Effect of variation of exposure to airborne chlorobenzene on internal exposure and concentrations of urinary metabolite

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Abstract

Objectives—This study aimed to develop a physiologically based pharmacokinetic model for chlorobenzene and to investigate the effect of variation in exposure to chlorobenzene on the chlorobenzene concentration in blood and the urinary concentration of 4-chlorocatechol.

Methods—A physiologically based pharmacokinetic model was developed and the simulated results of urinary 4-chlorocatechol concentrations were compared with the values found in experiments and field surveys. The area under the chlorobenzene concentration-time curve in blood (CBBauc) was selected as the measure of internal exposure related to the chronic effect of chlorobenzene. The maximum one-hour time weighted average value of chlorobenzene concentration in blood (CBBmax) was chosen as the measure of internal exposure related to the acute effect of chlorobenzene. The total amount of urinary 4-chlorocatechol (TOTCC) and that excreted during the last four hours (CC(4-8)) or two hours (CC(6-8)) of exposure as well as that excreted during two hours on the next morning (CC(22-24)) were used to represent concentrations of urinary metabolites. The effects of variation of the one-hour time weighted averages of airborne chlorobenzene exposure (CBAs) on the internal exposures and the concentrations of urinary metabolites were investigated with the pharmacokinetic model.

Results—The comparison of the simulated results with the observed data showed that the pharmacokinetic model can be used to estimate the urinary concentrations of 4-chlorocatechol. The CBBauc and TOTCC were not affected by changes in both the geometric SD (GSD) of CBAs or the variations in CBAs. The CBBmax varied with changes in both the GSD and CBAs. The CC(4-8) and CC(6-8) did not vary with the GSD, but these concentrations were affected by the change in the CBAs. Although there was little effect of the GSD and CBAs on the CC(22-24), this value highly reflected the exposure over the preceding days.

Conclusion—To protect workers from the chronic effect of chlorobenzene, it may be sufficient to control the daily average exposure. To protect from the acute effect, however, the short term exposure must be controlled as well. The values of

CC(4-8) and CC(6-8) were acceptable for estimating daily average exposure, but the CC(22-24) was not.

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Keywords: chlorobenzene; 4-chlorocatechol; pharmacokinetic model

Chlorobenzene is a chemical widely used as an organic solvent, a chemical intermediate, and a heat transfer medium. It is toxic to the liver and kidney of animals and also has an acute effect on the central nervous system.¹⁻³ Chlorobenzene is metabolised to 4-chlorocatechol (4-CC), *o*-, *m*- and *p*-chlorophenols, and 4-chlorophenylmercapturic acid in humans.⁴⁻⁷ Ogata *et al* found linear correlations between airborne exposure and urinary 4-CC and *p*-chlorophenol in an experimental study of humans.⁴ Yoshida *et al*⁶ and Kumagai and Matsunaga⁷ also found similar results with workers exposed to chlorobenzene.

In general, the airborne exposures vary with time in workplaces. Previously, we showed that urinary 4-CC varied with the within day variation of the airborne exposure to chlorobenzene.⁷ Thus, the concentration of urinary 4-CC may not be appropriate as an index of daily average exposure when the variation in airborne exposure is high. Also, internal exposures, such as the chlorobenzene concentration in blood, can change with the variation in airborne exposure even if the daily average exposure is fixed. Although it is not clear whether the toxicity of chlorobenzene is due to the parent chemical or its metabolites, the chlorobenzene concentration in blood is considered to be closely related to the toxicity. Consequently, it is important for industrial hygienists to clarify how the variation in airborne exposure acts on the internal exposures.

The physiologically based pharmacokinetic model has been developed to simulate uptake, distribution, metabolism, and elimination of organic solvents.⁸⁻¹⁵ Although such a model requires much information including ventilation rate, cardiac output, metabolic rate, and tissue to blood partition coefficients, the internal exposure and urinary metabolite can be estimated by inputting the appropriate scenario of airborne exposure into the model. In this paper, we developed a physiologically based pharmacokinetic model for chlorobenzene and investigated how variation in airborne exposure affects the concentrations of chlorobenzene in blood and 4-CC in urine.

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Methods

DESCRIPTION OF THE MODEL

Figure 1 shows the diagram of our model. Table 1 summarises the parameters in the model.

