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HISTORICAL REVIEW OF HEALTH RISK ASPECTS WITH THE LEADED GASOLINE REGULATION IN JAPAN, BASED ON THE PBPK MODEL

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Abstract

In many developing countries, the leaded gasoline regulation has been promoted these years to prevent the airborne lead related health risks. Japan established the unleaded gasoline systems in 1983. In this study, the Japanese leaded gasoline regulation was examined from the both aspects of the ambient air pollution control and the health risk reduction.

The lead exposure to the reference Japanese was evaluated through the both pathways of dietary and respiratory intake, and the lead concentration in blood (PbB) was estimated by using the physiologically based pharmacokinetic model (PBPK model). The lead concentration in ambient air (PbA) and the respiratory lead intake were reduced drastically by the leaded gasoline regulation, however, the total lead exposure was not reduced because of the larger contribution of the dietary lead exposure to the average reference Japanese. The present lead exposure level is low enough for keeping PbB under the threshold concentration of 30μg/dL.

KEYWORDS: *Lead exposure, Leaded gasoline regulation, Mathematical model, Japanese, Dietary intake, Health risk analysis, Historical analysis, PBPK model*

1. Introduction

In many developing countries, the unleaded gasoline supply system has been developed as a national policy, with higher priority to reduce the health risk due to the airborne lead, especially in the highly populated metropolitan area. For example in the Philippines, the unleaded gasoline supply system is now under construction and it will be completed by January in 2001 (The Daily Manila Shinbun, 1997). Until 1970 also in Japan, the 4-alkyl-lead had been added to gasoline to increase its octane value. The leaded gasoline regulation was strongly promoted with the administrative guidance by the national government since July in 1970. Along the road with heavy traffics in the Tokyo metropolitan area, it was a turning point of the severe lead pollution in ambient air. In 1975, the law first prohibited the lead addition to the regular gasoline, and then in 1983 to the premium gasoline, which completed the leaded gasoline regulation in Japan. As is shown in Fig.1 (Japanese

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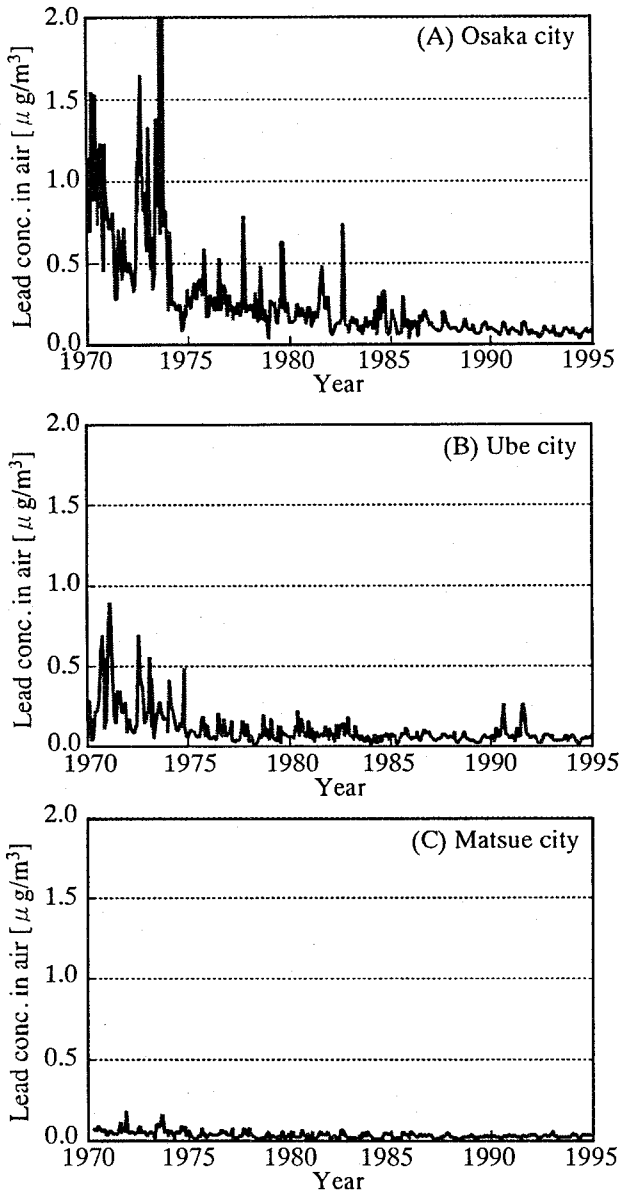


Figure 1 Variation of Lead Concentration in Ambient Air
(Monitoring data by Japanese EPA(1972-1997) is illustrated)

EPA, 1972-1997), the lead concentration in ambient air (PbA) was drastically reduced especially in the highly populated area with larger traffics. Fig.1 shows the change of PbA in several city areas such as Osaka City, which is the second largest city in Japan with heavy traffics and industry, Ube City, which is the intermediate size city with heavy industry, and Matsue City, which is the small size city without so much industry. The lead concentration reduction in ambient air after introducing the leaded gasoline regulation was also widely reported in many other countries, for example, in

Australia (Simpson et al., 1994), United Kingdom (Pattenden et al., 1987), Germany (Jost et al., 1979) and so on.

