*J. Toxicol. Pub. Health*
Vol. 17, Supplement, pp. 241-249, 2001

# Future of Toxicology and Role of Asian Chemical Safety Network

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***ABSTRACT*** *: Toxicology is under challenge from several new trends in science and technology, namely computer, the Internet, genome projects, genomic technologies, and combinatorial chemistry. These new trends will drastically change research style of toxicology. In addition to conventional uni cellular tests and animal tests using rodents, computer simulation, DNA chips (microarrays), in vivo tests using simple model organisms such as nematodesor flies become important routine screening tests. How to arrange these tests in tiers will become a new problem. Endocrine disruptors hypothesis is a good example for this kind of futuristic approach. Computer, particularly the Internet, is also enabling toxicologists and regulatory experts to collaborate more closely. The IPCS (International Program for Chemical Safety) which is a joint project of WHO, ILO and UNEP, is a well-known international collaborative research for chemical risk assessments. The GINC project of IPCS is an effort to utilize the Internet for such collaborations. Some efforts were also made to establish regional collaboration network in East Asia under this project.*

***Key Words*** *: Toxicology, Computer Simulation, Risk Assessment, Endocrine Disruptors, GINC, GINC Asia*

## I. INTRODUCTION

Chemicals are important ingredients of modern society. The pace that new chemicals are registered in an authorized database is less than 10 seconds per chemical. The number of such registration goes beyond 2000. Chemicals are used widely in daily life and are distributed and transported in both microscopic and macroscopic environments. Thus safe control of chemicals and/or chemical hazard management are becoming vital challenge to every country either developed or under developing. However such management is costly, for identifying hazard of chemicals and studying their effects on humans, wildlife, and the environment are not easy tasks. Management of their risks often requires international negotiations. Thus international collaborations on this subject are inevitable. IPCS and OECD existing chemicals testing and assessment projects are two most well known international programs for chemical safety.

Though OECD projects are projects of developed countries, IPCS is the core of all international collaborations for chemical hazard management worldwide. On behalf of Japanese Ministry of Health and Welfare the authors group, the division of Chem Bio Informatics, National Institute of Health Sciences is promoting one of the IPCS projects called GINC (Global Information Network on Chemicals). The aim of GINC is to support IPCS partners to use the Internet and to put relevant information contents on the network. Asia was assigned as the pilot study region from the very beginning. The author's group has been trying to carry GINC Asia project (or chemical safety network project in Asia) the mission of which is to enforce IPCS activities and to build a network among chemical safety experts in Asia. Because of limited budget the project is still in its start up phase and the region that was covered is still limited in East Asia.

Since the GINC and GINC Asia Project are based on IT (Information Technology) it is very natural to consider computer-based approach to toxicology and risk assessments. Salient feature of this approach is that once we succeed in developing some methodologies we can easily share the resultant systems, data, information, and knowledge by the network. Thus we can share the experts and expertise which are rare resource in almost every country in Asia at this time. In this paper we describe the state-of-the-art of GINC

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List abbreviations: CAS; Computer-based Assay Simulation, IPCS; International Programme for Chemical Safety, EDCs; Endocrine Disrupting Chemicals, GINC; Global Information Network on Chemicals.

Asia Project and sketch the outline the new computerized approach to toxicological and risk assessment problems taking endocrine disruptors (or endocrine disrupting chemicals, EDCs) as an example.

The potential hazardous effects that estrogen-like and androgen-like chemicals and other environmental hormone-like chemicals may have on wildlife and human health have attracted much attention of both the scientific community, particularly environmental toxicology, and the general public, Colborn (1996). Obviously conventional toxicological tests using animals such as fish, rats, or mice are not suitable to screen out endocrine disruptors from the so called existing chemicals, because the order of the latter chemicals is one hundred thousands. It is thus essential to develop some computer-based assay simulation (CAS) to pre-screen this large number of chemicals and reduce its number to that can be handled by conventional wet lab tests or the so called high through put screenings (HTPS) can be applicable (http://www.epa.gov/opptintr/opptendo/).