The body is considered to consist of five groups of tissue for distribution of chlorobenzene (fig 1): the lung, blood vessel rich tissues containing the brain, heart, and kidney, a group of tissues containing muscles and skin that have low perfusion rates, fatty tissues, and an organ of metabolism, the liver. The volume of each tissue group was determined by multiplying the body weight by the relative percentage of the tissue group, which was calculated from the equations described by Fiserova-Bergerova and Hughes¹⁶ (table 1). Partition coefficients for chlorobenzene were 30.8 blood/air, 4.1 water/air, and 3763 oil/air.¹⁷ Tissue/blood partition coefficients were calculated according to the equations proposed by Droz *et al*¹⁰ (table 1).

Alveolar ventilation at rest was taken from the data shown by Guyton¹⁸ and cardiac output from Stahl¹⁹ (table 1). At a physical workload of 40 W alveolar ventilation was assumed to be 2.6 times and cardiac output 1.6 times the resting values on the basis of linear relations between these physiological functions and workload as shown by Åstrand.²⁰ The blood flow to each tissue group was determined by multiplying the cardiac output by the relative percentage of flow to each tissue (table 1). The relative percentage values at rest were calculated from the data shown by Fiserova-Bergerova and Hughes¹⁶ and at 40 W from Åstrand.²⁰

It was assumed that metabolism of chlorobenzene occurs only in the liver and can be described by the "well stirred" model.²¹ Sullivan *et al* found the apparent half life of pulmonary chlorobenzene elimination in rats after inhalation exposure.²² With the elimination constant and physiological parameters in rats, the hepatic intrinsic clearance was calculated to be 5700 ml/h. The hepatic intrinsic clearance in humans was estimated to be 350 l/h (60–70 kg body weight) based on assumptions that the Michaelis constant (Km) value is fixed between species and the

Table 1 Simulated parameters for humans

Tissue	Volume (l)	Blood flow (l/h)		$\lambda_{tis}/b\lambda$
		Rest (0W)	Working (40W)	
Lung	VL*	Q (0)	Q (40)	
Blood vessel rich	0.067 × BW	0.47 × Q (0)†	0.32 × Q (40)‡	3.6
Muscles	0.491 × BW	0.24 × Q (0)†	0.47 × Q (40)‡	1.8
Fatty	0.149 × BW	0.05 × Q (0)†	0.06 × Q (40)‡	86
Liver	0.025 × BW	0.24 × Q (0)†	0.15 × Q (40)‡	3.6

Parameters: Q (0) = 11.2 × BW^{0.81}; Av (0) = 0.7 × 19.9 × BW^{0.74}; Q (40) = 1.6 × Q (0)**; Av (40) = 2.6 × Av (0)**; Hepatic intrinsic clearance = 350 l/h††; Proportion of 4 CC in total amount of urinary metabolites = 35%; Urinary excretion constant of 4 CC = 0.315 h⁻¹‡‡.

*VL = functional residual capacity + (volume of arterial blood) × λ (blood/air) + (lung tissue volume) × λ (tissue/air) by Fiserova-Bergerova *et al*.¹⁵

†Fiserova-Bergerova and Hughes.¹⁶

‡The values were calculated based on the data by Åstrand.²⁰

§ λ tissue/blood were calculated by the equations proposed by Droz *et al*.¹⁰

||Cardiac output (l/h) by Stahl.¹⁹

¶Alveolar ventilation (l/h) by Guyton.¹⁸

**The values were calculated based on the linear relations between these physical functions and workload as shown by Åstrand.²⁰

††The value was estimated from the experimental data in rats by Sullivan *et al*.²²

‡‡Ogata *et al*.⁴

BW = body weight (kg).

