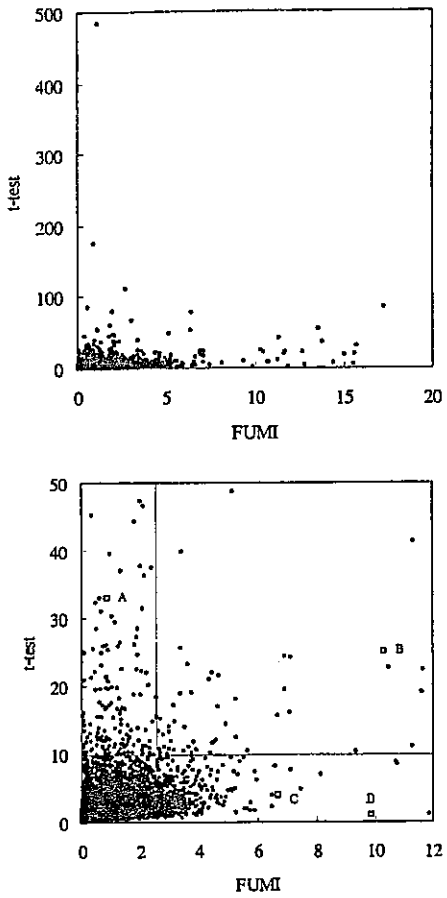

Fig. 4 Correlation between FUMI theory and *t*-test in TPA experiments. X axis, *t* value of FUMI theory (Eq. (4)); Y axis, *t* value of *t*-test (Eq. (2)). The original data of the test results (□) marked with letters A - D are shown in Fig. 5.

yield almost indistinguishable results. With the duplicate pairs of experiments, however, the power of the methods is limited and some differences are found between them. The FUMI theory may occasionally implicate genes as being differentially expressed, even if the *t*-test rejects the significant difference, and will not always implicate genes having large *t* values.

The *F*-test at 1% probability level, carried out before the *t*-test, denies the homoscedasticity for 309 genes out of 12559 in the TPA experiments. The Cochran-Cox method suggests that either of 309 genes shows no significant differences in the mean expression levels between the TPA exposure, $\bar{X}_E$, and control, $\bar{X}_C$. Therefore, the 309 genes are eliminated from the subsequent analysis.

The *t*-test at 1% level is conducted for the remaining 12250 genes. Consequently, the expression levels between the two conditions are significantly different for 205 genes. Without the *F*-test described above, the *t*-test alone selected additional 7 genes and the total sum was 212 genes.

The FUMI theory, starting with the original data (12559 genes), demonstrates that 391 genes show significant differences at 1% probability level. The genes selected by the FUMI theory are almost twice in number those by the *t*-test.

Figure 4 shows the correlation between the *t* values, $|\bar{X}_E - \bar{X}_C|/s$, of the *t*-test and FUMI theory (see Eqs. (2) and (4)). In the bottom figure, the horizontal line ($Y = 9.925$) and vertical line ($X = 2.58$) represent the critical values at 1% level of the *t*-test and FUMI theory, respectively. The number of genes

Table 1 Significance tests for control and TPA exposure ($n = 2$)

t-test	FUMI theory		
	99% significant	Not significant	Total
99% significant	56	149	205
Not significant	335	12019	12354
Total	391	12168	12559

Table 2 FUMI theory for control and TPA exposure ($n = 1$)

	Ctrl-1, TPA-1	Ctrl-1, TPA-2	Ctrl-2, TPA-1	Ctrl-1, TPA-2
99%	204	294	306	309

included in the four regions separated by the two lines is listed in Table 1. The top figure shows that the *t* values spread more widely for the *t*-test than for the FUMI theory: 50 times the critical value for the *t*-test and 7 times that for the FUMI theory.

Figure 5 stresses the similarities and differences between the *t*-test and FUMI theory at 1% level. The bar charts (A - D) show the original data of the genes indicated by the squares (A - D) in Fig. 4. The error bars on the Ctrl-1 and Ctrl-2 bars denote the 99% confidence intervals of the *t*-test (= $9.925s$) and FUMI theory (= $2.58s$), respectively.

In Fig. 5B, the expression levels are decided to be significantly different by both the methods. This judgment can also be made by the visual inspection of the error bars: if the duplicate measurements are both higher than the error bars on the control measurements, the difference can be significant.

Figure 5A presents the situation where the significant difference is indicated by the *t*-test, but not by the FUMI theory. The accidental coincidence of the measurements causes the *t*-test to estimate such a small SD, *s*, that the 99% confidence interval (= $9.925s$) becomes much narrower than the observed difference, $|\bar{X}_E - \bar{X}_C|$. On the other hand, the FUMI theory refers to the *a priori* SD (Eq. (6)) through the average of all the four measurements and the predicted 99% confidence interval (= $2.58s$) is wider than the real difference, $|\bar{X}_E - \bar{X}_C|$.

The above decision is reversed in Fig. 5D. For this example, the discrepancy between the methods springs from the large scattering of the duplicate measurements (see the bars of TPA-1 and TPA-2). In examples A and D, the judgment inconsistency is attributable to accidental events.

Even if the *a priori* SD is small enough to affirm a significant difference, the FUMI theory can reject it. This situation arises at which the scattering of the duplicate measurements is even larger than that expected (see Fig. 5C). The decision by the *t*-test is also reasonable due to the large scattering.

FUMI theory for a single pair of TPA experiments

We examine the validity of the FUMI theory with each possible combination of the results of Table 1. Table 2 lists the number of expressed genes chosen by the FUMI theory. About 200 - 310 expressed genes are selected, but they are less than those selected from the duplicate pairs of experiments (391 genes in Table 1). The similar tendency was observed by Ideker *et al.* [6]

The expressed genes commonly included in all the combinations in Table 2 are 60 in number. About 20 - 30% of the expressed genes out of 200 - 310 genes are always selected irrespective of experiments. This fact implies the high

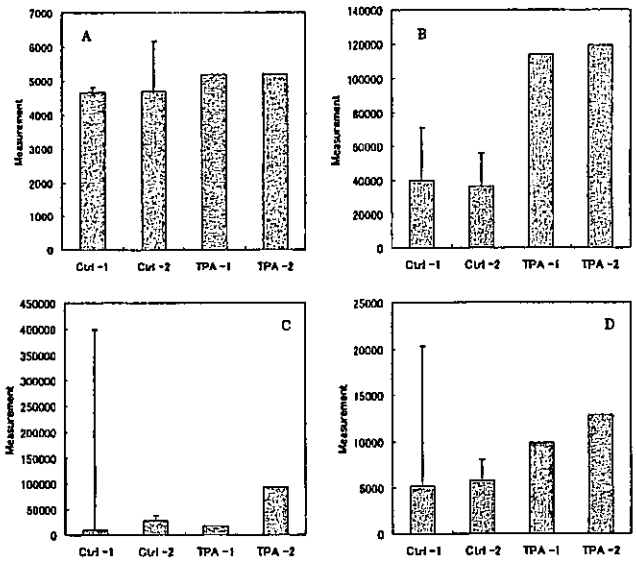

Fig. 5 Individual expression levels judged by *t*-test and FUMI theory differently (A and D) and equally (B and C) in TPA experiments. Figures A - D correspond to the data (□) with the same letters in Fig. 4. Bars (left to right): measurement of control 1; measurement of control 2; measurement of TPA 1; measurement of TPA 2. Error bars: $9.925s$ on Ctrl-1 bar (see Eq. (2)); $2.58s$ on Ctrl-2 bar (see Eq. (4)). Judgment (*t*-test, FUMI theory; s means significant and ns not significant): A: s, ns; B: s, s; C: ns, ns; D: ns, s.

reproducibility of not only the microarray measurement carried out here but also the FUMI theory.