Some feasibility studies have been carried out from this viewpoint, but it was pointed out, that the methods are not sufficient for such purpose, Tattersfield (1997). The reason is that the well-known ligand receptor binding model is not enough to characterize the function of suspected chemicals. For example, two different ligands that bind to a same receptor may not result the same phenomena (endpoints). The effect of a ligand binds to a receptor differs at different tissues. Moreover these approaches do not consider the so-called cross talk among different signaling pathways. Such phenomena can only be handled by taking the cellular signaling systems, gene expression mechanisms and post translational processing into explicit consideration. We are developing information and computing infrastructure for this problem, Kaminuma (1999). This paper briefly introduces the author's approach.

## II. MATERIALS AND METHODS

### 1. GINC Project

GINC was originally considered in order to overcome the deficiency and frustration of information dissemination and information exchange among those who are working for sound management of chemicals in international arenas. The heart of the problem was that the relevant information had been delivered on printed matters, such as reports, monographs, newsletters and etc. However the number of these printings were limited. Sometimes they were costly. It took months to get them by mail ordering. Moreover they had not been revised so often. Electric media such as on-line databases or CD-ROMs had not been solved these problem either, for they had also been costly, their access had been limited, and their contents had not been up dated so frequently.

The idea of exchange chemical safety information by world wide computer network was first proposed to IPCS by the National Institute of Health Sciences (NIHS) of Japan. First preparatory meeting was held in Geneva right after the Stockholm Conference for Chemical Safety, which is later called First International Forum for Chemical Safety (IFCS I) where the framework of the project which was later named GINC was discussed. NIHS then hosted the first informal meeting for GINC in Tokyo during 7-9 December 1994. At this meeting, usage of the Internet was emphasized, and the goal of the first phase of the project was set to connect national, regional and international organizations and institutions working for chemical safety by the computer networks and exchange information more efficiently than conventional means that are based on papers, telephones, and faxes.

### 2. GINC Asia Project

This project started with the site visits of NIHS staff to East Asian countries and hosting meetings for chemical safety experts and computer technicians (Table 1). Through these activities number of countries, institutions, and individual experts who have participated in GINC Asia activities are increasing. Presently Korea, China, Japan, Philippines, Vietnam, Thailand, Singapore, Malaysia, Indonesia, Australia, New Zealand, Sri Lanka, and Bangladesh had some contacts. US organizations such as EPA, NIOSH, NIH, NIEHS, EU Chemicals and OECD are always invited as observers in addition to IPCS central unit partners from Geneva, i.e. WHO/PCS, ILO/CIS, and UNEP Chemicals.

**Table 1.** GINC Relating Meeting

| | |
|---|---|
| 1994.12 | 1st GINC Tokyo Meeting (Preparatory meeting) |
| 1995.12 | 2nd GINC Tokyo Meeting (Technical meeting) |
| 1997.10 | 3rd GINC Tokyo Meeting (GINC-Asia meeting) |
| 1998.11 | 4th GINC Tokyo Meeting (GINC-Asia meeting) |
| 2000.02 | 5th GINC Tokyo Meeting (GINC-Asia web master workshop) |
| 2000.02 | 6th GINC Tokyo Meeting (GINC-Asia manager meeting) |

Based on these activities an informal network of institutions and experts have been constructed, and many home pages have been put on the Internet. The NIHS group has tried to develop a portal for this group. One of the advantages of Internet/WWW technology is discenterization. Those who are interested in participating in this project can easily become members if they connect their machines to the Internet and open their home pages if possible. GINC Asia is expanding just by this spirit. This process is very informal. However we recommend that those who wants to become a relevant partner of GINC Asia must provide two kinds of information contents. One is a guide to their domestic information for foreign users in English, and another is a guide to internal information for domestic users in domestic language (Fig. 1). As an example we provide both English and Japanese home pages for chemical safety. We have also developed GINC home page.

