Bull. Environ. Contam. Toxicol. (1985) 34:775–779

Environmental Contamination and Toxicology

Specific Molecular Connectivity Analysis of Pesticides and Related Compounds: A Preliminary Study

Makoto Murakami and Jun-ichi Fukami

The Institute of Physical and Chemical Research, Wako, Saitama 351, Japan

Molecular connectivity is a measure of extent of molecular branching. Its simple applicability and purely non-empirical nature make this method useful for toxicity prediction of chlorinated compounds of environmental concerns (Sabljić and Protić 1982; Sabljić 1983). This index is used as a descriptor for evaluating quantitative structure-activity relationships of compounds of various classes (Kier and Hall 1977). The molecular connectivity descriptor contributed most to the set of features used in the study of structure-activity relationships of N-nitroso compounds (Rose and Jurs 1982).

In this report we calculate molecular connectivity values of representative pesticides and their related compounds and compare them with the data of the uptake by cultured human cells (Murakami and Fukami 1978) and of the binding to cell proteins reported previously (Murakami and Fukami 1982). It can be found that the ratio of the zero-order molecular connectivity index (Sabljić 1983) to an information concerning the molecular size will serve as a useful measure for predicting a hazardous property of environmental chemicals. This novel index is termed as specific molecular connectivity.

MATERIALS AND METHODS

The zero-order molecular connectivity index, ${}^0\chi$, was calculated in the following fashion (Sabljić 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:

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

Table 1. Comparison of molecular connectivity indices and the data on cellular uptake and protein binding for pesticides and environmental chemicals

Compound	Cellular uptake[a]	Binding to cell protein[b]	$^0\chi$	$^0\chi/n$
DDT	Great	-	14.044	0.739
Dieldrin	Great	NT	13.533	0.712
Aldrin	Great	NT	13.086	0.727
PCB[c]	Great	-	13.448	0.747
Hexachlorobenzene	Moderate	-	9.464	0.789
Carbaryl	Moderate	+	10.674	0.712
Malathion	Moderate	NT	14.889	0.784
Parathion	Small	NT	13.596	0.755
Chlordimeform	Small	NT	9.845	0.757
2,4,5-T	Small	NT	10.715	0.765
2,4-D	Small	-	9.845	0.757
Benzo[a]pyrene	NT[d]	+	13.104	0.655

a Reference for cellular uptake: Murakami and Fukami 1978.

b Reference for binding to cell protein: Murakami and Fukami 1982. A plus sign indicates that the compound bound to proteins of human cells in culture; a minus sign indicates that the compound did not bind. NT, not tested.

c 2,4,5,2',4',5'-Hexachlorobiphenyl or an isomeric mixture of polychlorinated biphenyls containing approximately 54% chlorine by weight.

d NT, not tested.

where "n" is the number of non-hydrogen atoms in a molecule. The specific molecular connectivity index which is introduced here first, is expressed as $^0\chi/n$.

RESULTS AND DISCUSSION

The molecular connectivity indices of various pesticides and environmental chemicals are shown in Table 1 together with the summarized data on the cellular uptake and the binding to cell protein which have been published previously (Murakami and Fukami 1978,1982). It was found that the specific molecular connectivity indices of dieldrin (and aldrin), carbaryl and benzo[a]pyrene were lower than those of other chemicals examined.

The aim of this study was to determine the specific molecular connectivity index of carbaryl, and to compare

Table 2. Molecular connectivity indices of some carbamate insecticides and products of carbamate pesticides

Compound	$^0\chi$	$^0\chi_{/n}$
BPMC	11.389	0.759
Carbofuran	11.759	0.735
Propoxur	11.259	0.751
1-Naphthol	7.682	0.698
Ethylenethiourea	4.406	0.734

it with those of other pesticides and environmental chemicals. As reported previously, carbaryl bound to proteins of cells in culture (Murakami and Fukami 1982), although the compound was taken up moderately by the cells and the extent was considerably lower than those of organochlorine chemicals (Murakami and Fukami 1978). Carbaryl is biodegradable, its acute toxicity to mammals is quite low, and there is no evidence of its persistency in the macroscopic environments. Carbaryl has been reported to be non-mutagenic in bacteria (McCann et al. 1975; Shirasu et al. 1976; Marshall et al. 1976; Shirasu et al. 1977; Blevins et al. 1977; Moriya et al. 1983) and in Chinese hamster V-79 cells (Wojciechowski et al. 1982), and the data are inadequate for evaluation of the presence or absence of carcinogenicity of carbaryl (Tomatis et al. 1978). However, there is increasing concern over its reported teratogenic effects in mammals (Durham and Williams 1972; Fishbein 1976; Wilson 1977; Sternberg 1979). Furthermore, a placental transfer and a fetal accumulation of ^{14}C-carbaryl or its metabolites were revealed by autoradiography of the uterine cavity in pregnant rats and mice (Declume and Benard 1977). The high protein binding ability and low specific molecular connectivity value of carbaryl may serve as an index of teratogenicity or related toxicity of the insecticide.