Various studies on the effects of lead on human health have demonstrated relationships between the exposure to lead and variety of adverse health effects. These effects include impaired mental and physical development, decreased heme biosynthesis, elevated hearing threshold and decreased serum levels of vitamin D and so on. Especially the health effects are closely related to the hematopoietic system and blood. Lead invades into the cytoplasm of the bone marrow protometrocyte, inhibits the hemoglobin synthesis in red blood cells, and causes anemic symptoms (Horiguchi, 1993). Lead reacts with the red blood cell membrane to increase its mechanical fragility, and decreases the lifespan of the red blood cells. Among other chronic effects due to the long-term and low-level exposure to lead, there reported the renal functional disorder like arteriolar nephrosclerosis, blood pressure increase, infertility and endocrine disruptions (Horiguchi, 1993). As chronic effects due to the higher concentration exposure to lead, there reported the central nervous system impairment like encephalopathy and also the peripheral nervous system impairment, functional impairment of liver, headache, severe myalgia and so on.

Lead is placed in the Group 2B by the IARC (IARC, 1987), and in the Group B2 by the U.S.EPA, which means that lead is possibly carcinogenic to humans and there is sufficient evidence in experimental animals but inadequate evidence in humans for its carcinogenicity. The slope factor and/or the unit risk have not been presented for carcinogenicity evaluation.

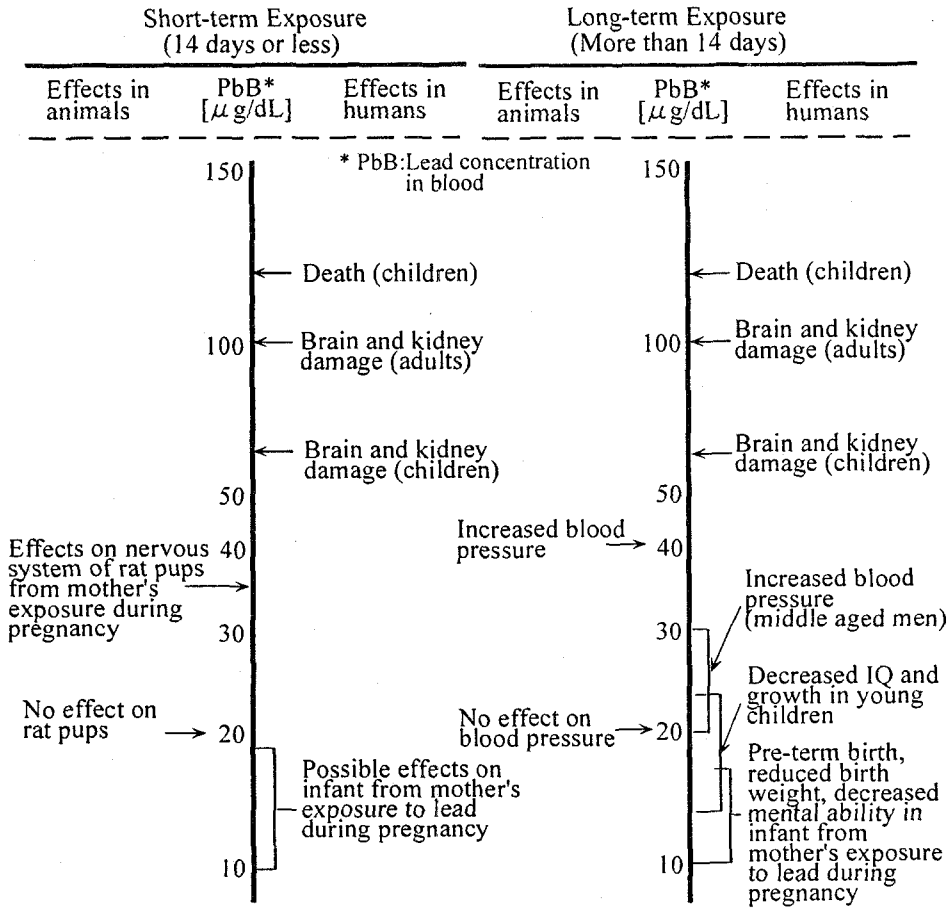
The epidemiological surveys on the adverse health effects are focused on the relationship between the lead concentration in human blood (PbB) and the exposure to lead in the environment, and various threshold PbB are presented for each kind of health effects (refer to Fig.2). In this study, the threshold lead concentration of 30μg/dL in blood is referred to examine the humans health effects, which is presented by the US.ATSDR (1993) for the functional impairment like the blood pressure increase and the elevated hearing threshold.

In this study, the effect of the leaded gasoline regulation, which had been substantially enforced in early 1970's in Japan, is evaluated by the reduction in PbA and in the respiratory and dietary exposure to lead as well as the reduction in the PbB. The PbA is related to PbB by the physiologically based pharmacokinetic (PBPK) model through the total lead exposure of the reference Japanese. The health risks are reviewed historically by comparing the estimated PbB with the threshold used in this study.

