It is the most comprehensive review on the toxicity of carbamates at present.

In a general way, it appears that a relationship does not exist between the specific molecular connectivity indices of the chemicals examined and their mutagenic activities. Also, a close correspondence cannot be found between the indices and carcinogenic potencies. However, it is clearly indicates that only two chemicals, carbaryl and benomyl, with the lowest zero- and second-order specific molecular connectivity indices show the teratogenic activity. More data are needed to establish the signifi-

Table 1. Zero- and second-order specific molecular connectivity indices and the data on mutagenicity, carcinogenicity and teratogenicity of carbamate pesticides[a]

Compound	$^0\chi$	$^0\chi_{/n}$	$^2\chi$	$^2\chi_{/s}$	Mutagenicity[b]		Carcinogenicity[b]	Teratogenicity[b]
					Ames	Other tests[c]		
Carbaryl	10.674	0.712	6.149	0.293	-	-,+	-,?	-,+ [d]
Benomyl	15.243	0.726	8.504	0.293	-,+	-,+	-,+	-,+
Carbofuran	11.759	0.735	7.437	0.298	-	-	-	-
Landrin	10.715	0.765	5.922	0.312	-	+		
Mexacarbate	12.293	0.768	6.862	0.312		-	-,?	?
Propoxur	11.259	0.751	6.183	0.325	-		-	
Diallate	12.008	0.801	6.133	0.341	+	+	-,+	-
Triallate	12.879	0.805	6.841	0.342	+	+		
Propham	9.682	0.745	5.475	0.342	-	-,+	-	?
Sulfallate	9.561	0.797	4.525	0.348	+	+	+	
Aldicarb	9.613	0.801	4.924	0.352		-	-	-
Methomyl	7.983	0.798	3.604	0.360	-	-	-	-

a Mutagenic, carcinogenic and teratogenic potencies: +, active; ?, questionable activity; -, inactive. A blank space indicates that these activities have not been reported. The results reported by various investigators are different in some cases.

b Mutagenic, carcinogenic and teratogenic potencies are quoted from a recent review article (Woo 1983).

c The tests include mutagenicity assays using microbial, insect and mammalian test systems except the Ames test (Woo 1983).

d The teratogenicity tests of carbaryl gave different results with species and by investigators. The positive result was obtained by using rabbit, dog, guinea pig and chick as test animals. Mouse, rat, hamster and monkey, and in some cases guinea pig and rabbit gave the negative result (Woo 1983).

cance of the specific molecular connectivity or other molecular topological values for evaluating teratogenicity of carbamate pesticides and other chemicals. We are now studying the structure-teratogenicity relationship of chemicals of various classes using more elaborate prediction methods.

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