The product set of the 60 commonly expressed genes from the single pair of experiments and 391 expressed genes from the duplicate experiments contains 58 genes. Almost all the genes common to the single experiment are also selected by the more reliable test for the duplicate experiments.

Table 3 lists the number of false positive expressions judged by the FUMI theory. As is expected from the critical level (1%), almost 1% of the entire genes (= 12559) is falsely selected as positive. This result corroborates the normality assumption of the distribution shown in Fig. 3.

Tables 2 and 3 lead to the conclusion, though slightly rough, that among the expressed genes judged by the FUMI theory, a quarter will be selected again from another experimental set, a quarter will be variant and a half will be false positive.

In an analysis proposed by Lee *et al.*,[1] false positives exceedingly dominated over false negatives in experiments using cDNA microarrays and 9% of 288 genes were classified as false positives. The performance of their model is dissimilar from that of the FUMI theory, but the straightforward comparison will make no sense because of different settings of experiments and the idiosyncracies of the classification rules.

Conclusion

The FUMI theory for microarray experiments can handle the data on a single pair of treatment and control experiments, while retaining the statistical characteristics of the *t*-test which can only cope with the data on plural pairs of experiments. Being straightforward, the FUMI theory can be adapted to a broad range of experimental settings. The inevitable requisite is the uncertainty model (*i.e.*, the *a priori* SD) which is intrinsic to an instrument employed in a laboratory.

Table 3 False positive expressions judged by FUMI theory ($n = 1$)

	Ctrl-1, Ctrl-2	TPA-1, TPA-2
99%	123	134

The correctness of the FUMI theory has not been verified completely in this paper. However, as far as a single pair of our TPA experiments is concerned, a quarter of expressed genes selected by the FUMI theory is selected again for another experiments under the same conditions. Furthermore, almost all of these common genes are also chosen by the more reliable test for duplicate experiments. These experimental facts are strong, though circumstantial, pieces of evidence for the FUMI theory.

Some biologically relevant genes are known to be regulated on treatment with TPA in the extensive literature.[29,30] Among them, Erg-1, Erg-2, JUNB, TNFAIP1, c-myb, c-myc, *etc.* have been found by the FUMI theory. The biological evaluation of the FUMI theory will be performed in a subsequent paper.

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Regular Article

Bioinformatics Research on Inter-racial Difference in Drug Metabolism II. Analysis on Relationship between Enzyme Activities of CYP2D6 and CYP2C19 and their Relevant Genotypes

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Summary: The enzyme activities of CYP2D6 and CYP2C19 show a genetic polymorphism, and the frequency of poor metabolizers (PMs) on these enzymes depends on races. We have analyzed frequencies of mutant alleles and PMs based on the published data in previous study (Shimizu, T. *et al.*: Bioinformatics research on inter-racial difference in drug metabolism, I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19.). The study shows that there were racial differences in the frequencies of each mutant allele and PMs. In the present study, the correlation between genotypes and drug-metabolizing enzyme activities was investigated. The result showed that enzyme activities varied according to the genotypes of subjects even in the same race. On the other hand, if subjects had the same genotypes, almost no racial differences were observed in drug-metabolizing enzyme activities. From these results, it was supposed that the racial differences in activities of these enzymes could be explained by the differences in distribution of genotypes. It would be possible to explain the racial differences in drug-metabolizing enzyme activities based on the differences on individual pharmacogenetic background information, not merely by comparison of frameworks such as races and nations.

Key words: inter-racial difference; drug metabolism; poor metabolizer; genetic polymorphism

Introduction

The enzyme activities of CYP2D6 and CYP2C19 show a genetic polymorphism, and the frequency of PMs on CYP2D6 and CYP2C19 depends on races. We have analyzed frequency of mutant alleles and PMs based on the published data in previous paper (Shimizu, T. *et al.*: Bioinformatics research on inter-racial difference in drug metabolism, I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19.). The study shows that the frequencies of PMs on CYP2D6 are 1.9% of Asians and 7.7% of Caucasians, and those of PMs on CYP2C19 are 15.8% of Asians and 2.2% of Caucasians. Therefore, there are some possibilities that polymorphisms of CYP2D6 and CYP2C19 would be the causal factors of racial differences in pharmacokinetics of drugs metabolized by these enzymes, and the causal factors of racial differences in efficacy and development of adverse drug reactions.

From the point of view as described above, it would be necessary to investigate the racial differences in pharmacokinetics of a drug which is metabolized by CYP2D6 or CYP2C19 to estimate the ethnic differences in its efficacy and safety. For this purpose, the variability and distribution of enzyme activities in each race should be also investigated. Additionally, when the variability and distribution of enzyme activities can be explained by genetic information regarding CYP2D6 and CYP2C19 of subjects, it would be easier to extrapolate foreign clinical data to domestic population. Therefore, investigation about the correlation between genetic information and enzyme activity of each subject would be required. In the present study, the correlation between genotypes and enzyme activities of CYP2D6 and CYP2C19 was investigated.

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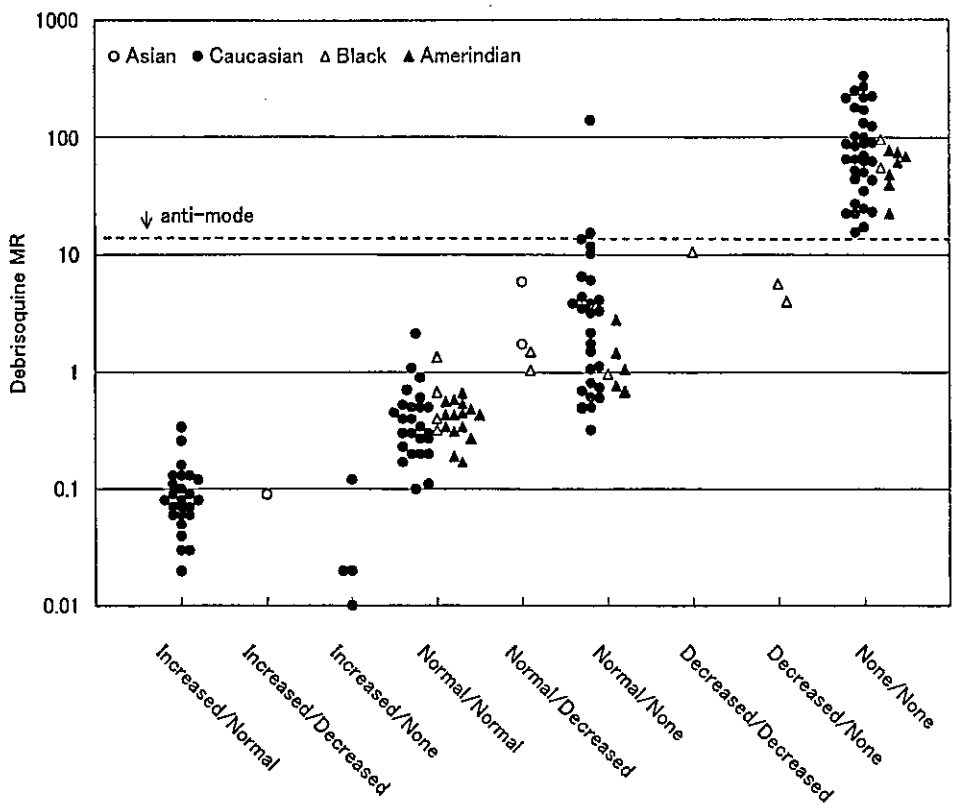

Fig. 1. Relationship between CYP2D6 genotypes and debrisoquine MRs. Data compiled from references 1 – 15.