### 3. Information System for GINC Projects

Several Unix machines are chosen for the network servers, databases, and WWW file managers. The main database management system is ORACLE. The inte-

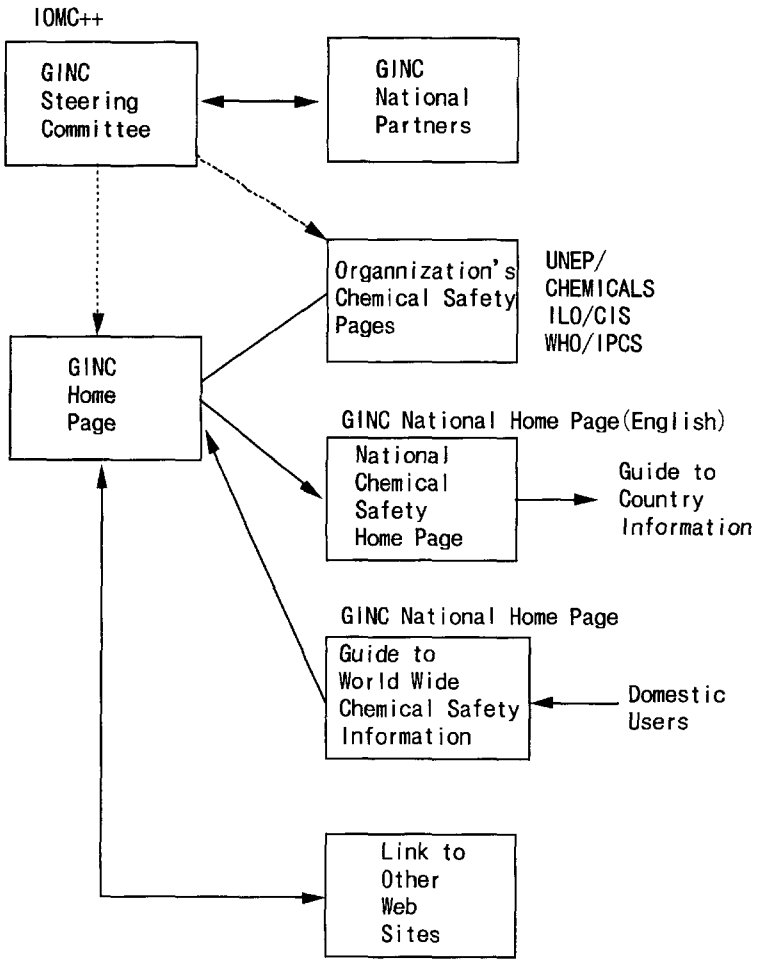


**Fig. 1.** Concept of GINC-Related Web Pages.

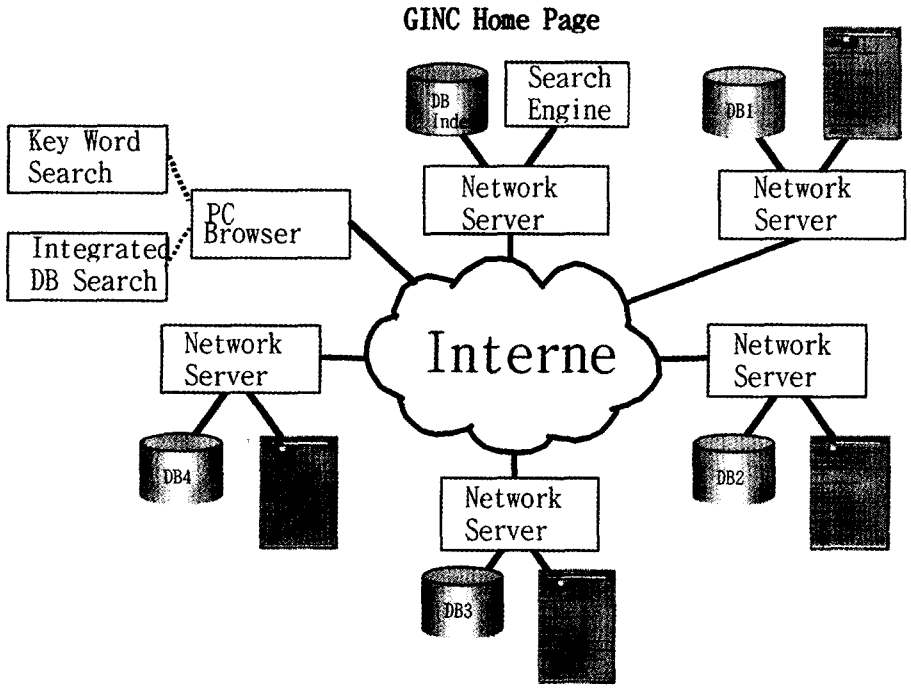


**Fig. 2.** GINC Home Page as a Portal.

grated database search mechanism can link databases on the Internet which have CGI to database management systems (Fig. 2). A database index file which is nothing but a table of chemical names and the database identifications is used to link different databases on the Internet. A freeware information collection robot called wget and a commercial software OPEN TEXT are chosen for making search engine. Same hardwares and softwares are used for GINC Asia Project (Home Pages).

## 4. Information and Computing System for Endocrine Disruptors Problem

Figure 3 shows the over all approach and information and computing infrastructure for EDCs research. The first step of this approach is to produce lists of probable endocrine disruptors, related chemicals and reference chemicals. Based on a literature survey of potential endocrine disruptors on different categories of chemicals that include synthetic estrogens for medicine, phytoestrogens, pesticides, industrial chemicals, environmental pollutants, and metals and their compounds, we made lists of the chemicals per category and add regulatory and other relevant information (http://www.nihs.go.jp/hse/endocrine-e/paradigm/paradigm.html). From these preliminary lists of endocrine disruptors a database was produced. This database has three dimensional structure data which is important for predicting chemical properties and QSAR. These structure data are mostly obtained by theoretical (*ab initio* molecular orbital) calculation.

For each of the potential endocrine disrupting chemicals the mode of action was surveyed, and their receptors were identified if possible. A molecular interaction (affinity binding) database that stores binding data of xenobiotic chemicals (ligands) and their target biomolecules (mainly receptors) has been developed. This database is called Binding Affinity Database. We consider the three basic modes of actions in our model; 1) interaction with extracellular binding proteins, 2) interaction with enzyme systems that metabolize hormones, and 3) interaction with hormone receptors. Best examples are given by estrogen case.

Those receptors or interacting biomolecules are the "gate-points" at which some signals will be evoked by these xenobiotic chemicals. These chemical signals will be transmitted or amplified by cellular signaling networks, will transcribe mRNA, will produce a protein, and will eventually effect the organism. The effects may be gene mutation, apotheosis, cancer, abnor-

