

Review Article

Polymorphism of Drug-Metabolizing Enzymes in Relation to Individual Susceptibility to Industrial Chemicals

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Abstract: Polymorphism and the induction/inhibition of drug-metabolizing enzymes, such as cytochrome P450, aldehyde dehydrogenase (ALDH), glutathione S-transferase (GST), *N*-acetyltransferase (NAT), and NAD(P)H-quinone oxidoreductase (NQO1), were reviewed in relation to susceptibility to disease and to inter-individual difference in biological monitorings. A number of genetic and acquired factors can influence the susceptibility of an individual to chemicals, creating a so-called predisposition. Most cases in which genetic factors were present resulted from polymorphism of drug-metabolizing enzymes. However, conflicting reports have appeared on the relationship between polymorphism and risk of disease; in some cases, biologically plausible mechanisms linking genotypes and disease are not yet in evidence. Current findings based on biological monitoring of chemicals are insufficient to evaluate the relationship between genetic polymorphism and acquired risk when exposure has occurred in an occupational area. Investigation of such situations has generated data implicating *GSTT1*, *GSTM1*, *NAT2*, and *NQO1* polymorphisms in biological monitoring of some chemicals; the *ALDH2* polymorphism is the likely link between the genotype and the metabolism of low molecular aliphatic aldehydes. Although this polymorphism is limited in the case of Japanese as well as other Asian subjects, the inhibitors of ALDH2 activity such as trichloroethylene may produce a false polymorphism of this gene. As to the effect of factors influencing acquired predisposition, such as ethanol intake, intake of low carbohydrate diet or diabetes, corroborative epidemiological studies may be further required.

Key words: *N*-acetyltransferase 2, Aldehyde dehydrogenase 2, Acquired factors, Biological monitoring, Cytochrome P450, Glutathione S-transferase, Polymorphism, Susceptibility to disease

Introduction

Humans are exposed to a number of chemicals in the general and occupational environment. The toxic nature of these chemicals are dependent on the type of toxicity as well as its potential, whereas the intensity and duration of toxic responses are dependent on the concentration in the

target organ, which is determined by the quantitative description of absorption, distribution, metabolism, and excretion of the chemical¹⁾. Of these factors determined by pharmacokinetics, the metabolism is garnering more and more attention because i) it is essential as a biomarker for exposure in biological monitoring, ii) it determines the half-life of chemical substances inhaled into the body, and iii) metabolic activation often occurs during the metabolic process.

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The metabolism of chemicals can be divided roughly two types of reaction: functional reactions and conjugation reactions. The former consists of oxidative, reductive, and hydrolytic reactions that create a new functional group, usually increasing the polarity. Cytochrome P450 (CYP), a superfamily of hemoprotein enzymes, alcohol dehydrogenase (ADH), and aldehyde dehydrogenase (ALDH) are involved in this group. On the other hand, UDP-glucuronyltransferase (UDPGT), glutathione S-transferase (GST), *N*-acetyltransferase (NAT), and NAD(P)H-quinone oxidoreductase (NQO) are representative enzymes included in the process of the conjugation reactions, which couple chemicals, or most often metabolites, to endogenous substrates and further increase the polarity.

These drug-metabolizing enzymes are sometimes expressed polymorphically²⁾, or induced and/or decreased in relation to several factors such as age; gender; lifestyle, including cigarette smoking and alcohol drinking; nutritional status; and disease, all of which may affect the distribution and persistence of chemicals³⁻⁵⁾. Recently, the effects of these factors have attracted attention as biomarkers of susceptibility, which may increase or decrease the risk posed by toxic substances⁶⁾. In this paper, polymorphism of drug-metabolizing enzymes is reviewed and discussed with regard to risk assessment of industrial chemicals.

Genetic Polymorphism

CYP1A1

CYP1A1 catalyzes the oxidation of polycyclic aromatic hydrocarbons to phenols and epoxides, and is primarily involved in chemical-induced lung cancer (Table 1). Therefore, this isozyme plays an important role in biological monitoring as well as in occupational-related disease of workers engaged in coke ovens and plants, or in the aluminum industry, where many kinds of these chemicals are possibly produced.