Figure 1 Diagram of the physiologically based pharmacokinetic model used to simulate the pattern of distribution of chlorobenzene in the body and urinary excretion of 4-CC. V_x = volume of tissue group X (l); C_x = chlorobenzene concentration in tissue group X ($\mu\text{g/l}$); C_m = chlorobenzene concentration in inhalation air ($\mu\text{g/l}$); C_e = chlorobenzene concentration in exhalation air ($\mu\text{g/l}$); λ_x = tissue/blood partition coefficient in tissue group X; λ_b = blood/air partition coefficient; A_v = alveolar ventilation (l/h); Q_m = cardiac output (l/h); Q_x = rate of blood flow to tissue group X (l/h); V_{max} = maximum enzymatic reaction rate ($\mu\text{g/h}$); K_m = Michaelis constant ($\mu\text{g/l}$).

maximum enzymatic reaction rate (Vmax) is linear to the 0.7 power of body weight. The proportion of 4-CC in all metabolites of chlorobenzene was assumed to be 35% (as chlorobenzene) so that the total amount of urinary 4-CC (as chlorobenzene) was close to

26.5% of the total amount of chlorobenzene passing through the lungs, which was based on the study by Ogata *et al.*⁴ The urinary elimination rate of 4-CC was assumed to be linear to the body burden. The urinary elimination constant of 4-CC was determined to be 0.315/h according to the urinary excretion curve after inhalation exposure to 10 and 50 ppm by human volunteers.⁴ We expressed the urinary 4-CC concentration relative to creatinine excretion, assuming that the urinary elimination rate of creatinine is 1.5 g/day in a human of 60 kg body weight and is a linear function of the volume of the muscle group of tissues.¹⁰

COMPUTER SIMULATION

The simultaneous differential equations describing the kinetics of chlorobenzene and 4-CC are as follows:

$$\begin{aligned} \text{Lung} \\ V_L(dC_{out}/dt) = AvC_{in} + Q_M C_M/\lambda_M + \\ Q_F C_F/\lambda_F + Q_R C_R/\lambda_R + Q_H C_H/\lambda_H - \\ Q_{tot} \lambda_B C_{out} - Q_L C_{out} \end{aligned}$$

$$\begin{aligned} \text{Liver} \\ V_H(dC_H/dt) = Q_H \lambda_B C_{out} - \\ (Q_H + V_{max}/K_m)(C_H/\lambda_H) \end{aligned}$$

$$\begin{aligned} \text{Blood vessel rich} \\ V_R(dC_R/dt) = Q_R \lambda_B C_{out} - Q_R C_R/\lambda_R \end{aligned}$$

Equations for muscle and fatty tissues are similar to that for blood vessel rich tissues.

$$\begin{aligned} \text{Metabolism and excretion} \\ dCC/dt = 0.35(V_{max}/K_m) \\ (C_H/\lambda_H) - 0.315CC \end{aligned}$$

Figure 1 explains the symbols in these equations. The differential equations were solved with a software package developed by Yamaoka,²³ and were run on an NEC personal computer PC9801FA (NEC, Tokyo).

COMPARISON WITH OBSERVED DATA

To check the appropriateness of our model, the simulated concentrations of urinary 4-CC were compared with values found in experimental and field studies.

Experimental data

Urinary 4-CC concentrations were simulated with an exposure of 10 ppm for three hours in the morning and for four hours in the afternoon with a break of one hour in between. The simulated results were compared with the human experimental results reported by Ogata *et al.*⁴ Because the mean minute ventilation of the human volunteers was reported to be 8.49 l/min, alveolar ventilation of

5.94 l/min was introduced by multiplying the minute ventilation by 0.7. The body weight was assumed to be 60 kg, which is the average for Japanese men.

Field survey data

Previously, we measured consecutive one-hour time weighted averages (TWAs) of chlorobenzene concentration in air (CBAs) and urinary 4-CC concentrations over full shifts (0800–1700) on Tuesday and Wednesday in workers A (60 kg body weight) and B (69 kg).⁷ The urinary 4-CC concentrations caused by the exposure to chlorobenzene in the workplace were simulated based on the following assumptions. (1) The body burdens of chlorobenzene and 4-CC were zero on Monday morning. (2) Daily average exposure concentrations of chlorobenzene on Monday were assumed to be 17 ppm for worker A and 13 ppm for worker B. These values were estimated from urinary 4-CC concentrations on Tuesday morning (just before the workshift), because the relation between daily average exposure and urinary 4-CC concentration on the morning of the next day had been taken in our field survey (unpublished data). (3) Because consecutive CBAs were measured over full shifts on Tuesday and Wednesday in the two workers, the urinary 4-CC concentrations were simulated based on the scenarios of observed exposure. (4) The physical workload was 40 W during working hours and 0 W at the noon break and after the working hours. These values were measured in the workplace with calorie counters combined with an accelerometer (Kenz Calorie Counter, Suzuken, Nagoya, Japan).²⁴