Molecular connectivity indices of three carbamate insecticides other than carbaryl and two degradation products of carbamates, 1-naphthol and ethylenethiourea (ETU), are presented in Table 2. The specific molecular connectivity indices of the carbamate insecticides, BPMC, propoxur and carbofuran, and ETU, a degradation product of ethylene-bis-dithiocarbamates (Czeglédi-Jankó 1967), were higher than that of carbaryl. The major hydrolysis product of carbaryl, 1-naphthol, showed lower specific molecular connectivity than that of the parent compound. The naphthalene ring in carbaryl and 1-naphthol molecules may

contribute to their low specific molecular connectivities. We are now examining extensively the structure-toxicity relationship of carbamates of environmental concerns using the specific molecular connectivity method.

The molecular connectivity value is obtained by adding successively valences of non-hydrogen atoms in a molecule, and the value increases with increasing molecular size. To compare the molecular connectivity values among various molecules, therefore, the concept of "specific molecular connectivity" which is obtained by dividing the molecular connectivity value by the number of non-hydrogen atoms in a molecule, has to be introduced. Low specific molecular connectivity index indicates that the molecule has a massed and complicated structure. The specific molecular connectivity method would be of value to predict toxicity of compounds with such structures.

REFERENCES

Blevins RD, Lee M, Regan JD (1977) Mutagenicity screening of five methyl carbamate insecticides and their nitroso derivatives using mutants of Salmonella typhimurium LT2. Mutat Res 56:1-6

Czeglédi-Jankö G (1967) Determination of the degradation products of ethylene-bis-dithiocarbamates by thin-layer chromatography and some investigations of their decomposition in vitro. J Chromatog 31:89-95

Declume C, Benard P (1977) Foetal accumulation of [^{14}C] carbaryl in rats and mice. Autoradiographic study. Toxicology 8:95-105

Durham WF, Williams CH (1972) Mutagenic, teratogenic, and carcinogenic properties of pesticides. Ann Rev Entomol 17:123-148

Fishbein L (1976) Teratogenic, mutagenic, and carcinogenic effects of insecticides. In: Wilkinson CF (ed) Insecticide Biochemistry and Physiology. Plenum, New York, pp. 553-603

Kier LB, Hall LH (1977) The nature of structure-activity relationships and their relation to molecular connectivity. Eur J Med Chem 12:307-312

Marshall TC, Dorough HW, Swim HE (1976) Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants. J Agr Food Chem 24:560-563

McCann J, Choi E, Yamasaki E, Ames BN (1975) Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc Natl Acad Sci USA 72:5135-5139

Moriya M, Ohta T, Watanabe K, Miyazawa T, Kato K, Shirasu Y (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185-216

Murakami M, Fukami J (1978) Persistent pesticides and environmental chemicals are taken up to a greater extent than non-persistent compounds by cultured human cells. Bull Environ Contam Toxicol 19:423-427
Murakami M, Fukami J (1982) Carbaryl binds to proteins of human cells in culture but chlorinated organic chemicals do not. Bull Environ Contam Toxicol 28:500-503
Rose SL, Jurs PC (1982) Computer-assisted studies of structure-activity relationships of N-nitroso compounds using pattern recognition. J Med Chem 25:769-776
Sabljić A (1983) Quantitative structure-toxicity relationship of chlorinated compounds: A molecular connectivity investigation. Bull Environ Contam Toxicol 30: 80-83
Sabljić A, Protić M (1982) Molecular connectivity: A novel method for prediction of bioconcentration factor of hazardous chemicals. Chem-Biol Interact 42:301-310
Shirasu Y, Moriya M, Kato K, Furuhashi A, Kada T (1976) Mutagenicity screening of pesticides in the microbial system. Mutat Res 40:19-30
Shirasu Y, Moriya M, Kato K, Lienard F, Tezuka H, Teramoto S, Kada T (1977) Mutagenicity screening on pesticides and modification products: A basis of carcinogenicity evaluation. In: Hiatt HH, Watson JD, Winsten JA (ed) Origins of Human Cancer. Cold Spring Harbor Laboratory, Cold Spring Harbor, pp. 267-285
Sternberg SS (1979) The carcinogenesis, mutagenesis and teratogenesis of insecticides. Review of studies in animals and man. Pharmacol Ther 6:147-166
Tomatis L, Agthe C, Bartsch H, Huff J, Montesano R, Saracci R, Walker E, Wilbourn J (1978) Evaluation of the carcinogenicity of chemicals: A review of the monograph program of the International Agency for Research on Cancer (1971 to 1977). Cancer Res 38:877-885
Wilson JG (1977) Teratogenic effects of environmental chemicals. Fed Proc 36:1698-1703
Wojciechowski JP, Kaur P, Sabharwal PS (1982) Induction of ouabain resistance in V-79 cells by four carbamate pesticides. Environ Res 29:48-53

Received April 14, 1984; accepted August 8, 1984