Methods

1) Collection of data

Published reports (published from 1980 to 2001) were retrieved regarding genetic polymorphism of CYP2D6 and CYP2C19 using PubMed provided by NCBI to collect information. Same key words were used as in our previous paper.

2) Evaluation of correlation between genotypes and enzyme activities

The correlation between the genotypes of CYP2D6 and metabolic ratio (MR) of each probe drug was evaluated based on the information from literatures in which relationships between the genotypes of CYP2D6 and MR of each probe drug were investigated individually. Similarly, correlation between genotypes of CYP2C19 and S/R ratio of mephenytoin in the urine were evaluated based on the information investigated individually. Mutant alleles of CYP2D6 were classified into "Normal", "Increased", "Decreased", and "None" as described in our previous report. As for CYP2C19, *CYP2C19*1* was classified as "Normal" and *CYP2C19*2* and **3* were as "None". The subjects for analyses were restricted to healthy volunteers. Each subject was classified into each race as reported in our previous report.

Results

1) Correlation between genotypes of CYP2D6 and enzyme activities

Correlations between genotypes of CYP2D6 of each subject and MRs of debrisoquine, sparteine and dextromethorphan were evaluated (**Figs. 1 – 3**). MR of each probe drug was less in individuals who have a mutant allele of "Increased", and it became gradually larger by influence of an allele of "Normal" or "Decreased", and MR in subjects having a pair of mutant alleles of "None" ("None/None") tended to be larger than the anti-mode of each probe drug. Additionally, MR showed a similar distribution in the same genotype of different races. It was confirmed that the genotype of subject was a causal factor for inter-individual difference in MR. However, inter-individual difference in MR could not be explained only by the genotype, since there were still some inter-individual differences in MR after classification by genotypes.

2) Correlation between genotypes of CYP2C19 and enzyme activities

Correlation between genotypes of CYP2C19 and S/R ratio of mephenytoin in the urine was evaluated

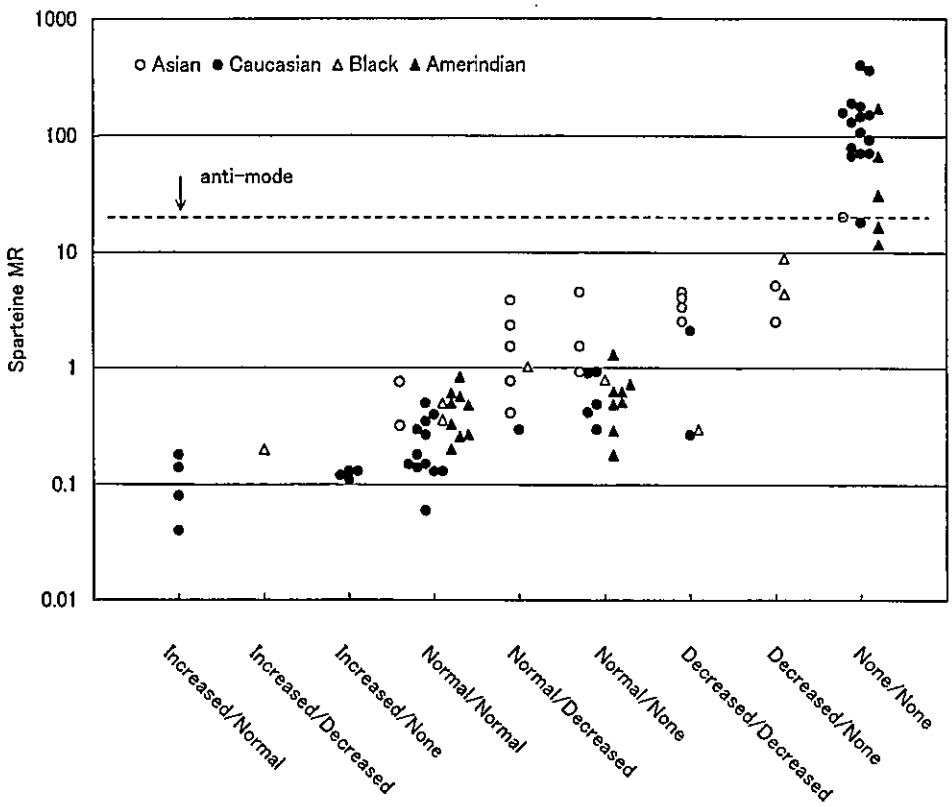

Fig. 2. Relationship between CYP2D6 genotypes and sparteine MRs. Data compiled from references 1, 10, and 17~22.

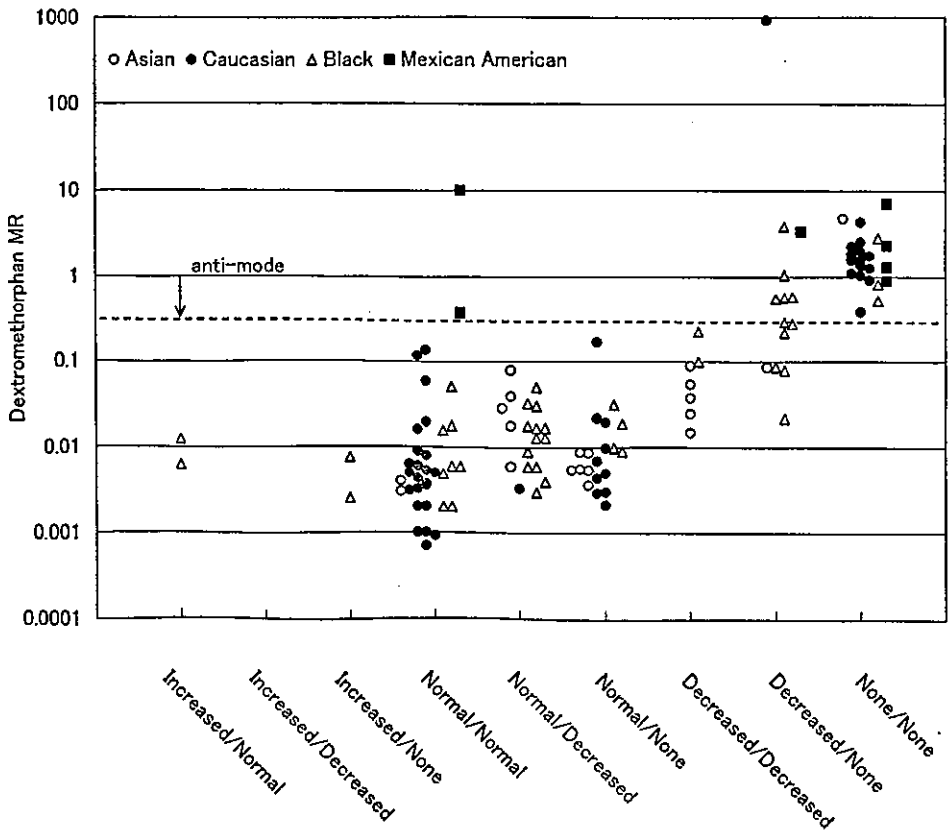

Fig. 3. Relationship between CYP2D6 genotypes and dextromethorphan MRs. Data compiled from references 1, 14, and 23~33.