EFFECT OF VARIATION IN AIRBORNE EXPOSURE ON INTERNAL EXPOSURE AND CONCENTRATIONS OF URINARY METABOLITES

We assumed that the airborne exposure varied in a log normal manner, so three sets of seven CBAs for three hours in the morning and four hours in the afternoon were selected (table 2). The arithmetic mean in each set was 10 ppm and the geometric SDs (GSDs) were 1.5, 2.0, and 3.0, which represent low, moderate, and high variations.²⁵ The CBAs at the noon break and after working hours were 0 ppm. The physical workload was assumed to be 40 W during working hours and 0 W at the noon break and after working hours.

The area under the chlorobenzene concentration-time curve in blood (CBBauc) was selected as the measure of internal exposure that might be related to the chronic effect of chlorobenzene. The CBBauc was defined as:

$$CBBauc = \int_0^{\infty} CBB(t)dt$$

where CBB(t) is chlorobenzene concentration in blood at time t. The maximum one-hour TWA value of chlorobenzene concentration in blood (CBBmax) was chosen as the measure of internal exposure that might be connected with the acute effect of chlorobenzene.

Table 2 Three sets of seven 1 h TWAs of exposure to airborne chlorobenzene

Variation of 1 h TWAs		
GSD = 1.5 (ppm)	GSD = 2.0 (ppm)	GSD = 3.0 (ppm)
5.1	3.0	1.2
6.8	4.7	2.6
7.8	6.1	3.9
9.3	8.2	6.2
11.0	10.8	9.8
12.8	14.2	14.8
16.9	22.7	31.1

Table 3 Comparison of simulated results with experimental values

	CC(4-8) (mg/g creatinine)	CC(6-8) (mg/g creatinine)	Excretion ratio* (%)
Simulation	51.9	59.4	26.5
Experiment†	56.7	65.6	26.5

*Ratio of urinary 4-CC (as chlorobenzene) to the total amount of chlorobenzene passed through the lungs.

†Ogata *et al.*⁴

The total amount of urinary 4-CC (TOTCC), the 4-CC concentration in urine excreted during the last four hours of exposure (CC(4-8)), that during the last two hours of exposure (CC(6-8)), and that during two hours the next morning (CC(22-24)) were selected as being representative of the concentration of urinary metabolites.

Simulation for the first exposure day was repeated 200 times. In each simulation, the seven CBAs were permuted at random by a generator of random numbers in a personal computer. Finally, the mean and coefficient of variation (CV) of the internal exposure and the concentration of urinary metabolites among the 200 trials were calculated. In workplaces, the internal exposure and concentration of urinary metabolites are considered to be affected by the exposure on the previous days and weeks. With our model, the body burdens of chlorobenzene and 4-CC were simulated based on the weekly schedule of five working days and two days holiday, and these burdens were estimated to reach steady state on or after the third week. Consequently, simulation on Thursday in a steady state week was also carried out.

Results

COMPARISON WITH OBSERVED DATA

Table 3 and fig 2 show the simulated and human experimental results of urinary 4-CC. The CC(4-8) was estimated to be 51.9 and the CC(6-8) 59.4 mg/g creatinine, which agreed well with the experimental results. The simulated urinary 4-CC excretion curve after the exposure was very close to the experimental one (fig 2).

Figures 3 and 4 show the results of the simulation and the field study. For worker B (fig 4), although the simulated concentrations of urinary 4-CC were about half of the corresponding values found in the first half of the shift, the agreement was within 15% over the last four hours. For worker A (fig 3), all estimated values except one were within 20% of the values found over the last four hours.

EFFECT OF VARIATION IN AIRBORNE EXPOSURE ON INTERNAL EXPOSURE

Table 4 lists the means and CVs of CBBAuc among the 200 trials. The means of CBBAuc were 3.01 mg h/l, and these values were fixed regardless of the change in the GSD of CBAs. Because the CVs of CBBAuc were <0.01, the CBBAuc value of each trial was almost never

Figure 2 Comparison between simulated and observed urinary excretion curves of 4-CC after exposure to chlorobenzene at 10 ppm.