Human *CYP1A1* expressed polymorphically is shown in the common form to have *Ile* at position 462, and in the rare form to have *Val* at the same position. The rare allele has been associated with enhanced susceptibility to lung cancer in Japanese populations⁷⁾, though not in Caucasian populations⁸⁾. This raises the question whether the activity of the rare allele type in response to carcinogens is greater in this type than in the common type. Zhang *et al.*⁹⁾ investigated the metabolic activity of benz[a]pyrene in reconstituted *CYP1A1-Ile462* and *CYP1A1-Val462* together with epoxide hydrolase: the activity was almost the same in both cases. They concluded that the apparently greater

susceptibility of the *CYP1A1-Val462* genotype to lung cancer is probably not related to a greater extent of carcinogen bioactivation.

We compared the *CYP1A1* genotype with arylhydrocarbon hydroxylase (AHH) activity in human lung microsomes from Finnish cancer and non-cancer patients¹⁰⁾. Although only 3 of 28 subjects had a *CYP1A1-Val/Ile* genotype, the activity was not greater in these three subjects than that in subjects having a *CYP1A1-Ile/Ile* type. The AHH activity was significantly related to tobacco use, not to the *CYP1A1* genotypes. Thus, *CYP1A1* genetic polymorphism may be linked to the development of lung cancer without involvement of carcinogen bioactivation.

The relationship between *CYP1A1* polymorphism and the risk of breast cancer was also analyzed¹¹⁾. In African-Americans, the frequency of homozygous *Msp*I polymorphism was 3.5% in control and 19% in breast cancer cases. The odds ratio of breast cancer with the *Msp*I homozygous variant was 9.7 (95% CI 2.0–47.9). This association, however, was not observed in Caucasians.

CYP2E1

CYP2E1 is the primary isozyme of CYP responsible for the metabolism of volatile hydrocarbons of low relative molecular mass such as organic solvents, alcohol, and carcinogenic *N*-nitrosoamines as a low-*km* isoform^{4, 12)}. The polymorphic expression of this isozyme is designated as the genotype of *Rsa*I or *Pst*I *CYP2E1* restriction fragment length polymorphisms (*c1* and *c2*, respectively), which may lead to inter-individual differences of microsomal drug oxidation activity *via* changing the transcriptional regulation and the susceptibility to disease¹³⁾. The relationship between the *CYP2E1* genotype and the development of alcohol-induced liver disease has been investigated^{14, 15)}. The frequency of patients of alcohol liver disease with the *c2* genotype was 84%, which was significantly greater than that of controls (62–68%), suggesting that *CYP2E1* genotypes are related to the development of this disease. On the contrary, Maezawa *et al.* reported that the *c1* homozygotes were more prevalent in patients with fibrotic alcohol liver disease than in those without it¹⁶⁾.

The *CYP2E1* genotype has also been studied in relation to the lung cancer susceptibility^{17, 18)}. Wu *et al.* assessed the genotype frequency of *CYP2E1* and a cancer susceptibility marker in the form of a mutagen sensitivity that quantitates the number of bleomycin-induced chromatid breaks in short term peripheral lymphocyte culture, in 137 lung cancer cases (92 African Americans and 45 Mexican Americans) and 206 controls (114 African Americans and 92 Mexican

Table 1. Drug-metabolizing enzymes in relation to established and suspected genetic polymorphism and susceptibility to disease

