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Computational Models and Databases for Studying Endocrine Disrupter Hypothesis

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The concept of endocrine disrupters (EDs) has not yet been completely understood. It is still gray in nature, includes many controversies, and even conflicts within the hypothesis. From quantitative structure activity relation (QSAR) view point this working hypothesis gives a big challenge, for conventional QSAR approach which is based on the lock and key concept is not at all relevant to this problem. A more so called systems approach which contains such new concepts as multi-gate points, multi-binding modes、post binding signal transduction pathways (PBSTPs), cross talks among them is needed. We have developed several data and knowledge bases and computational tools for studying the hypothesis based on this new approach.

The Endocrine Disrupting Chemical Database is a database of both natural and xenochemicals that were found some evidence of effects on endocrine systems. These chemicals were classified into such categories as drugs, pesticides, industrial chemicals, environmental pollutants, and metals with their names, synonimus, CAS Numbers, and structural data. The Relative Binding Affinity Database contains relative binding affinity data of various ligands and estrogen receptors based on literature search for in vitro competitive-binding assays. A QSAR model calculation for dioxins using CoMFA and binding energy calculation for ligands and estrogen receptors (alpha and beta) using a high quality approximation of the ab initio Molecular orbital method called the Fragment MO Method gave results that show good correlations with experimental data. The PBSTP database is under construction using our receptor database (RDB) and cell signal transduction database (CSNDB). These databases are linked by the WWW hyper link technology. The databases are available from our Web site (http://www.nihs.go.jp/hse/endocrine-e/index.html).

Recently variety of effects of estrogens on other systems than reproductive system are unveiling. In case of the cardiovascular system both “nongenomic” and “genomic” actions are being studied. This fact suggests that estrogen receptor binding is not at all enough for characterizing ED action. In order to build a platform for both theoretical and experimental studies of endocrine disrupters, it is necessary to extend our PBSTP database to cover cell-cell, tissue-tissue, and organ-organ interactions.

References

Kaminuma, T., Takai-Igarashi, T., Nakano, T., and Nakata, K. : Modeling of Signaling Pathways for Endocrine Disruptors, Bio Systems, Vol. 55, 21-31 (2000)

Kitaura, K., Ikeo, E., Asada, T., Nakano, T. and Uebayasi, M. : Fragment Molecular Orbital Method : An Approximation Computational Method for Large Molecules ; Chem. Phys. Letters 313 (1999) 701-706

Koyano, K., Nakano, T. and Kaminuma, T. : Electrostatic Potentials and CoMFA Analysis of Toxicity of Dioxins, Chem-Bio Informatics Journal Vol. 1, No.2 (2001)