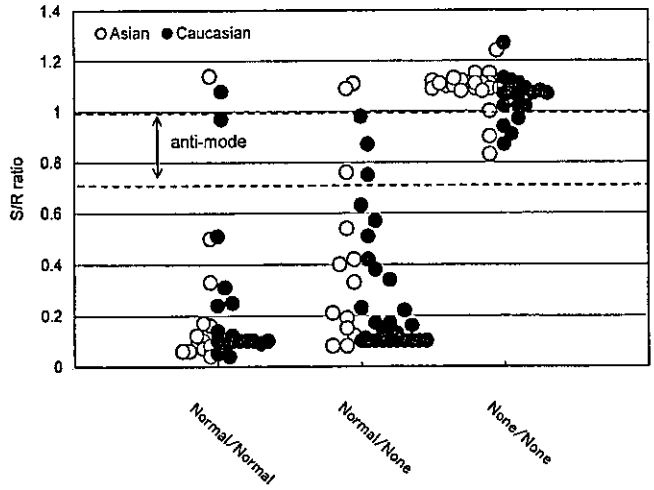

Fig. 4. Relationship between CYP2C19 genotypes and mephenytoin S/R ratios. Data compiled from references 34～39.

(Fig. 4). S/R ratios were low in individuals having a pair of *CYP2C19*1*, and high in individuals having a pair of mutant alleles. However, in some cases, S/R ratios were high even though having a pair of *CYP2C19*1*. Additionally, distributions of S/R ratios were similar in Asians and Caucasians when classified by genotypes of subjects.

Discussion

We have reported that there were racial differences in the frequencies of mutant alleles of CYP2D6 and CYP2C19 and in the frequency of PMs in our previous report (Shimizu, T. *et al.*: Bioinformatics research on inter-racial difference in drug metabolism, I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19.). It was suggested that there would be racial differences in the frequencies of PM subjects whose blood concentrations might be higher for drugs metabolized by these enzymes. Additionally, it was suggested that genetically determined enzyme activities would vary according to the number of functional alleles even in subjects judged to be extensive metabolizers (EMs). Therefore, correlations between genotypes and enzyme activities (MR of each probe drug for CYP2D6, and S/R ratio of mephenytoin in the urine for CYP2C19) were investigated using relevant literature sources in which data of each subject were analyzed individually. In those studies, subjects were not selected at random. Therefore, it was not possible to analyze statistically differences among genotypes and races. However, as shown in **Figs. 1～4**, it was shown that enzyme activities varied according to the genotypes of each subject, and that the genotype pattern was a causal factor of inter-individual differences in enzyme activities. Additionally, almost no racial difference in enzyme activity was observed if the genotype was the same. From these results, it was supposed that racial differences in enzyme activities could be almost explained by differences in distributions of genotypes of CYP2D6 and CYP2C19.

Additionally, inter-individual differences were still observed in enzyme activities even if subjects were classified by genotype and race. One cause of these inter-individual differences can be reasoned by a likelihood that all uninvestigated and all unknown mutant alleles might be analyzed as *CYP2D6*1* or *CYP2C19*1*. If any new mutant allele or alleles and further information on enzyme activities come out by further investigations, correlation between genotype of a subject and enzyme activity would further become stronger. Recently, it has been reported that −1584 promoter polymorphism in CYP2D6 was related to expression level of the enzyme and its enzyme activity.[40,41] Mutations that affect on the protein expression will be a causal factor of inter-individual differences.

Another issue as a problem in the technique of phenotyping is whether S/R ratio of mephenytoin used in phenotyping was reliable.[42] It has been suggested that accurate phenotyping would be difficult only with S/R ratio, because S/R ratio would change during storage by degradation of acid labile metabolite existing in the urine of subjects administered with mephenytoin. These issues, i.e., technique of phenotyping and factors regarding inter-individual differences other than genotype, should be investigated further.

From the results as described above, it is confirmed that genetic polymorphisms of CYP2D6 and CYP2C19 can be a causal factor for racial and inter-individual differences in pharmacokinetics. If a drug candidate under development is metabolized by CYP2D6 or CYP2C19, attentions should be paid to the possibility that pharmacokinetics, and therefore efficacy and safety of the drug could differ among subjects depending on their genotypes. Additionally, we have to be careful about the possibility that distributions of enzyme activities may differ among races because of inter-racial differences in frequency of PMs when foreign clinical data are to be accepted. However, no racial differences in enzyme activities were observed when the genotypes were same. Therefore, it is supposed that the bridging of foreign clinical data to domestic development could be carried out more easily by confirming the efficacy and safety of the drug in each of genotypes or phenotypes which are observed both in the foreign clinical study and domestic population. If it was confirmed from the results of foreign clinical studies that there were no problems in efficacy and safety when the drug was administered at the same dose to subjects of various phenotypes, it would be possible to use the same dose in domestic clinical studies. On the other hand, if it has

Table 1. Relationship between CYP2D6 or CYP2C19 genotypes and pharmacokinetic parameters

	Drug	Race	Parameter	Ratio	Ref
CYP2D6	codeine	Chinese	Formation morphine from codein	C/C188:C/T188:T/T188 = 1:0.52:0.23	43
		German	morphine AUC	(*1/*1 or *1/*4):(*3/*4 or *4/*4 or *5/*5) = 1:0.068	44
		German	morphine AUC	(*1/*1 or *1/*2 or *1/*5 or *1/*10 or *2/*3):(*3/*5 or *4/*4 or *4/*5) = 1:0.060	21
	fluvoxamine	German	AUC	*1/*1:*4/*6 = 1:3.3	45
	metoprolol	Chinese	AUC (S-from)	*1/*1:*1/*2:*1/*10:*10/*10 = 1:1.10:1.43:2.70	46
		Bulgarian	AUC	*1/*1:*1/*4 = 1:2.44	47
		Finnish	AUC	*1/*1:*1/*4 = 1:5.62	48
	nortriptyline	Chinese	AUC	*1/*1:*1/*10:*10/*10 = 1:1.37:2.20	49
		Swedish	AUC	*2×13/*4:*2×2/*1:*1/*1:(*1/*4 or *1/*5):*4/*4 = 0.21:0.66:1:2.79:3.32	50
	propranolol	Chinese	AUC	C/C188:C/T188:T/T188 = 1:1.52:2.29	51
	paroxetine	Korean	AUC	*1/*1:*1/*10:*10/*10 = 1:4.06:3.43	52
	venlafaxine	Japanese	AUC	(*1/*1 or *1/*2 or *2/*2):(*1/*10 or *2/*10):*1/*5:*10/*10 = 1:2.20:4.47:5.54	53
		Canadian	oral clearance	(*1/*1 or *1/*4):(*3/*4 or *4/*4 or *7/*7) = 1:0.22	54
CYP2C19	diazepam	Chinese	AUC	*1/*1:*1/*2:*2/*2 = 1:2.47:6.11	55
		Japanese	AUC	(*1/*1 or *1/*2 or *1/*3):(*2/*2 or *2/*3) = 1:1.43	56
	lansoprazole	Japanese	AUC	*1/*1:(*1/*2 or *1/*3):(*2/*2 or *2/*3) = 1:1.77:3.76	57
		Japanese	AUC	*1/*1:*1/*3:(*2/*2 or *2/*3 or *3/*3) = 1:1.80:5.55	58
	moclobemide	Korean	AUC	*1/*1:(*2/*2 or *2/*3) = 1:3.54	59
	omeprazole	Japanese	AUC	*1/*1:*1/*2:*1/*3:*2/*3:*2/*2 = 1:2.78:2.66:7.85:6.97	60
		Japanese	AUC	*1/*1:(*1/*2 or *1/*3):(*2/*2 or *2/*3) = 1:2.09:10.7	61
		Japanese	AUC	*1/*1:(*1/*2 or *1/*3):*2/*3 = 1:2.24:14.9	62
		Japanese	AUC	(*1/*1 or *1/*2):(*2/*2 or *3/*3) = 1:3.41	63
	pantoprazole	Japanese	AUC	(*1/*1 or *1/*2 or *1/*3):(*2/*2 or *3/*3 or *2/*3) = 1:5.95	64
	phenobarbital	Japanese	p-hydroxy phenobarbital formation clearance	*1/*1:(*2/*2 or *3/*3) = 1:0.71	65
	proguanil	Tanzanian	cycloguanil AUC	wt/wt:wt/mut:mut/mut = 1:2.93:3.35	66
	rabeprazole	Japanese	AUC	*1/*1:(*1/*2 or *1/*3):(*2/*2 or *3/*3) = 1:1.34:3.06	67
		Japanese	AUC	*1/*1:(*1/*2 or *1/*3):(*2/*2 or *2/*3) = 1:2.31:3.34	61
		Japanese	AUC	*1/*1:*1/*3:(*2/*2 or *2/*3 or *3/*3) = 1:1.53:3.28	58
	sertraline	Chinese	AUC	(*1/*1 or *1/*2 or *1/*3):(*2/*2 or *2/*3) = 1:1.41	35