Polymorphism		Environmental substrate		Disease
		Carcinogen	Other chemicals	
CYP1A1	Yes	Polycyclic aromatic hydrocarbon		Lung and breast cancer
CYP1A2	Yes	Arylamine, nitrosamine, benzene	Toluene, styrene, phenol	Lung and bladder cancer
CYP2A6	No	Aflatoxin B1, coumarin		
CYP2B6	No	Aflatoxin B1, Benzene	Toluene, styrene	
CYP2C8	Yes		Toluene, styrene	
CYP2D6	Yes	NNK	Debrisoquine, bufaralol	Lung and bladder cancer, leukemia
CYP2E1	Yes	N-Nitrosodimethylamine, benzene	Toluene, styrene, phenol	Lung cancer, alcoholic liver disease
CYP3A3	No	Aflatoxin B1	Nifedipine, erythromycin	
CYP3A4	?	Aflatoxin B1	Nifedipine	
CYP3A5	Yes	Aflatoxin B1	Nifedipine	
EH	Yes	Benzo[a]pyrene epoxide	Styrene oxide	Cancer
ALDH2	Yes		Formaldehyde, acetaldehyde	Degreasers' flush, alcoholism
ADH	Yes		Alcohol	Alcoholism
GSTM1	Yes	Benzo[a]pyrene epoxide	Trans-Stilbene oxide	Lung, skin, breast, and colon cancer
GSTM3	Yes			Larynx cancer
GSTT1	Yes	1,3-butadiene	Dichloromethane	MDS
GSTP1	Yes			Lung and oral cancer
UDPGT	Yes		Bilirubin	
NAT2	Yes	Arylamine		Bladder cancer
NAT1	Yes	Arylamine		Bladder cancer
NQO1	Yes	Benzene metabolites		Leukemia, MDS

CYP, cytochrome P450; EH, epoxide hydratase; ALDH, aldehyde dehydrogenase; ADH, alcohol dehydrogenase; GST, glutathione S-transferase; UDPGT, UDP-glucuronyltransferase; NAT, N-acetyltransferase; NQO1, NAD(P)H quinone oxidoreductase; NNK, 4-(methylnitrosoamine)-1-(3-pyridyl)-1-butanone; MDS, Myelodysplastic syndromes.

Americans)¹⁸). The *CYP2E1 c1* genotype was found to be associated with a 14.0-fold increased risk of lung cancer in Mexican Americans but no association was found in African Americans; the interaction between mutagen sensitivity and the *CYP2E1 c1* genotype was especially strong in former smokers judging from the odds ratios. Therefore, Wu *et al.* concluded that Mexican American individuals who lack a *c2* allele might be at higher risk for developing lung cancer.

CYP2E1 is an essential isozyme responsible for benzene metabolism, and thereby thought to be primarily involved in hematotoxicity¹⁹). Rothman *et al.* investigated the relationship between interindividual variation in the enzymes that activate (*CYP2E1* genotype and metabolic activity of the enzyme specific substrate, chlorozoxazone) and inactivate (*NQO1* genotype) benzene and its metabolites and benzene hematotoxicity by a case-control study in Shanghai, China²⁰). Subjects with both a rapid metabolic rate of chlorozoxazone and two copies of the *NQO1 609C* T mutation had a 7.6-fold (95% confidence interval, 1.8–31.2) increased risk of hematotoxicity compared to that of subjects with a slow metabolic rate who carried one or two wild-type *NQO1* alleles; the *CYP2E1 c1/c2* polymorphism did not influence

the hematotoxicity. Thus, *NQO1* polymorphism and catalytic activity of the *CYP2E1*, not the *CYP2E1* genotype, plays an important role in the development of benzene-induced leukemia and myelodysplastic syndromes. Namely, the *CYP2E1* genotypic difference is not always reflected in the catalytic activity.

CYP2D6

The well-described genetic polymorphism of the *CYP2D6* gene influences response to a wide variety of therapeutic agents metabolized by the gene product²¹). *CYP2D6* also plays a role in the metabolic activation of the tobacco specific nitrosamine, 4-(methylnitrosoamine)-1-(3-pyridyl)-1-butanone (NNK)²²). From that point of view, the relationships between the polymorphism and susceptibility to lung²³) and bladder cancer²⁴), and to leukemia²⁵) have been investigated. Bouchardy *et al.*²⁶) evaluated *CYP2D6* activity, determined by *in vivo* metabolic rate of dextromethorphan, in 128 cases of lung cancer and 157 controls. The effect of tobacco on lung cancer risk increased with increasing *CYP2D6* activity. They concluded that smokers with both the highest *CYP2D6* activity and daily tobacco consumption are at very high risk

for lung cancer. Namely, the *CYP2D6* polymorphism may be a risk factor for this cancer only among heavy smokers with the phenotyped changes. In contrast with the tobacco specific nitrosamine and therapeutic agents, this isozyme appears not to be responsible for the metabolism of industrial chemicals.