2. Exposure Analysis

2.1 Dietary Intake of Lead

The reference Japanese are to be exposed to lead in the environment both through the respiratory and dietary pathways. For the periods between mid-1970's and early 1980's, Horigichi et al. (1980) studied the lead content in various foodstuffs in the typical composition of Japanese diet. They showed that the lead concentration in various kinds of foodstuffs is around 100μg/kg and no larger than that, except the larger concentration of 200μg/kg in fish and shellfish. As is shown in Table 1,



Source: US Agency for Toxic Substances and Disease Registry (1993)

Figure 2 Health Effects from Ingesting and Breathing Lead

Table 1 Dietary Intake of Lead Observed for Each Kind of Food Menu

Menu	Dietary intake[μg/day]	
	Minimum	Maximum
Reference menu No.1*	76.2	137.1
Reference menu No.2*	77.0	146.3
Reference menu No.3*	61.0	131.8
School food menu No.1	78.0	142.6
School food menu No.2	76.4	144.6
Self-Defense-Force menu No.1	95.4	273.7
Self-Defense-Force menu No.2	116.5	263.5

Note: * guided by the public health center.
Source: Horiguchi et al. (1980)

Horigichi et al. (1980) showed the dietary lead intake in three kinds of reference menu given by the public health center, in two kinds of menu given by the school meals providing center, and in two kinds of menu for the soldiers in the Japanese Self-Defense Forces.

Horigichi et al. (1980) reported that the Japanese average dietary intake of lead from drinking water is ranging between 11.6 and 20.3μg/day. If we consider the menu by the public health center and by the school meals providing center as the general domestic foods, and the menu for the soldiers as the hard and heavy worker foods; the dietary intakes of lead are about 60 to 150μg/day for the general public and 95 to 275μg/day for the hard and heavy workers. By adding the lead intake through drinking water, total dietary intakes are about 70 to 170μg/day and 105 to 295μg/day for the general public and the hard and heavy workers, respectively.

Horiguchi (1959) had also surveyed the dietary intake of lead in 1950's by using the almost similar procedures, and reported that the total lead intakes are 100 to 195μg/day through the general domestic foods, 90 to 250μg/day through the hard worker foods, and 150 to 400μg/day through the heavy worker foods.

Available survey data of lead in foods are so limited in 1990's, and the dietary intake of lead is kept rather constant including drinking water throughout 1950's and 1980's. Environmental monitoring data of lead in soil are also kept constant in 1980's and these years. In this study, therefore, the Japanese dietary intake of lead in these years including drinking water is set to be same level as those reported for 1980's by Horiguchi (1980): the average dietary intakes of lead are 70-170μg/day for the general public, and 105-295μg/day for the hard and heavy workers. This assumption might overestimate the PbB.

2.2 Respiratory Intake of Lead

The PbA has been monitored monthly by the Japanese EPA (1972-1997). Some of the monitoring data at 14 locations in Japanese big cities are shown in Table 2. Table 2 shows that lead

Table 2 Lead concentration in Ambient Air Observed in Several Cities in Japan in 1994

Conc. / Cities	Lead conc. in air [μg/m³]		
	Ann. average	Minimum	Maximum
Sapporo	0.014	0.005	0.020
Sendai	0.021	0.014	0.028
Niigata	0.034	0.018	0.047
Tokyo	0.068	0.030	0.130
Kawasaki	0.082	0.039	0.130
Nagoya	0.054	0.030	0.076
Kyoto	0.071	0.055	0.099
Osaka	0.074	0.034	0.100
Amagasaki	0.057	0.028	0.084
Kurashiki	0.048	0.021	0.065
Matue	0.027	0.005	0.038
Ube	0.043	0.010	0.065
Ogouri	0.039	0.018	0.056
Oomuta	0.063	0.016	0.120

Source: Japanese EPA(1996)

concentration level in ambient air in 1994 is a little bit larger in the cities near Tokyo and Osaka than in the other cities, and that the lead concentration varies in the range from 0.005 to 0.130μg/m^3. Inthis study, the respiratory intake of lead is evaluated based on these data.