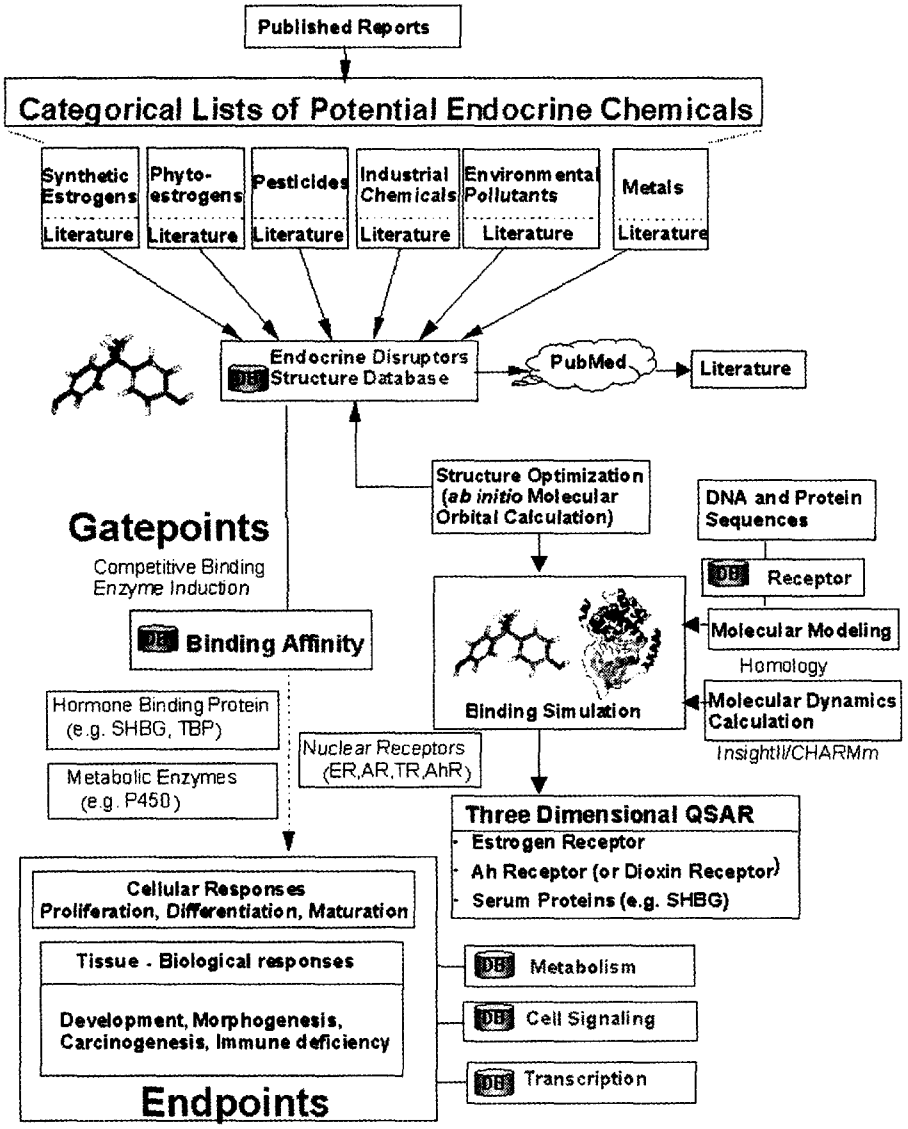


**Fig. 3.** Conceptual framework of the research support system for endocrine disruptors.

mal development, organism lethality, reproductive failure, etc. Such effects are called endpoints.

The problem is then to find causal network system that enables one to trace the effect of exogenous endocrine disrupting chemicals on biological signaling systems at the cellular and organism levels. For that purpose we need complete a knowledge base and databases that can describe the complete bio-signaling systems. However at present such a network system is incomplete. Instead we can only find receptor databases, metabolic pathway databases, cell signaling pathway databases, transcription factor databases. Among these we have developed a receptor database, Nakata (1999), and cell signaling database, Takai-Igarashi (1999), by ourselves. These knowledge and database system were developed almost independently. However the emerging WWW technology enables us to integrate these systems into an integrated system complex, which will become the infrastructure for endocrine disruptors research.

## III. RESULTS

In June 1995 GINC home page was first designed and implemented on the NIHS server under the collaboration with ILO/CIS, UNEP/IRPTC, WHO/PCS,

and NIHS. NIHS then hosted the second GINC meeting in Tokyo during 13-14 December 1995. Since that time because of the rapid progress of the Internet many organizations and institutions opened their home pages where some useful information were put on. It became very realistic to send electronic mails crossing borders, to transfer documents via computer network in the so-called file transfer protocols, and to disseminate reports and monographs in Web pages in addition to conventional databases or CD-ROMs. Also the WWW and its browser technology is replacing concept of "central system" to virtual center which is nothing but Web pages and databases at different sites connected by the Internet. Thus part of the preliminary goal of the GINC project, that is to say, providing relevant information on chemical safety in computerized forms, strengthen on computers and linking these computer sites by world wide computer network was partially fulfilled.