ALDH2

Of the metabolizing enzymes of aldehydes in the human liver, ALDH2 is the primary isozyme responsible for the alcohol intermediate metabolite, acetaldehyde. This isozyme is known to be expressed polymorphically, and especially in the Asian population: active homozygote *ALDH2*1/1*, active/inactive heterozygote *ALDH2*1/2* and inactive homozygote *ALDH2*2/2*. These genotypes are closely related to flushing phenomenon subsequent to drinking and drinking behavior^{27, 28}. We investigated the *ALDH2* genotypes and substrate specificity by using human liver specimens from 32 Chinese patients who were undergoing surgery for either primary liver tumor or hepatic metastases at the Fourth hospital of Hebei Medical College in China (Wang *et al.*, unpublished data). The genotype of *ALDH2* was classified into two groups: one including 25 subjects with *ALDH2*1/1*, the other including 7 subjects with *ALDH2*1/2*. No subjects in this series had *ALDH2*2/2*. In liver mitochondria and cytosol fractions, the metabolic activities of low molecular aldehydes such as formaldehyde and acetaldehyde were significantly lower in persons with *ALDH2*1/2* than in those with *ALDH2*1/1*. In contrast, no difference was observed in the metabolic activity of aromatic and high relative molecular aldehydes such as benzaldehyde and vitamin A aldehyde.

Figure 1 shows the comparison of total ALDH activity in 700 g supernatant of human liver for aliphatic aldehydes with a different length of carbon chain (Wang *et al.*, unpublished data). The activities for acetaldehyde, butylaldehyde, and capronaldehyde (1-hexanal) were significantly greater in subjects with *ALDH2*1/1* than in those with *ALDH2*1/2*. However, no differences were observed in the activities for heptaldehyde and octaldehyde between the two groups. The affinity of aldehydes with a carbon chain of more than five for *ALDH2*1/2* may be negligible. Thus, the *ALDH2* polymorphism may not always influence the metabolism of all aldehydes.

GSTM1

GSTs comprise a complex supergene family of soluble isozymes and plays a major role in the cellular metabolism and detoxification of carcinogens²⁹. Human GSTs exist

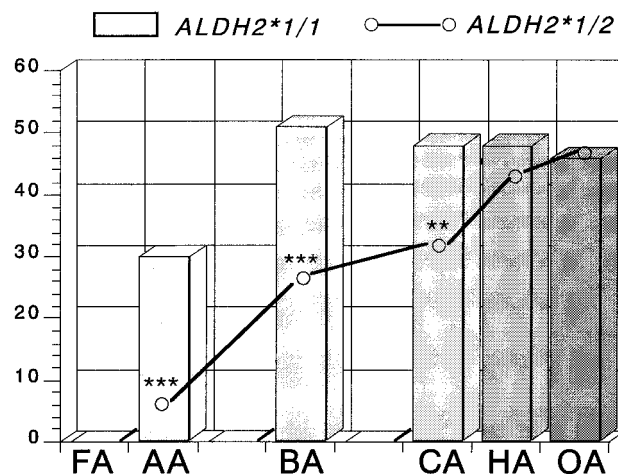


Fig. 1. Comparison of total ALDH activities (nmol NADH/min/mg protein) in 700 g supernatant of human liver for aliphatic aldehydes with different lengths of carbon chain.