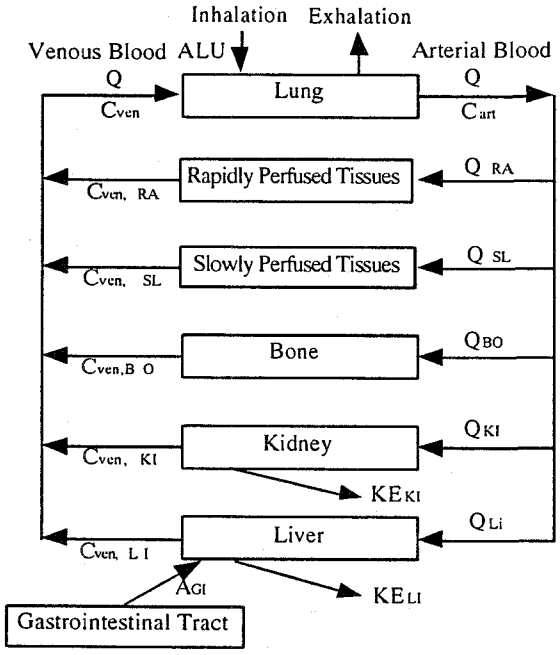


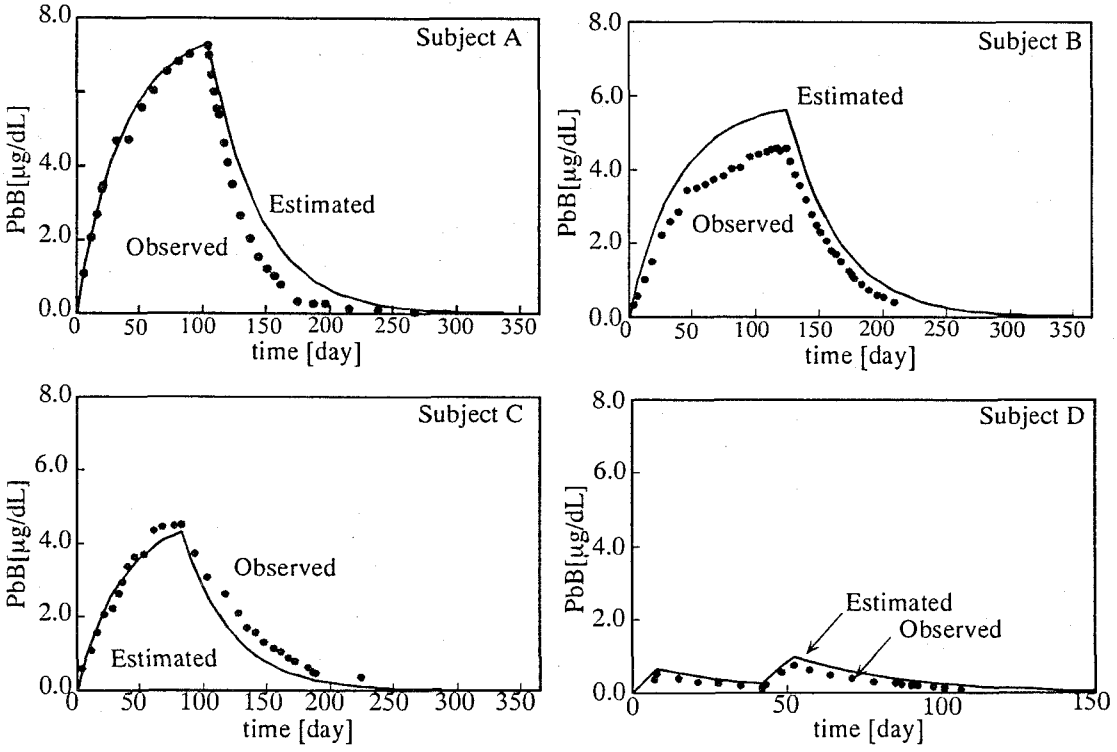
Figure 3 PBPK Model of Lead Used in This Study

2.3 Lead Concentration in Blood (PbB)

The PBPK model, presented by O'Flaherty (1991), was simplified by neglecting the detailed performances of lead in bone, which is used to relate the respiratory and dietary lead exposures with PbB. The PBPK model is in a mathematical sense one of the compartment models, described by a set of ordinary differential equations (refer to Appendix for the detail of the PBPK model). The simplified model (refer to Fig.3) was examined for its reliability by comparing the simulated estimates with the experimental data. The results are shown in Fig.4 with the experimental data reported by Rabinowitz et al. (1976), and in Fig.5 with the experimental data reported by Azar et al. (1975). Fig.4 and Fig.5 show that the simplified model can well depict the experimental data.

The dependence of PbB on the dietary lead intake and PbA is numerically simulated and the results are shown in Fig.6 for each category of Japanese. Fig.6(A) shows that PbB increases almost linearly with the dietary intake, and that PbB is independent on the actual PbA or the respiratory lead intake. Fig.6(B) and (C) show that the actual level of respiratory lead intake does not contribute to PbB so much. The respiratory lead intake contributes significantly when PbA is larger than 1 μg/m^3. These facts indicate that PbB is mainly dependent on the dietary intake in the present lead exposure situations.

PbB is simulated under the condition where same amount of exposure is given through either dietary or respiratory intake, and the results are shown in Fig.7. Fig.7 shows that the efficiency to contribute to PbB is larger in the respiratory exposure than in the dietary exposure, mainly due to the difference in the lead absorption between respiratory and dietary intake. These results imply that the respiratory and dietary exposures should be treated separately, without summing up these two exposure pathways to calculate the total exposure as an input value for the PBPK model.