been known that dose adjustment for the drug is necessary according to the phenotype of each subject, we would be able to ensure efficacy and safety of the drug by estimating enzyme activity of each subject using his/her genetic information.

Table 1 shows some published reports on correlations between genotypes of CYP2D6 and CYP2C19 and pharmacokinetic parameters investigated using normal subjects. As shown in this table, reports on correlations between genotypes of subjects and pharmacokinetic parameters are increasing recently, and actually, genetic information of subjects were utilized for dose designing in some cases such as proton pump inhibitors.[68] As discussed in those reports (see references cited in **Table 1**), it would be possible to identify the factors for inter-individual and racial differences in enzyme activities for certain drugs, which are metabolized by CYP2D6 or CYP2C19, by analyses of genotypes of subjects during the developing stages. Moreover, explanation of the racial differences in enzyme activities would be possible based on the differences in various factors by identification of intrinsic factors other than genetic information, such as pathophysiological status, liver and renal functions, and extrinsic factors such as diet, smoking and concomitant medication. Finally, we would be able to analyze differences in enzyme activities based on individual background information, not merely by comparison of frameworks such as races and nations.

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Global information network on chemicals (GINC) and its Asian component☆

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Abstract

The Global Information Network on Chemicals (GINC) is an effort to build a global information network that links international, national, and other organizations working for the safe management of chemicals in order to exchange information and improve communications. The project was originally proposed in 1993 by one of the authors then at the National Institute of Health Sciences (NIHS) of Japan to the International Program on Chemical Safety (IPCS), which is a joint project of World Health Organization (WHO), International Labor Organization (ILO), and United Nations Environment Program (UNEP). The base support system was first implemented at NIHS using the Internet/World Wide Web (WWW) technology in 1995. The project was then endorsed by the Intergovernmental Forum on Chemical Safety (IFCS) and was adopted by the Inter-Organization Program for the Sound Management of Chemicals (IOMC). However, the base system (http://www.nihs.go.jp/GINC/index.html) has been developed and maintained solely by the NIHS group under the support of the Ministry of Health and Welfare (MHW), Japan. Asia, particularly East Asia and the Pacific region, was chosen as the feasibility study region for this project. During the period from December 1994 to July 2002, NIHS hosted eight meetings on this project held in Tokyo.

Keywords: GINC (Global Information Network on Chemicals); GINC Asia; IPCS (International Program on Chemical Safety); Chemical safety; Internet; Information exchange; NIHS (National Institute of Health Sciences)

1. Introduction

Chemicals are important components of modern society. Today new chemicals are being registered and input into official databases at a remarkably quick pace. By some accounts, the number of such registered chemical substances exceeds 20 million. 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 is becoming a vital challenge to every country whatever its stage of development. However, such

☆ This review article is written according to the authors' viewpoints, which do not necessarily represent those of the International Organizations or Governments or individuals who have participated in the project.

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management is costly, because identifying the hazards of chemicals and studying their effects on humans, wildlife, and the environment are not easy tasks. Management of chemical risks often requires intra-governmental and international negotiations. Thus international collaborations on this subject are inevitable. The existing chemical testing and assessment projects of the International Program on Chemical Safety (IPCS) and Organization for Economic Co-operation and Development (OECD) are the two most well known international programs for chemical safety.

While OECD projects are for the economically developed countries, IPCS is the core of all international collaborative activities for chemical hazard identification and risk assessment worldwide. On behalf of the Japanese Ministry of Health, Labor and Welfare (MHLW), the authors' group, the Division of Chem-Bio Informatics at the National Institute of Health Sciences (NIHS) has promoted one of the IPCS projects called the Global Information Network on Chemicals (GINC). The aim of GINC was to support IPCS partners to use computers and networks in order to provide and exchange relevant information on chemical safety. Asia was chosen as the pilot study region when the project was started. The authors' group has taken the initiative to carry out this chemical safety network project in Asia (the GINC Asia). The project's mission was to enforce IPCS activities in Asia and to build a network for chemical safety experts in this region.

Since the GINC and GINC Asia Project were based on Information Technology (IT), it was natural for us to pay attention to computer-based approaches to toxicology and risk assessment. The advantage of the computerized approach is that once we succeeded in developing some software or information contents, we could easily share the resultant systems, data, information, or knowledge by the network (Milen and Heller, 1977; Kaminuma and Kurihara, 1981). Thus the experts and expertise that are the rarest resources in almost any country can be utilized most effectively. In this paper we shall describe the state-of-the-art of GINC and GINC Asia Project and touch on their significance to computerized approaches to toxicological and risk assessment.

2. Concept of GINC project

2.1. Original idea of GINC project

The original idea of GINC was to overcome the deficiency and frustration of information dissemination and information exchange among those who were working for sound management of chemicals in international arenas. The authors' group had collaborated with IPCS for producing the risk assessment monograph series called Environmental Health Criteria Monographs (EHCs) as well as the International Chemical Safety Cards (ICSC). The group also had coordinated the attendance of domestic participants at the IPCS-related meetings, and disseminated information sent from IPCS to domestic organizations and the public. At the heart of this coordination was the problem that the relevant information was delivered as printed matter, such as reports, monographs, newsletters, etc. And yet, the numbers of these printings were limited; sometimes they were costly. It took months to order them by mail. Moreover, they were not often revised. Electronic media, such as on-line databases or CD-ROMs, had not solved the problem, either for they had also been costly, their access had been limited, and their contents had not been up-dated so frequently.