FA, formaldehyde HCHO; AA, acetaldehyde CH_3CHO ; BA, butylaldehyde $\text{CH}_3(\text{CH}_2)_2\text{CHO}$; CA, *n*-capronic aldehyde (1-hexanal) $\text{CH}_3(\text{CH}_2)_4\text{CHO}$; HA, *n*-heptaldehyde $\text{CH}_3(\text{CH}_2)_5\text{CHO}$; OA, *n*-octaldehyde $\text{CH}_3(\text{CH}_2)_6\text{CHO}$. *, **, *** Significant differences in the activities were seen between persons with *ALDH2*1/1* and *ALDH2*1/2* (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

in four classes, alpha (*GSTA1/2*), mu (*GSTM1*, *M2*, *M3*), pi (*GSTP1-1*), and theta (*GSTT1*)^{30, 31}. Some members of the superfamily are expressed polymorphically (e.g., *GSTM1*³²⁻³⁴, *GSTM3*³⁵⁻³⁷, *GSTT1*³⁸⁻⁴⁰, *GSTP1*⁴¹⁻⁴³); such polymorphism may lead to wide interindividual variation in the metabolic activation of chemical carcinogens^{44, 45}.

In general, individuals who lack the *GSTM1* gene are more likely to contract lung cancer than those who have the gene³²⁻³⁴. This finding may be due to the important role ascribed to the *GSTM1* enzyme in the detoxification of hazardous compounds. Since GST isozymes other than *GSTM1* also contribute to the detoxification of toxic hydrophobic electrophiles⁴⁶, knowledge of the contribution of other GST isozymes is important for a better understanding of interindividual variation in responses to carcinogens.

We analyzed *GSTM1* genotype and total GST activity, measured by the metabolic rate of 1-chloro-2,4-dinitrobenzene in lung cytosol fractions from patients with lung cancer or other lung disease¹⁰. Although no difference in pulmonary GSH content was seen between the patients with and without the gene, GST activity was greater in patients with the *GSTM1* gene than in those without it, suggesting that, regardless of the other *GST* genotype or phenotype, *GSTM1* genotype plays an important role in detoxification of toxic chemicals. Interestingly, smoking

did not influence GST activity, in contrast to its effect on the activity of CYP1A1.

Interaction between *GSTM1* genotypes and benzo[a]pyrene DNA adducts through air pollution in urban and rural areas was investigated in 120 healthy residents without a smoking habit⁴⁷. A regional-dependent difference in the adducts level was seen, whereas no influence of *GSTM1* genotypes was found.

GSTT1

GSTT1 has two exclusive roles, that of inactivation and that of activation, for chemical substances. Individuals with the *GSTT1* null genotype are less able to detoxify metabolites of several carcinogens, including 1,3-butadiene, methyl bromide, and ethylene oxide^{38, 39}. In contrast, individuals who inherit the *GSTT1* enzyme can produce a mutagenic metabolite of dichloromethane following conjugation with glutathione³⁹.

Sosa *et al.* demonstrated an importance of the *GSTT1* genotype in occupational-related disease⁴⁸. They analyzed the *GSTT1* genotype and cytogenetic parameters such as chromosomal aberrations, sister chromatid exchanges and micronuclei in peripheral blood lymphocytes from 1,3-butadiene-exposed workers. Although no relationship was established between the exposure levels and the cytogenetic parameters, chromosomal aberrations were significantly increased among the workers lacking the *GSTT1* gene compared to their frequency in workers with the gene.

Chen *et al.*⁴⁰ also reported an increased risk for myelodysplastic syndromes (MDS) in individuals with a *GSTT1* gene defect. They investigated *GSTT1* and *GSTM1* genotypes in 190 controls and 92 MDS cases. The frequency of patients without *GSTT1* in MDS case was 46%, which was significantly higher than that in the controls. On the other hand, the frequency of patients without *GSTM1* in MDS cases was 42%, which was equal to that in the controls. They concluded that individuals with the *GSTT1* null genotype may have enhanced susceptibility to MDS. Unfortunately, they did not mention whether the MDS cases were exposed to chemicals catalyzed by *GSTT1*.