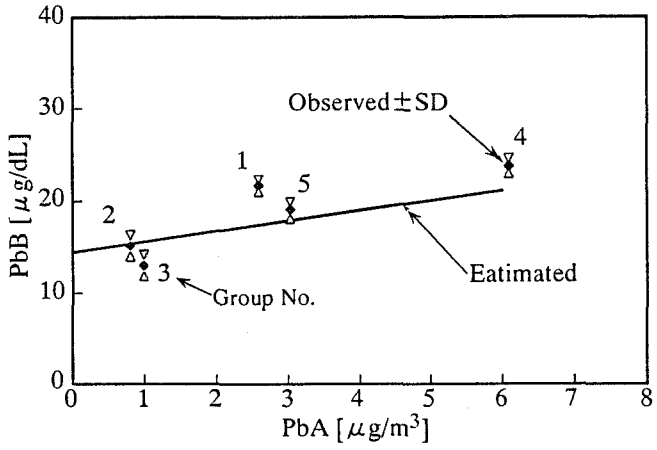
Experiment by Rabinowits et al. (1976)

Subject	Dose pattern	BW[kg]	Dose rate [μg/day]	Dose period [day]	Exp. period [day]
A	Dietary	70	204	104	407
B	Dietary	89	185	124	209
C	Dietary	58	105	83	224
D	Dietary	84	99	1-8,42-52	106

Figure 4 Comparison of the Estimated Lead Concentration in Blood with the Observed by Rabinowits et al. (1976)

2.4 Health Risk Evaluation

Table 3 shows PbB, estimated by the PBPK model for the general public and the hard/heavy



Experiments by Azar et al. (1975)

Group No.	Region	Occupation	Mean PbA [μg/m³]	PbB [μg/dL] Mean	SD
1	Philadelpia	cab driver	2.62	22.4	0.62
2	Starke, FL		0.81	16.4	1.10
3	Barksdale, WI		1.01	13.8	1.11
4	Los Angeles	cab driver	6.10	24.6	0.81
5	Los Angeles	office worker	3.06	19.9	0.92

Note: PbA and PbB are the lead concentrations in ambient air and in blood, respectively.

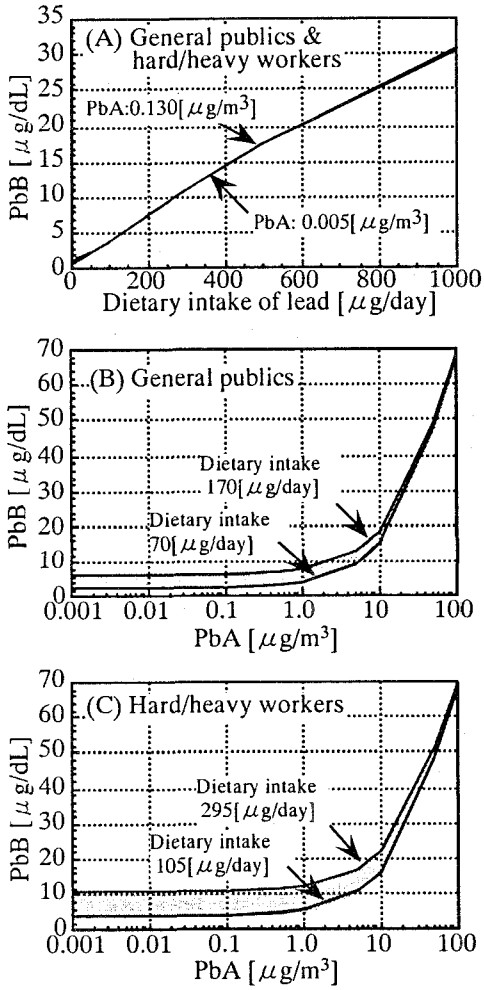
Figure 5 Comparison of the Estimated Lead Concentration in Blood with the Observed by Azar et al. (1975)

Table 3 Lead Concentration in Ambient Air and Blood, Estimated for the General Public and the Hard/Heavy Workers

Simulation condition / PbA [μg/m³]	Lead concentration in blood [μg/dL]			
	General publics		Hard/heavy workers	
	Minimum (Dietary intake 70[μg/day])	Maximum (Dietary intake 170[μg/day])	Minimum (Dietary intake 105[μg/day])	Maximum (Dietary intake 295[μg/day])
0.005	2.9	6.6	4.2	11.0
0.130	3.0	6.8	4.3	11.2

Note: PbA means lead concentration in an ambient air.

workers under the ranges of actual respiratory exposure conditions. The values of PbB are in almost the same level though those of PbA are so different. This is because the low contribution of the respiratory exposure under the PbA range lower than 1μg/m³ (refer to Fig.6). Table 3 indicates that PbB is estimated to be 2.9-6.8μg/dL for the general public and 4.2-11.2μg/dL for the hard/heavy workers. These estimates are lower enough than the reference threshold value of 30μg/dL used in this study.