Thus, the idea of exchanging chemical safety information by means of a worldwide computer network was first proposed by one of the authors (Kaminuma) to an IPCS (WHO/IPCS) officer, Dr Michael Gilbert. Based on this proposal, the first preparatory meeting was held in Geneva right after the Stockholm Conference for Chemical Safety, which was later called the First Intergovernmental Forum on Chemical Safety (IFCS I). At this informal meeting, the framework of the project was discussed, and the project was then named GINC. NIHS proposed to take the initiative and offered to host the first informal meeting that was held in Tokyo on 7–8 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 computer networks and to

exchange information more efficiently than by conventional means that were based on paper, telephones, and faxes. At this meeting, GINC was accepted as a project of IPCS, and NIHS was admitted as one of its most active partners.

2.2. GINC Asia project

This project started with site visits to East Asian countries by an officer from the Ministry of Health and Welfare (MHW) of Japan and one of the authors (Kaminuma). The NIHS then invited experts from these countries to the GINC Meetings. The number of countries, institutions, and individual experts who have participated in GINC Asia activities has increased at each meeting. Thus Korea, China, Japan, the Philippines, Vietnam, Thailand, Singapore, Malaysia, Indonesia, Australia, New Zealand, Sri Lanka, Bangladesh, India, Iran, Nepal and Papua New Guinea had participated in some of the GINC Asia meetings. US organizations such as the EPA, NIOSH, NIH, and NIEHS, the EU Chemicals, and OECD have always been invited as observers in addition to the IPCS central unit partners from Geneva, i.e. WHO/IPCS, ILO/CIS, and United Nations Environment Program (UNEP) Chemicals.

Based on these activities, an informal network of institutions and experts was established, and these partners started to construct their home pages on the Internet. The NIHS group then tried to develop a portal site for integrating these websites. One of the advantages of Internet/WWW technology is decentralization. Those who are interested in participating in this project can easily do so if they only connect their machines to the Internet, open their home pages, and access the GINC (Asia) Home Page. GINC Asia has expanded just by this informal process and spirit. Nevertheless, the NIHS had recommended that those who wanted to be a collaborative partner of GINC Asia should provide two kinds of information contents. One was a guide to their domestic information for foreign users in English, and another was a guide to internal information for domestic users in the country's native language (Fig. 1). As an example, Japan has developed both English and Japanese home pages for this purpose.

2.3. Management of the GINC project

Formally the GINC project started as a project of IPCS. Later it was adopted into the Inter-Organization Program for the Sound Management of Chemicals (IOMC) when IFCS was established and set six program areas to fulfill the statement in Chapter 19 of Agenda 21 of the 1992 United Nations Conference on Environment and Development (UNCED, Rio Environmental Summit). GINC was placed in the third program area, Program Area C, for it is related to information exchange. The responsible organization of Program Area C was assigned to be the UNEP/Chemicals. However, the NIHS Japan collaborates directly with WHO/IPCS instead of the UNEP/Chemicals, for the institute is under the umbrella of the MHW, which was collaborating with World Health Organization (WHO) rather than UNEP. The focal point of the IPCS project in Japan is the MHW, which makes decisions on regulatory matters, while the NIHS works for IPCS as one of the participating institutions and plays the role of scientific advisor to the Ministry. The budget that has mainly supported the GINC project was the Japanese domestic fund to WHO that has been provided by the Japanese MHW. This structural complexity has very much complicated the management of the GINC project.

In spite of complications, however, the authors' group took the initiative and made various decisions quickly in case of the GINC Asia project, for such initiative was authorized by IPCS from the very beginning of the project.

2.4. Information system for the GINC project

In 1995, right after the first GINC meeting, the authors' group started to develop the GINC server system at NIHS. The system was designed to be the World Wide Web (WWW) based system that links other GINC partners' websites so that one can find any contents provided by the partners on the Internet from this site. Such an information system on the Internet was later called a "one-stop-shopping site" or more simply "portal," but this terminology was not yet devised at the time. In addition, the authors' group developed an inte-

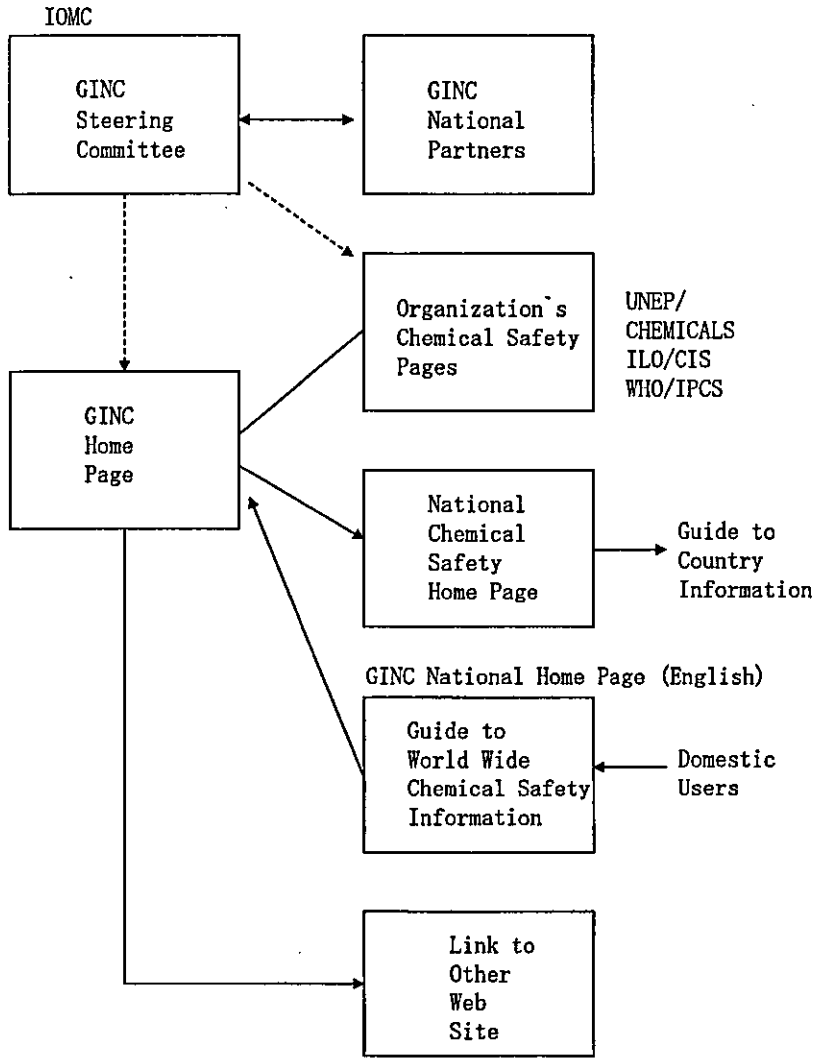

Fig. 1. Concept of GINC and GINC Asia collaboration.

grated database search system. The mechanism of this system was as follows. At that time there already existing chemical databases that could be accessed from remote sites via a WWW interface (Common Gateway Interface). We have tried to develop a system that can access all databases that have some attribute data on a given chemical. For that, the system contained a look-up table for the databases and chemicals that were included in these databases. Given a chemical or chemicals, the system explored databases and their websites (URLs) that had information on these chemicals by means of this look-up table. The system then sent a message to request these data that were in the remote websites. Because of the URL mechanism of the Internet, the system did not separate "in house" systems from "remote" ones. Several UNIX machines were used for the network servers, database managers, and WWW file managers. First SYBASE (Sybase Inc.) and later ORACLE (Oracle Co.) was used for the database management system.

The one-stop-shopping mechanism for websites or portal was implemented much later. A freeware

called wget was used for the information collection robot, and a commercial software called OPEN TEXT (Open Text Co.) was used for text searches.