The integrated search mechanism of chemical databases was implemented and was first demonstrated at IFCS Inter Sessional Group held in Camberra in March1996. The first version of the dedicated search engine was first implemented at the time of next IFCS Inter Sessional Group held in Yokohama in November 1998. However this system was too slow for practical purpose. A new system with dedicated hardware and more powerful software was implemented last year. At present this system is also in operation.

The home page of GINC Asia has also been imple-

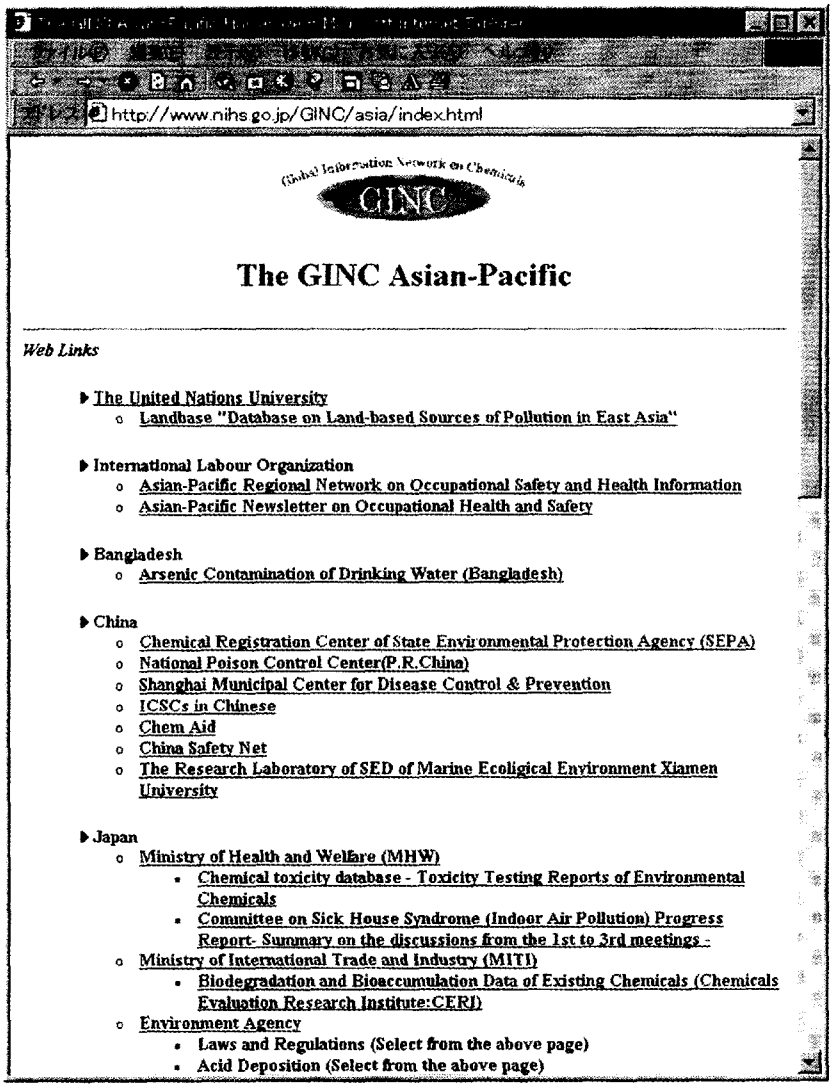


**Fig. 4.** GINC Asia Home Page.

mented at the NIHS server machines by our group under collaboration with the so-called GINC Asia Partners (See Fig. 4). At present several collaboration themes using this network are under discussion among the Partners.

(1) Provide computers, link them to the Internet, and provide relevant information for chemical safety on these machines.

(2) Exchange pesticides information collection.

(3) Link chemical databases in different languages on the Internet.

(4) Develop common environmental health maps using Geographic Information System (GIS).

(5) Collect human data for chemical exposures.