PbA: Lead concentration in ambient air
PbB: Lead concentration in blood

Figure 6 Relationships between Dietary Intake of Lead and Lead Concentration in Ambient Air, Estimated by PBPK Model

Watanabe et al. (1996) surveyed the dietary intake of lead and PbB for more than 450 citizens in Japan in 1980's (1979-1983) and 1990's (1991-1994). They reported that the dietary intake of lead is 32.2±1.88μg/day and 7.10±2.80μg/day (geometric mean ± geometric standard deviation) for 1980's and 1990's survey, respectively, and that the corresponding PbB are 33.9±1.60 and 23.2±1.61μg/dL, respectively. Fukaya et al. (1987) reported PbB of 7.6±4.69μg/dL (arithmetic mean ± standard deviation) in 1984 for 348 male workers in a vinyl-chloride manufacturing company and a newspaper publishing company. Williams (1992) reviewed the human exposure to pollutants in several countries to show that the lead concentrations in Yokohama, Japan are 6μg/dL in 1981 and 3μg/dL in 1988. These observed values of PbB are varied in the wider range, however, these concentrations

are generally comparable with the simulated concentration.

One exposure was hypothetically increased while another kept constant at the present level, in order to obtain the limit exposure reaching the threshold lead concentration of 30μg/dL. As can be easily estimated from Fig.6(A) and (B), the limit exposures are about 1,000μg/day in dietary intake (3.4 to 14 times larger than the present average intake level) and about 20μg/m^3 of PbA in respiratory exposure (150 to 4,000 times larger than the present average concentration level), respectively.

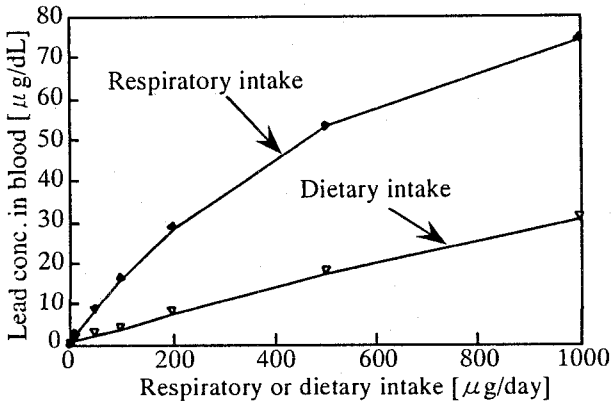


Figure 7 Relationships between Lead Concentration in Blood and Respiratory or Dietary Intake of Lead, Estimated by PBPK Model

3 Effect of Leaded Gasoline Regulation

3.1 Reduction of PbA and Average PbB

The monitored PbA values in 1970 by the monitoring network by Japanese EPA (1972) are shown in Table 4. The concentration was ranging between 0.05 and 4.71μg/m^3 in early 1970's, and was one or two orders larger than the present concentration. Based on the petroleum statistics (Ministry of International Trade and Industry, 1965-1975) and the energy production, demand-supply statistics (Ministry of International Trade and Industry, 1980-1997), the annual gasoline supply in 1997 was about 54.2 billion liters, which is about 2.7 times larger than the supply in 1970 when the leaded gasoline regulation was started.

The lead consumption except for gasoline has been about the same level in Japan after 1970's until these years and the contribution of lead in gasoline to PbA was so high, for example, 83-97% was referred by Simpson et al. (1994). Based on these information, the conservative assumption that PbA will increase proportional to the gasoline consumption growth is set here to estimate the present PbA if the unleaded gasoline had not introduced in early 1970's. The hypothetical PbA is estimated to be 0.14-12.7μg/m^3, which is 2.7 times as large as the concentration in 1970 (0.05-4.71μg/m^3). By introducing these PbA to the PBPK model, PbB was estimated and the results were shown in Table 5 under the assumption of the constant dietary lead exposure as was mentioned before by referring to the survey data of .Horiguchi (1959) and Horiguchi et al. (1980).

Table 4 Lead Concentration in Ambient Air Observed in Several Cities in Japan in 1970

Conc. / Cities	Lead concentration in air [μg/m^3]		
	Ann. average	Minimum	Maximum
Sapporo	0.30	0.14	0.60
Tokyo	0.65	0.08	1.08
Kawasaki	1.57	0.74	4.71
Nagoya	0.28	0.05	0.49
Osaka	1.06	0.45	1.54
Amagasaki	0.64	0.13	1.12
Kurashiki	0.37	0.10	1.00

Source: Japanese EPA (1972)

Table 5 Lead Concentration in Blood, Estimated in the Cases with and without Leaded Gasoline Regulation

Simulation condition / Cases	Lead Conc. in air [μg/m^3]	Lead concentration in blood [μg/dL]			
		General publics		Hard/heavy workers	
		Minimum (Dietary intake, 70[μg/day])	Maximum (Dietary intake, 170[μg/day])	Minimum (Dietary intake, 105[μg/day])	Maximum (Dietary intake, 295[μg/day])
Without leaded gasoline regulation*	0.14	3.0	6.8	4.3	11.2
	12.72	18.5	21.3	19.5	24.7
With leaded gasoline regulation	0.005	2.9	6.6	4.2	11.0
	0.130	3.0	6.8	4.3	11.2

Note:Evaluation was done in 1997.

* Simulation under the assumption that the lead concentration in ambient air is proportional to the gasoline consumption.