3. GINC in operation

In June 1995, the first version of the GINC home page was implemented on the NIHS server under the collaboration with the ILO/CIS, UNEP/IRPTC, WHO/IPCS, and the NIHS. The NIHS then hosted the second GINC meeting in Tokyo on 13–14 December 1995. Since that time, because of the rapid expansion of the Internet, many organizations and institutions have opened their home pages, which include some useful information. It then became very feasible to send electronic mail across borders, to transfer documents via computer networks in the so-called file transfer protocols, and to disseminate reports and monographs on Web pages in addition to conventional databases or CD-ROMs. Also the WWW and its browser technology has replaced the concept of a "central system" with that of "virtual center", which is nothing but Web pages and databases at different sites connected by the Internet. Thus, a part of the preliminary goals of the GINC project, namely, providing relevant information contents on chemical safety in digital forms and exchanging them by worldwide computer networks was fulfilled.

The integrated search mechanism of chemical databases was first demonstrated at the IFCS Inter Sessional Group (ISG) held in Canberra, Australia, in March 1996. The first version of the dedicated search engine was implemented at the time of the next IFCS ISG held in Yokohama in December 1998. However, this system was found to be too slow for practical use, and a new system with dedicated hardware and more powerful software was implemented at the NIHS in the next year. At this time, so far as the hardware and software are concerned, there is no distinction between the GINC and the GINC Asia systems (http://www.nihs.go.jp/GINC/index.html). Only the websites linked and information contained are different.

4. GINC Asia in operation

4.1. Sub-regional approach

According to the UN (IFCS) definition, Asia extends from the Western Pacific islands to the Middle East. Both languages and statuses of economic development in this region are diverse. Thus, we took a sub-regional approach for the GINC Asia project in that we grouped the countries in this region into sub-regional countries: the Pacific island countries such as Tonga and Papua New Guinea; East Asian countries such as China, Korea, Japan, Indonesia, Thailand, New Zealand, and Australia; Middle Asia such as Sri Lanka and India; and Middle Eastern countries such as Iran and Oman. From the viewpoint of capacity building, New Zealand and Australia seemed to need no help to build their Internet environment. From the language viewpoint, countries like Singapore, Sri Lanka, the Philippines or India use English as one of their official languages, and there seems to be no difficulty in providing information contents in English. Because of limited budgets, geographical location, and economic status, the authors' group concentrated their collaborative efforts on the East Asian countries. Thus, one of the authors (Kaminuma) visited Korea, China, the Philippines, Vietnam, Thailand, Malaysia, and Indonesia, and discussed the project with the government organizations responsible for safety management of chemicals, and invited some of the experts of these countries to the GINC Meetings.

4.2. Present status

The authors' group has developed the home page of GINC Asia project on the NIHS server. Simultaneously, collaborative groups have developed their own home pages, and tried to link these pages with each other. Year by year, the number of such countries and organizations has increased, and their status has been reported at the GINC Meetings (see Table 1).

Table 1
Record of GINC meetings

	Meetings	Non Asian members	Asian members
June 1992	United Nations Conference on Environment and Development (UNCED) at Rio de Janeiro, Chapter 19 of Agenda 21, Program Area C: Information Exchange		
7–8 December 1994	The 1st GINC Tokyo Meeting, (Preparatory Meeting)	IPCS/WHO, WPRO, ILO, IRPTC/UNEP, BIBRA, USEPA, Comm./Canada	Korea, Japan
13–14 December 1995	The 2nd GINC Tokyo Meeting, (GINC Technical Meeting)	IPCS/WHO, OECD, ILO, IRPTC/UNEP, USEPA, NIEHS CCOHS(Canada)	Australia, Singapore, Malaysia, Korea, Japan
3–8 March 1996	GINC Demonstration at ISG2 Meeting at Canberra		
10–14 February 1997	GINC Demonstration at IFCS at Yokohama		
15–18 October 1997	The 3rd GINC Tokyo Meeting (Network Building for Chemical Safety in Asia–Pacific Countries)	IPCS/WHO, WRPO, ILO, IRPTC/UNEP, UK, USEPA, NIEHS, CCOHS(Canada), OPPT	Korea, Sri Lanka, China, Thailand, The Philippines, Vietnam, New Zealand, Indonesia, Japan
26–28 November 1998	The 4th GINC Tokyo Meeting (Building and Promotion of Network for Information Exchange on Chemical Safety)	IPCS/WHO, IRPTC/UNEP, IARC, ILO, UNITAR, EC, CCOHS(Canada), USEPA, NIOSH	Bangladesh, China, Thailand, Vietnam, Korea, Sri Lanka, New Zealand, Japan
1–4 December 1998.12	GINC Demonstration at ISG3 Meeting		
22–25 February 2000	The 5th GINC Tokyo Meeting (Web Master Workshop)	IPCS/WHO	Thailand, Vietnam, China, Korea, Japan
23–25 February 2000	The 6th GINC Tokyo Meeting (for Information Exchange and Collaboration in East Asia on Chemical Incidents and Chemical Toxicology)		Thailand, Vietnam, China, Korea, Japan
18–20 April 2001	The 7th GINC Tokyo Meeting (for Information Exchange and Collaboration in Asia on Chemical Management and Pesticide Poisoning)	IPCS/WHO, Italy	Malaysia, Korea, Vietnam, Australia, The Philippines, Iran, Sri Lanka, Nepal, China, Bangladesh, India, Thailand, Indonesia, Japan
8–10 July 2002	The 8th GINC Tokyo Meeting (GINC and Capacity Building for Management of Chemicals in Asia-Pacific countries)	IPCS/WHO	China, Korea, Vietnam, Thailand, Iran, New Zealand, Australia, India, Papua New Guinea, Japan

4.3. Some common goals and collaborative themes

As time went on, and the Internet became widely accepted all over the world. The original mission of GINC Asia was fulfilled in many countries in East Asia, and we started to look for new goals to keep driving this project. One possibility was to use this computer and human network to solve some problems concerning the safety control of chemicals common in this area. From this viewpoint, several themes for collaborations have been discussed at recent GINC Asia meetings. Some of them include the exchange of pesticides information, and the development of common environmental health maps that represent hazardous chemical substance data, and human risk and incident data using Geographic Information Systems (GIS). Pesticides and pesticide poisoning have always been one of the topics of highest interest among the GINC Asia partners. Some of these topics matched those of the new IPCS project called Human Data Initiative, which was proposed by Dr T. Meredith, the director of IPCS. This theme was then adopted as the main theme for the 8th GINC Meeting.

4.4. Japan as a partner of GINC Asia

In the beginning of the 1980s, when IIPCS was established in Japan, Japan had already established a sound infrastructure for toxicology research and chemical safety regulations and participated in this project as one of the active partners. The Japanese Government assigned the Office of Chemical Safety of MHW to be the Japanese focal point and the NIHS to be the Japanese participating research institution. The NIHS had participated in the pre-IPCS projects including ones on short-term mutagenicity and carcinogenicity tests and immunological assays. At that time the existing chemical acts were adopted by the Japanese Government, and safety data for existing chemicals began to be submitted by industries to the three ministries controlling these acts: MHW, the Ministry of Labor (MOL), and the Ministry of International Trade and Industry (MITI). There was a reform among the Japanese Ministries in 2001, and the MHW and MOL were combined into the MHLW; MITI changed its name to the Ministry of Economy, Trade and Industry (METI); and the Environmental Agency changed its name to the Ministry of the Environment (MOE). However, all of this information was submitted as paper documents, and no efforts were made to convert them into computerized files. The Environmental Agency was another Government player for chemical safety. The agency controlled environmental chemical monitoring. Since some of those data were being collected on-line, they were digitized data. But these raw data are not relevant as toxicological data. These ministries have been carrying out surveys on chemical safety problems, and some of these survey reports were made available to the public, but they are basically written in Japanese.