As for endocrine disruptors research support systems are concerned we have implemented the Endocrine Structural Database, the Receptor Database and the Binding Affinity Databases. With these basic systems one can have fairly wide view on how xenobiotic endocrine modulating chemicals interact with their receptor molecules. At present we are studying three typical cases: estrogen like chemicals and the estrogen receptors, dioxins which interact with Ah receptors, and the interaction of hormone transport proteins. For these studies we use various computational tools such as CoMFA, *ab initio* MO methods, Discover/Insight II, etc. We get good results in correlating the experimental data and theoretical calculations estimating binding affinity and predicting the toxicity of the dioxins.

## IV. DISCUSSION

GINC and GINC Asia home pages have been in operation in more than 5 years. Publicity of these pages and the projects are gradually penetrating into both regulatory and scientific society. The new tools we have developed for the GINC project, the integrated chemical databases and the domain specific search engine are also in daily operation. However as the Internet revolution penetrate deeply into our working environment, the distinction between the GINC project and the general Internet environment has been blurred in worldwide. Therefore our new approach to promote GINC and GINC Asia is to focus our effort on attacking more specific problems. We set high priorities on several areas which are relevant in East Asia.

For example pesticides or safe use of pesticide chemicals are undoubtedly considered as the most important theme. Environmental disruptors (EDCs) study will be considered as the second, for EDCs include wide variety of chemicals including pesticides, industrial chemicals, and environmental pollutants. Dioxins and related chemicals are one important chemical family of this kind. Since these chemicals are of interests in both underdeveloped and developed countries in East Asia. Thus these are very good collaborative research theme in this area and among toxicology and computer science researchers or the so-called bioinformatis experts. The author would like to propose some concrete plan to accomplish such a goal.

First the author suggests to organize some committee for IPCS in Asian or at least in East Asian Region. The IPCS activities have not yet been so well known in this area. Not so much experts have ever been involved in the IPCS core activities such as risk assessments. So far Asian countries have mostly been acceptors of IPCS products but not the donors. However there now exist high possibilities that Asian countries can directly contribute to IPCS core activities. One example is human data collection that Dr. T. Meredith, the newly appointed director of IPCS, is proposing. There exists many occupational, health, medical, or environmental institutions in East Asian countries which may collaborate for such human data collection.

The function of IPCS Asia Committee may be very much like that of IPCS PAC (Program Advisory Committee) which consists of managers from various institutions which collaborate IPCS activities. Right now the number of PAC members are limited. Even so it is not easy to organize the full-scale formal meetings. Therefore PAC steering committee which consists of seven members (from seven main donor countries) was organized, and some "Informal Consultation Meetings" have been held time by time. These PAC and PAC related meetings may be considered as models for the IPCS Asia Committee. The function of this committee is to promote usage of IPCS products and to foster collaborations for various IPCS and related actives. Promoting GINC Asia Project is a highly prioritized task of this committee, for information network provides infrastructure for

collaboration among participating institutions.

Another recommended action is Webmaster's efforts to start up or shape up their Web sites. The authors group is keeping in touch with the Webmasters of GINC Asia partners for this purpose. NIHS group is revising the GINC Asia and other related pages constantly. This group shall continue technical supports to other GINC Asia partners if they are necessary, to host GINC Meetings if the budget allows doing so, and to support for other GINC Asian partners to host GINC Asia related meetings. This may include making agenda, assisting technical sessions as instructors, and providing workshop materials.

After the 5th and informal GINC Asia Meetings several countries offered to host a GINC meeting or at least showed great interest in doing so. One consequence is this workshop which is arranged by Dr. Pu Young Kim who attended one of the above meetings. The author also hopes that the Korean experts play important roles in GINC Asia. They may include researchers from KFDA (Korea Food & Drug Administration) and NIER (National Institute of Environmental Research). Some Chinese senior researches expressed their will to host the next GINC Asia Meeting. As was stated in the above general rules, this meeting may be coupled with some IPCS meeting like that of CICAD.