NAT

Acetylation catalyzed by NAT is the major route of arylamine phase II metabolism. The two genes (*NAT1** and *NAT2**) that encode NATs have been sequenced, and are located at distinct loci on chromosome 8⁴⁹. The *NAT1* is polymorphically distributed in humans, and individuals that inherit rapid *NAT1* are at a high risk of bladder cancer⁵⁰. Independent of this, *NAT2* exhibits a polymorphism due to

point mutations in the coding region, and individuals possessing it can be designated as phenotypically slow or fast metabolizers⁵¹.

Risch *et al.*⁵² investigated the distribution of fast and slow *NAT2* acetylator genotypes and tobacco use in 189 bladder cancer patients and 59 control patients who had non-malignant urological complaints. All patients were of Caucasian origin. A significant excess of genotypic slow acetylator was found in cancer patients who were smokers, and in those with high risk occupations. They concluded that the slow *N*-acetylation genotype is a susceptibility factor in occupational- and smoking- related bladder cancer.

Knudsen *et al.* reported on the interaction between *NAT2* and *GSTM1* genotypes and genotoxic damage in 106 nonsmoking bus drivers and 101 postal workers in the Copenhagen metropolitan area⁵³. Bus drivers with the *GSTM1* null and slow acetylator *NAT2* genotype had an increased frequency of cells with chromosomal aberrations. Postal workers who possessed the *NAT2* slow acetylator also showed elevated chromosomal aberrations. Recently, interaction between *NAT2* genotypes and the metabolism of occupationally-used hydrazine was also investigated^{54, 55}. The biological half-life of hydrazine was greater in workers with the slow *NAT2* genotype, followed in descending order by the intermediate and rapid types. Thus, *NAT2* genotypes play an important role not only in susceptibility to cancer but also in biological monitoring of occupational chemicals.

We investigated *NAT2* genotypes in Japanese subjects, including 149 bladder cancer patients and 163 sex- and age-matched controls who had non-malignant urological complaints (Kontani *et al.* unpublished data). The frequency of the *NAT2* slow acetylator genotype was less than 10% in all subjects. We failed to implicate *NAT2* polymorphism as cancer risk factor in this sample Japanese population. In contrast, we found that tobacco use and occupational exposure to carcinogens such as manufacture of rubber, rubber products, and dyestuffs are major risks for bladder cancer in Japanese populations investigated by us.

Acquired Factors

The acquired factors that influence the metabolism and toxicity of xenobiotics *via* induction or inhibition of CYP, or other enzymes involved in functionalization and conjugation reactions, are listed in Table 2. In many cases, the effects were investigated by use of experimental animals. For example, low carbohydrate diet⁵⁶, fasting⁵⁷, or ethanol intake⁵⁸ induces hepatic CYP2E1 in rats, and significantly affects the toxicity of chemicals such as carbon

Table 2. Drug-metabolizing enzymes in relation to established and suspected biomarkers of susceptibility: acquired factors

	Induced/inhibited enzymes	
	Animal	Human
Nutrition		
Carbohydrate	CYP2E1	
Protein	CYP2C11/6	
Fasting	CYP2E1	
Ethanol	CYP2E1	CYP2E1
Smoking	CYP1A1/2	CYP1A2
Sex	CYP2C11, CYP2C12	
Age	CYP2E1, CYP2C11	
Pregnancy	CYP2E1	
Disease		
Diabetes	CYP2E1, CYP2B1	
Chemicals		
Polychlorinated hydrocarbon	CYP1A1/2	
Phenobarbital	CYP2B1/2, GST, UDPGT	CYP2C8
Trichloroethylene	CYP2E1, ALDH	ALDH2

tetrachloride⁵⁹), chloroform⁶⁰), and trichloroethylene (TRI)⁶¹). CYP2E1 slightly decreases during pregnancy⁶²), whereas this isozyme increases after treatment of diabetes-induced chemicals⁶³). In rats, a typical sex difference is observed in the expression of sexual hormone-dependent CYP, CYP2C11, and CYP2C12, after maturity⁶²). There are a large number of chemicals that induce drug-metabolizing enzymes; most of these cases induce more than one isozyme⁵). However, for a few cases, the relationship between these acquired factors and susceptibility to disease has been identified.