Japanese ministries and agencies, which were responsible for chemical safety management, have research institutions. Various toxicological research projects have been carried out at these institutions. For example, METI supported a testing center for chemical safety, where toxicological tests had been carried out using fish. The Ministry recently set up a new testing center called the Chemicals Evaluation and Research Institute. MOE operates the National Institute for Environmental Studies (NIES), which is actively carrying out a wide range of toxicological research projects including studies on the effects of diesel exhausts and endocrine disruptors. The Research Center for Environmental Risk and Center for Global Environmental Research also belong to MOE. MHW is now combined with MOL, to which the National Institute of Industrial Health (NIIH) belongs. Work on various topics in toxicology is actively being carried out at these laboratories and at those of many universities. Risk assessment has attracted more interest in these institutions. For example, the National Institute of Advanced Industrial Science and Technology (NIAIST) of METI is also interested in risk assessment. Although these organizations publish papers in English, there exists almost no systematic effort for producing large-scale databases that can accumulate toxicological data systematically and disseminate them for research and public use.

Other important players for safety control of chemicals in Japan are the health and environmental laboratories operated by local governments, such as prefectures and municipalities. They also carry out many regulatory research projects requested by their local governments, including the analysis of food residues and air and water quality. Unfortunately, not much effort is paid for providing these data in digital form or in English. There is only one Poison Information Center (that has two call centers) in Japan, but the mission of this Center is to provide an emergency information response service rather than to disseminate public information on research.

Experts from these domestic institutions have always been invited to the GINC Meetings, and they have started to open English websites. Although there are little contents relevant for scientific use in these websites, they are guides for overseas assessors to find out what kinds of activities are being carried out at these institutions. Almost all of these websites have been linked to the GINC Home Page. An effort is continuing to find toxicological databases that are in English, available on line, and relevant for scientific usage and link them to the GINC Home Page by one of the authors (Nakata). A Database for Genotoxicity of Chemicals (http://www.members.jcom.home.ne.jp/mo-ishidate/) developed by Dr Motoi Ishidate, who is an ex-director of the Department of Mutagenecity of NIHS, is an example of such a website.

5. Impact of GINC

Although many on-line data retrieval systems in the fields of toxicology and chemical safety have been proposed and developed, to the authors' best knowledge, GINC was probably the first project that proposed to integrate existing information resources on chemical safety on a worldwide scale. It was the good fortune of this project that the timing of this proposal coincided with the flowering of the Internet. Though the Internet project started at the end of the 1960s, its true dispersal occurred during 1993–1994 when the American government opened the gate of the Internet to commercial users and the WWW technology was taking shape. The original idea of GINC included the development of both the technology and mechanism for computerized communication and data exchange. The advances of the Internet have quickly solved the technical problems and have provided the infrastructure for this project.

However, not many people recognized the innovative nature of the Internet nor did they anticipate its rapid spread over not only developed countries but also over developing countries. In the initial phase of the GINC project, there were some arguments on how to extend this technology to Asian countries. Some specialists insisted on the use of telephone and fax rather than a computer network, and in case of the Internet usage some insisted on using GOPHER rather than WWW. The fact was that even developing countries and underdeveloped regions wanted advanced technologies rather than conventional technologies, and, so far as the Internet was concerned, advanced technologies were more smoothly adopted by their countries and regions than were conventional communication tools, contrary to the opinion of some experienced UN organization regional officers.

At the demonstration session of the second GINC Meeting, Internet information resources were demonstrated, one by one, by participants from the NIEHS, NIOSH, and EPA of the United States, as well as from several Japanese organizations. These demonstrations stimulated thinking by participants from International organizations and Asia. Within several years many United Nations organizations and the OECD implemented Internet servers and opened their Web sites, and so did many Asian organizations. While the GINC project has been focused on the Asian region, similar projects for Africa and South America were proposed and discussed among UNEP Chemicals, the United Nations Institute for Training and Research (UNITAR), and the US EPA. The UNITAR showed their interests, because they were responsible for capacity building, in one of the six action programs for the chemical safety, in Chapter 19 of Agenda 21 of UNCED. In this way, GINC undoubtedly accelerated the adoption of the Internet for many

International and regional organizations working for chemical safety.

The GINC Asia projects have two meanings for participating countries. One is regulatory and another is technical. Since it is a project for the chemical safety program of UN, it supported the governments working for chemical safety. In any country, safety management of chemicals is a matter handled by more than one and usually several departments and agencies. Negotiations among these organizations are always a matter of conflict-who should be elected as the representative for participation in international or intergovernmental meetings and which organization should be assigned to be the information center, etc. If the number of representatives or delegates to a meeting were limited to only one department or agency from a country, the information delivered at the meeting would not always be smoothly transferred to other departments or agencies in that country. Therefore, it is always very difficult to transfer the information produced by international collaborations to regional and developing country organizations working for chemical safety. Asia was not an exception. The decentralized mechanism of the Internet resolved part of this problem, because information no longer needs to be circulated only from the central organization. Any information contents put on the Web can easily be linked with each other by a portal mechanism. Once this mechanism was understood, psychological barriers that separated these organizations were greatly lowered and a more collaborative mood emerged among the organizations working for chemical safety. They understood that they could work collaboratively rather than competitively for building an intra-country network on chemical safety. The GINC Asia project contributed to such betterment of communication among domestic organizations.

Another impact was related to the building of technical capacity. In order to participate in the GINC project, one must be affiliated with some Internet environment. Fortunately, this prerequisite was met very rapidly by many Asian countries. However, it was not such an easy task to provide information in both English and a native language. In the GINC project, the building of a good infrastructure for translating between English and the domestic language was emphasized, and the production mechanism of the ICSC was introduced as a successful example for easy translation. In the 5th GINC Asia meetings (2000), tutorial sessions were organized for computer techniques to handle toxicology information and data by computer. These sessions introduced technology for building an Internet server system, computer software for drawing molecular formulas and three-dimensional structures of molecules, how to develop chemical databases, the software package for translating ICSC from English to local languages efficiently, and how to use GIS such as ArcView (ESRI, Inc.) or MapInfo (MapInfo Co.) for representing environmental chemical data graphically, etc. Such tutorial sessions stimulated the interests of the participants and opened their eyes to new computer technologies.

Government representatives who are handling chemical safety matters or researchers working on toxicology have many opportunities to meet and get acquainted with each other, for there are many intergovernmental and international meetings on these subjects today. However, there is almost no chance for those who are working on producing information contents or building real information systems to convene. Currently there are few, if any, professional toxicology "information" societies in Asian countries, Japan included. GINC Asia provided a good opportunity for many computer specialists and technicians working on chemical safety information to get acquainted with each other. The building of computational skills of those who are working on chemical safety in Asian countries may become a subject for the capacity building program of UNITAR. A project called INFOCAP is being carried out by UNITAR within the framework of the IFCS (http://www.who.int/ifcs/infocap). The experiences of GINC Asia will be relevant for this project, and some future collaboration will be fruitful for both projects.

6. Future perspectives

Although the GINC system is still alive on the NIHS server (http://www.nihs.go.jp) and a GINC