Table 5 shows that current PbB will increase up to 3.0-21.3μg/dL for the general public and 4.3-24.7 μg/dL for the hard/heavy workers, respectively if leaded gasoline has been used until now. This
estimation indicates that the average PbB is still kept under the threshold (30μg/dL) even if the leaded gasoline was not regulated in 1970's. This is mainly because that the total lead exposure depends largely on the dietary pathway but not on the respiratory pathway.

Table 5 shows that the upper PbB for persons who are exposed to the larger PbA is effectively reduced at present, but that the lower PbB for persons who are exposed to the lower PbA is kept almost constant. This means that the leaded gasoline regulation worked well to reduce the potential health risk of persons who are exposed to the larger concentration of lead in the environment.

3.2 Reduction of the Higher Risk Group

The adverse health effects may eventually be developed on the persons who are likely to be exposed to the higher level of lead, for example due to their specific dietary habits and lifestyle like smoking, and who have some unknown constitution sensitive to lead. Here the probability that PbB

becomes larger than 30μg/dL is evaluated for both cases with and without leaded gasoline regulation.

The PbB is the direct reflection of the total exposure to lead. The PbB is observed to have the log-normal distribution (Watanabe et al., 1996), of which normalized probability density function f(z) can be described as follows.

$$f(z)=(1/2\pi)^{1/2}\exp(-z^2/2)$$

Here, $z=\{\log(PbB)-m\}/\sigma$. Parameter m and σ are mean and standard deviation (SD) of log(PbB), respectively.

To estimate the probability that PbB becomes larger than 30μg/dL, here let simply suppose that the PbB can always be expressed by the log-normal distribution with the constant SD of 1.61μg/dL as was reported by Watanabe et al. (1996). As shown in Table 5, if leaded gasoline has been used until now, PbB at present will increase up to 3.0-21.3μg/dL for the general public. The geometric mean is 8.0μg/dL ($=(3.0\times21.3)^{1/2}$), and the SD can be 1.61μg/dL. After the leaded gasoline regulation, the current mean PbB is 4.4μg/dL ($=(2.9\times6.8)^{1/2}$), and the SD is 1.61μg/dL by assumption. The probability distribution is shown in Fig.8 for both cases.

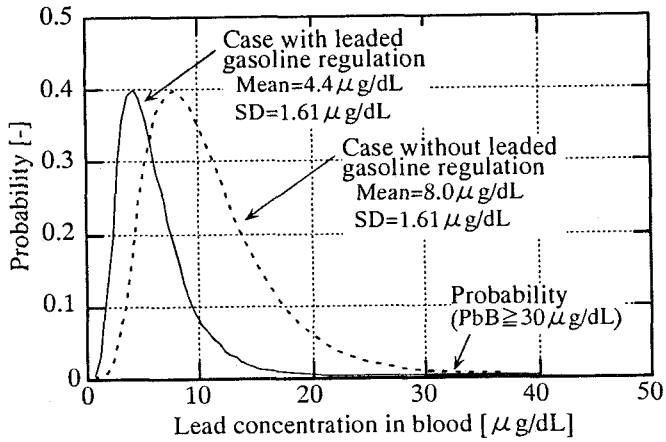


Figure 8 Probability Distribution of Lead Concentration in Blood Estimated for Both Cases with and without Leaded Gasoline Regulation

After all, the probability that PbB becomes larger than 30μg/dL (the small shaded area in Fig.8) is calculated to be 2.7×10^{-3}, which is given by integrating the probability density function f(z) from z=2.78 [={log(30)-log(8.0)}/log(1.61)] to infinitive. The same calculation for estimating the current PbB (geometric mean is 4.4μg/dL, refer to Table 5) gives the probability of 2.8×10^{-5}, which is given by integrating f(z) from z=4.03 [={log(30)-log(4.4)}/log(1.61)] to infinity.

These probabilities were obtained under the quite simple assumptions, and the results should be examined based on the sufficient data samples and information to be compiled later. However, the calculation indicates that the probability, that PbB becomes larger than 30μg/dL, is reduced to two orders by the leaded gasoline regulation. In some cases, for example in drinking water quality standard for carcinogenic chemicals in Japan, the risk level of 10^{-5} is referred as the *de minimis* risk level for setting the standard for the general public. Therefore, it might be concluded that the leaded

gasoline regulation policy, substantially enforced in early 1970's, was to reduce the fraction of the population whose PbB is larger than 30μg/dL to around the *de minimis* risk level of 10^{-5}.

4 Conclusions

Main results obtained in this study under the limits considered are summarized as follows:

1. The lead concentration in the environment was related to PbB by using the PBPK model together with the environmental and dietary survey data. The PBPK model was simplified and validated by comparing the estimated PbB with the observed.
2. The respiratory lead exposure of the reference Japanese was drastically reduced by the leaded gasoline regulation, however, the total lead exposure was not reduced so much because the dietary lead exposure had been kept almost constant in larger level than the respiratory exposure.
3. The PbB was estimated to be kept under the threshold of 30μg/dL even if the leaded gasoline was used until now. The average PbB estimated for the people who were exposed to the larger PbA was reduced effectively by the leaded gasoline regulation, but was not reduced for the people who were exposed to the smaller PbA.
4. The numerical simulation indicates that the probability, that PbB becomes larger than 30μg/dL, is reduced to two orders by the leaded gasoline regulation.