Figure 3 Comparison between simulated and observed values of urinary 4-CC in worker A.

Figure 4 Comparison between simulated and observed values of urinary 4-CC in worker B.

Table 4 Effect of variation of airborne chlorobenzene exposure on internal exposure (CBBAuc)*

Airborne exposure variation (GSD)	CBBAuc (mg h/l)	
	Mean	CV
1.5	3.01	>0.01
2.0	3.01	>0.01
3.0	3.01	>0.01

*Area under chlorobenzene concentration-time curve in blood.

Table 5 Effect of variation of airborne chlorobenzene exposure on internal exposure (CBBmax)*

Airborne exposure variation (GSD)	CBBmax (mg/l)	
	Mean	CV
First exposure day:		
1.5	0.39	0.08
2.0	0.47	0.09
3.0	0.60	0.08
Thursday in a steady state week:		
1.5	0.41	0.08
2.0	0.50	0.09
3.0	0.62	0.07

*Maximum 1 h TWA value of chlorobenzene concentration in blood.

Table 6 Effect of variation of airborne chlorobenzene in exposure on TOTCC

Airborne exposure (GSD)	TOTCC (mg)	
	Mean	CV
1.5	82.9	>0.01
2.0	82.9	>0.01
3.0	82.9	>0.01

affected by a change in the permutation of CBAs.

Table 5 lists the means and CVs of CBBmax. The means of CBBmax increased from 0.39 to 0.60 mg/l with an increase in the GSD of CBAs on the first day of exposure. The CVs were 0.08 to 0.09, so that the CBBmax value in each trial was affected to a certain extent by a change in the permutation of CBAs. Similar tendencies were found in CBBmax on Thursday in a steady state week.

EFFECT OF AIRBORNE EXPOSURE VARIATION ON CONCENTRATIONS OF URINARY METABOLITES
Table 6 shows the simulated results of TOTCC. The means of TOTCC were 82.9 mg with CVs of <0.01, which suggest that TOTCC did not vary with changes in both GSD and the permutation of CBAs.

Table 7 shows the simulated results of CC(4-8), CC(6-8), and CC(22-24) on the first day of exposure and on Thursday in a steady state week. The means of CC(4-8), CC(6-8), and CC(22-24) were 89.0-89.7, 102-103, and 6.1 mg/g creatinine on the first day, and 101-102, 114-115, and 12.8 mg/g creatinine on Thursday in a steady state week. Consequently, these mean values almost

never varied, regardless of any changes in the GSD of CBAs. The CC(4-8) and CC(6-8) values in each trial were affected to a certain extent by changes in the permutation of CBAs, especially in the case with the largest GSD, because the CVs ranged from 0.06 to 0.18. The relation found between these urinary 4-CC concentrations and the variation in seven CBAs was that when the CBAs at the start and end of the shift were low and the CBAs in the middle of the shift were high, the CC(4-8) and CC(6-8) were the largest. Inversely, when the CBAs at the start and end of shift were high and the CBAs in the middle of shift were low, the CC(4-8) and CC(6-8) were the smallest. On the other hand, the CVs of CC(22-24) were 0.02-0.08, which were less than those of CC(4-8) and CC(6-8). Consequently, the effect of the permutation of CBAs on CC(22-24) was low.

The means on Thursday in a steady state week increased by 13% of the means on the first day of exposure for CC(4-8), by 12% for CC(6-8), and by 110% for CC(22-24). This finding suggests that the CC(22-24) value is greatly influenced by the previous exposures in comparison with CC(4-8) and CC(6-8).

Discussion

A physiologically based pharmacokinetic model that consisted of five tissue groups was used in general to describe uptake, distribution, metabolism, and elimination of organic solvents in the human body.^{9,13} The metabolic rate for chlorobenzene was assumed to be of the first order in our model. The simulations in this paper were not of high exposure, because the daily average CBAs was 10 ppm and the maximum CBA was 31.1 ppm. The maximum one-hour TWA value of chlorobenzene concentration in the liver from all 1200 trials was 0.46 mg/l, so that the chlorobenzene concentration in venous blood leaving the liver was <0.13 mg/l. Koizumi estimated the Michaelis constants (Km) for trichloroethylene to be 2.5 mg/l and for tetrachloroethylene to be 1.0 mg/l in humans.⁸ The Km value for styrene was shown to be 0.36 mg/l and for n-hexane 0.58 mg/l.^{12,13} If the Km value for chlorobenzene is similar to that for these organic solvents, the metabolic rate is considered to be roughly of the first order in our exposure scenarios, because the chlorobenzene concentration in venous blood leaving the liver was much less than the Km value.