TRI, a degreasing solvent, was one of the most widely used chlorinated aliphatic hydrocarbons. Gross overexposure resulted in the full spectrum of responses, including central nervous system depression, hepatic injury, and dermatitis. In 1974, Stewart *et al.*⁶⁴) reported an interesting dermal response, a fascinating phenomenon referred to as "Degreaser's Flush": workmen drinking beer following industrial exposure to TRI vapor were observed to develop vivid red blotches on their faces.

In order to investigate the effect of TRI exposure on the metabolism of acetaldehyde, rats treated with TRI were killed, and ALDH activity was measured by measuring the formation of NADH⁶⁵). TRI treatment clearly decreased the activity. Thus, Degreaser's Flush resulted from the decreased metabolism of acetaldehyde in the liver.

There are many endogenous and exogenous aldehydes or chemicals with aldehydes as intermediates in the metabolism. The question is whether TRI exposure decreases the metabolism of all aldehydes or whether TRI exposure

decreases only acetaldehyde metabolism. In order to answer this question, the effect of TRI on the metabolism of ten kinds of aldehydes in rat liver was analyzed. TRI exposure clearly decreased activity for formaldehyde, chloral hydrate, propionaldehyde, and phenylacetaldehyde. TRI, however, did not influence the metabolism of nonyl aldehyde, benzaldehyde, 3-propionaldehyde, or retinaldehyde, and, inversely, it increased the metabolism of 2,5-dihydroxybenzaldehyde. Thus, aldehydes whose metabolism is inhibited by TRI are limited to low molecular aliphatic aldehydes, and aldehydes with a carbon length of more than five may not be affected.

These results, combined with those from the *ALDH2* genotype and phenotype analysis, show that the TRI intermediate metabolite chloral hydrate preferentially binds *ALDH2*, resulting in the inhibition of acetaldehyde metabolism and causing Degreaser's Flush: TRI produces a false *ALDH2* polymorphism. It should be clarified whether *ALDH2* genotypes as well as TRI exposure affect the toxicity of low molecular aldehydes such as formaldehyde or chemicals with aldehydes as intermediate metabolites *in vivo*.

Smoking induces the expression of CYP1A1/2 in some individuals^{66,67}), in whom there may be increased production of reactive intermediates from carcinogens such as polycyclic aromatic hydrocarbon. The AHH activity in lung microsomes from current smokers was significantly higher than that from non-smokers, showing an average 14-fold increase¹⁰). There was no difference in AHH activity between cancer and non-cancer groups; the higher average activity of AHH in cancer

patients was considered to be due to the larger number of smokers and ex-smokers in this group. Tobacco use did not influence GST activity measured by 1-chloro-2,4-dinitrotoluene, or epoxide hydrolase activities.

Conclusion

Numerous reports have appeared concerning genetic polymorphism of drug-metabolizing enzymes and susceptibility to disease, though the accumulated data may be insufficient to evaluate inter-individual differences in the risk of industrial chemicals. The reasons are as follows: i) the interaction between the genetic polymorphism and observed susceptibility to disease could not be interpreted based on the phenotyping findings, or on the metabolic activity in the target organ; ii) conflicting results between studies concerning the existence or absence of such a relationship have been reported. In the former case, we consider that a biologically plausible mechanism linking genetic polymorphism and susceptibility to disease has yet to be resolved; in the latter case, we consider that additional studies are required. Among the varied findings, however, some coincident data has been presented regarding the isozymes involved in conjugation reactions, such as GSTM1, GSTT1, NAT2, and NQO1, as well as regarding CYP2D6 and ALDH2, which are involved in functionalization reactions, though CYP2D6 may not play an important role in response to industrial chemicals.

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