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Appendix

The PBPK model to relate the dietary and respiratory lead intakes to PbB is described by the following set of ordinary differential equations. Refer to Fig.3 for the transfer and accumulation diagram of lead in human body.

$$V_{LI}\,(dC_{LI}/dt)=Q_{LI}(C_{art}-C_{ven,LI})+A_{GI}D_{GI}-KE_{LI}C_{LI}V_{LI} \quad (A1)$$

$$V_{KI}\,(dC_{KI}/dt)=Q_{KI}(C_{art}-C_{ven,KI})-KE_{KI}C_{KI}V_{KI} \quad (A2)$$

$$V_{RA}\,(dC_{RA}/dt)=Q_{RA}(C_{art}-C_{ven,RA}) \quad (A3)$$

$$V_{SL}\,(dC_{SL}/dt)=Q_{SL}(C_{art}-C_{ven,SL}) \quad (A4)$$

$$V_{BO}\,(dC_{BO}/dt)=Q_{BO}(C_{art}-C_{ven,BO}) \quad (A5)$$

$$Cp_{ven,i}=C_i/P_i \quad (A6)$$

$$C_{ven,i}=0.55\,Cp_{ven,i}+0.45Cp_{ven,i}\{1+BIND/(KBIND+\,Cp_{ven,i})\} \quad (A7)$$

$$C_{ven}=(Q_{LI}C_{venLI}+Q_{KI}C_{ven,KI}+Q_{RA}C_{ven,RA}+Q_{SL}C_{ven,SL}+Q_{BO}C_{ven,BO})/Q \quad (A8)$$

$$C_{art}=(QC_{ven}+A_{LU}Q_AC_{inh})/Q \quad (A9)$$

Where, V_i means the volume of i-th organ or tissue (L). Q_i is the blood flow into the i-th organ or tissue (L/day). Q_A is the alveolar ventilation (L/day). C_i is the lead concentration in the i-th organ or tissue (mg/L). Cinh is the lead concentration in an ambient air (mg/L). C_{art} is the lead concentration in arterial blood (mg/L). $C_{ven,i}$ is the lead concentration in venous blood flew out from the i-th organ or tissue (mg/L). $Cp_{ven,i}$ is the lead concentration in venous blood plasma flew out from the i-th organ or tissue (mg/L). D_{GI} is the dietary intake of lead (mg/day). P_i is the partition factor of lead between blood plasma and the i-th organ or tissue (-). BIND and KBIND are the partition constants of lead between blood and blood plasma (mg/L). A_{GI} and A_{LU} are the lead absorption coefficient from gastrointestinal tracts and lung, respectively. KE_i is the lead clearance rate coefficient from the i-th organ or tissue (1/day). The suffix i stands for Liver (LI), Kidney (KI), Rapidly perfused tissues (RA), Slowly perfused tissue (SL) and Bone (BO), respectively.

These equations were numerically differentiated with respect to time and were solved by using the parameter values listed in Table A.

$$C(t+\Delta t)=C(t)+\{dC(t)/dt\}\Delta t \quad (A10)$$

The time step 'Δt' for numerical simulation was set to be 0.0001 (day).

Table A Parameters for PBPK Model Used in this Study to Estimate the Lead Concentration in Blood from the Dietary and Respiratory Lead Intake

Parameter	Symbol	Value	Unit
Body weight [kg]	BW	70.0	kg
Volume of organ/tissue			
Liver	V_{LI}	0.04*BW**0.85	L
Kidney	V_{KI}	0.0085*BW**0.84	L
Rapidly perfused tissues	V_{RA}	0.10*BW**0.85-V_{LI}-V_{KI},	L
Slowly perfused tissues	V_{SL}	BW-V_{LI}-V_{KI}-V_{RA}-V_{BO}	L
Bone	V_{BO}	0.039*BW**1.02	L
Flow			
Cardiac output	Q	340*BW**0.74	L/day
Alveolar ventilation	Q_A	1.01*Q	L/day
Fraction of cardiac output			
Liver	Q_{LI}	0.25	-
Kidney	Q_{KI}	0.17	-
Rapidly perfused tissues	Q_{RA}	0.44	-
Slowly perfused tissues	Q_{SL}	0.09	-
Bone	Q_{BO}	0.05	-
Partition coefficient			
Liver/blood plasma	P_{LI}	100	-
Kidney/blood plasma	P_{KI}	100	-
Rapidly perfused/blood plasma	P_{RA}	100	-
Slowly perfused/blood plasma	P_{SL}	20	-
Bone/blood plasma	P_{BO}	1000	-
Metabolic constant			
Elimination from Liver	KE_{LI}	0.2	l/day
Elimination from Kidney	KE_{KI}	0.47	l/day
Absorption			
Oral Absorption	A_{GI}	0.11	-
Inhale Absorption	A_{LU}	0.5	-
Partitioning in blood			
BIND	BIND	2.7	mg/L
KBIND	KBIND	0.0075	mg/L