The urinary metabolites of chlorobenzene are 4-CC, *o*-, *m*- and *p*-chlorophenols, and 4-chlorophenylmercapturic acid. The amount of 4-chlorophenylmercapturic acid is negligible. Ogata *et al* reported that the proportion (as chlorobenzene) of urinary 4-CC in the total amount of the four urinary metabolites was 64%.⁴ When that proportion was applied in our model the excretion ratio of 4-CC to the total amount of chlorobenzene that passed through the lungs was 48.2%, which was considerably different from the value (26.5%) obtained experimentally. Consequently,

Table 7 Effect of variation of exposure to airborne chlorobenzene on urinary 4-CC concentration

Airborne exposure (GSD)	Urinary 4-CC concentration (mg/g creatinine)					
	CC(4-8)		CC(6-8)		CC(22-24)	
	Mean	CV	Mean	CV	Mean	CV
First exposure day:						
1.5	89.0	0.07	102	0.07	6.1	0.03
2.0	89.4	0.11	102	0.12	6.1	0.05
3.0	89.7	0.17	103	0.18	6.1	0.08
Thursday in a steady state week:						
1.5	101	0.06	114	0.06	12.8	0.02
2.0	101	0.10	114	0.10	12.8	0.03
3.0	102	0.15	115	0.16	12.8	0.04

assuming that unknown metabolites exist, the proportion of 4-CC in the total amount of all metabolites was determined to be 35% in our model. When this proportion was applied, the simulated excretion ratio (26.5%) was equal to the observed ratio.

The simulated results were in good agreement with the experimental data. For worker B in the field survey, the simulated values were about half of the observed values in urine collected at 1030 on the two days. Because chlorobenzene exposure was measured as a one-hour time weighted average, the exposure concentration was assumed to be constant for one hour in the simulation. In general, exposure concentration, however, varies from minute to minute in workplaces. If worker B was exposed at a higher level from 1000 to 1030 and at a lower level from 1030 to 1100, the discrepancy between the simulated and observed values can be explained. In the last half of the exposure period of the field survey, the simulated results were in good agreement with the observed values. Consequently, our model is considered to be able to describe the kinetic behaviour of chlorobenzene in the human body.

Animal experimental studies have shown that chlorobenzene is toxic to the central nervous system, kidney, and liver.^{1,3} It is not clear whether the toxicity is due to the parent chemical or its metabolites, but the chlorobenzene concentration in blood may be closely related to the toxic intensity on the organs. Consequently, CBBauc and CBBmax were selected as measures of internal exposure related to the chronic and acute effects. Because our simulation showed that CBBauc was not affected by changes in GSD and variation in CBAs, it may be sufficient to control the daily average exposure to protect workers from the chronic effects of chlorobenzene exposure. For protection from the acute effects, the short term exposure must also be controlled, as the CBBmax varied with changes in the GSD and permutation of CBAs.

Urinary 4-CC has been shown to be a good biological exposure index in previous studies.^{4,6,7} The present simulation showed that the CC(4-8) and CC(6-8) did not vary with the GSD of CBAs. Although these concentrations of urinary metabolite were affected by the permutation of CBAs, the CC(4-8) and CC(6-8) were acceptable for estimating the daily average exposure, because the CVs (0.07-0.18) were not very high. Although the effect of the GSD and permutation of CBAs on the CC(22-24) was low, this concentration of urinary metabolite was not acceptable for estimating the daily average exposure, because it highly reflected the exposures of the previous days.

Our study examined the effects of variation in airborne exposure on the internal exposure and concentrations of urinary metabolites. Between worker variations in hepatic and kidney functions and fat content also affect these

concentrations.^{10,11} Consequently, the CVs of these concentrations in workplaces are expected to be greater than the values shown here.

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