As a more ambitious plan the author propose to work endocrine disruptors problem together among Asian experts. Our research support system for this problem will be considered as a step stone to this goal. The author's group is now trying to develop

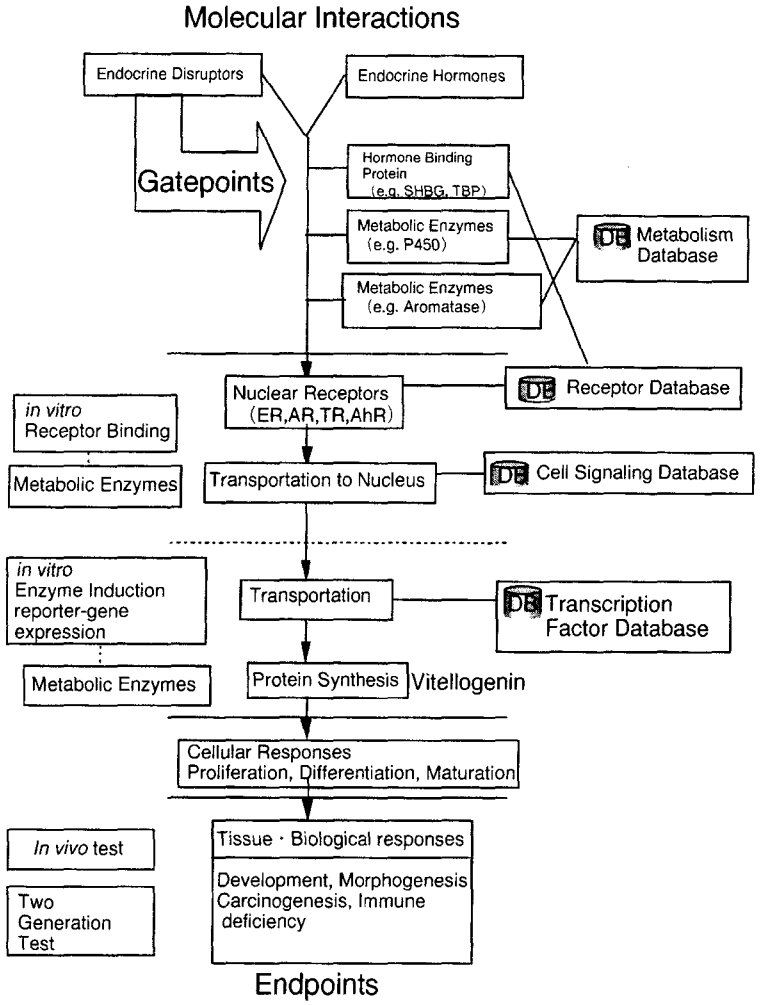


**Fig. 5.** Simplified diagram that represent molecular interactions and signal pathways of endocrine disruptors and their stimulus.

some computerized system that links gate points to endpoints.

Endpoints are the biological phenomena or simply makers by which researchers identify positive effects of chemical agents. Since the mechanisms of endocrine modulation due to xenobiotic chemicals have not been totally understood, we do not exactly know proper endpoints. Nevertheless wide varieties of endpoints were proposed by experimental researchers. From purely theoretical viewpoint, it would be possible some day to identify signal pathways to the reactions of biological systems at molecular base. Of course cell-cell interactions also play very important roles here. However our current knowledge is far from such view points. We simply take these pictures as conceptual frame for the future studies (Fig. 5). Current lack of knowledge on signal pathway at organism level and the fact that many assay experiments are still on going make it difficult to develop reliable computer system to predict organism reaction to endocrine disrupting chemicals at organism level. Our current system is only relevant to predict cellular response to exogenous hormones. Predicting higher level responses that are characteristic to multi-cellular organisms such as cancer or reproductive abnormalities are our next research targets.

## ACKNOWLEDGEMENT

The author thanks to Dr. Miyako Yamamoto and Ms. Chiyoko Ohtake who have developed and managed the GINC Asia Home Page. The author also thanks to national GINC Asia partners.

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