Doctoral Thesis (Abridged)

博士論文（要約）

Mercury exposure among general Pakistani population — Personal care products as a source of excessive exposure.

（パキスタンの一般公衆の水銀曝露－過剰曝露源としてのパーソナルケア製品）

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Abstract

Mercury is one of the persistent and toxic elements to which humans are exposed from both natural and anthropogenic sources. The adverse health effects of mercury on humans depend on its chemical forms, concentrations and vulnerability between exposed subjects. Due to its long-range transport, biogeochemical cycling and toxicity, a mercury programme was established by the governing council of United Nations Environmental program (UNEP) to review the strategies that had been taken in the past for reducing mercury levels from the environment. Governing council decided after extensive review that old strategies was not sufficient to reduce mercury levels and decided to take actions internationally. For this purpose, intergovernmental negotiating committee (INC) was established in 2010 and concluded its sessions in 2013 by agreement on the Minamata Convention on Mercury. The main objectives of the convention were; i) to protect the human health from the release of mercury and its compounds particularly generates due to anthropogenic activities, and ii) to set out the range of measures for the mercury levels reduction from the environment. Pakistan is one of the signatories of Minamata Convention.

Despite its serious environmental concerns, studies on mercury exposure levels in Pakistan are quite limited. Based on this fact, the present study was conducted to assess the current mercury exposure status of Pakistani urban dwellers to check contamination levels by using hair samples. Current mercury exposure levels of Pakistani individuals will be valuable as a background information in the future for the evaluation of effectiveness of the Convention. The second major objective of this study was the characterization of high mercury concentrations in excessively exposed subjects with speciation analysis and mercury stable isotopes analysis. The assessment of health risks of Pakistani individuals due to the use of mercury containing products was also one of the objectives of this study.

The ethical review committee of The University of Tokyo approved this study. To achieve the objectives of the study, hair sampling was carried out in six major cities (Lahore, Islamabad, Karachi, Peshawar, Sialkot and Rawalpindi) of Pakistan. Hair samples were collected from the 291 subjects (136 males and 155 females), stored in a polythene bags and shipped to Japan for further analysis. Questionnaires data were also filled by the subjects during sampling in which the information of subjects was also collected. The informed consent of participating in this study was also obtained from the subjects. Total mercury concentrations were measured in the hair samples of subjects. Overall, results showed that 70 % of the subjects

of this study had hair total mercury concentrations below 1 µg/g, the permissible limit of mercury in hair samples recommended by United States Environmental Protection Agency (USEPA). In addition, a part of the subjects had excessive hair mercury levels that can pose significant health risks to the exposed subjects. Use of skin lightening creams, soaps and its usage frequency were found as statistically significant factor associated with the excessive mercury concentrations of the subjects. Speciation analysis of hair samples showed that subjects were exposed to excessive inorganic mercury levels. Methylmercury concentrations were considerably low in the hair samples of exposed subjects.

In this study, skin lightening cream and soap samples reported by excessively exposed subjects in the questionnaires were also collected from Pakistan. These samples were measured for the total mercury concentrations to analyse either these products contained mercury or not. Mercury stable isotope ratios were measured in the hair samples of exposed subjects and skin lightening cream samples used by those subjects. Results showed that mercury stable isotope ratios of hair of one of the subjects was matched with the skin lightening creams isotope ratios reported by the subject. Moreover, hair isotope ratios of the other subjects did not match with skin lightening creams isotope ratios reported by those subjects. The results of mercury stable isotopes analysis indicated that the skin lightening cream samples reported by the subjects are not the sole source of excessive inorganic mercury exposure among subjects except in one subject. Skin lightening cream samples (detected with excessive mercury concentrations) were also checked for the possible health risks to which Pakistani people can be exposed after using these products. For this purpose, hazard quotient (HQ) was estimated for the assessment of health risks which showed that some of the skin lightening cream samples had HQ greater than 1, indicated that the use of these skin lightening creams may pose significant health risk to its users. It is recommended in future studies to explore other possible sources of inorganic mercury through which people in Pakistan are exposed to excessive levels. Identification of inorganic mercury exposure sources is essential to reduce excessive levels of mercury from the environment.

Chapter 1

General Introduction

1.1. Mercury

Mercury is one of the toxic elements exist in the environment. The adverse health effects of mercury on humans depend on its chemical form, concentration in the particular environment and vulnerability of the exposed subjects (USEPA, 2011). Historically, mercury and its compounds were widely used for the preparation of products. Some of the most common applications of mercury and its compounds in the past include; i) calomel (form of mercurous chloride) used for the preparation of teething powders, ii) mercury ore used for the preparation of ink in China, iii) mercury compounds used for medicinal purposes; for the treatment of syphilis (Clarkson et al., 2003b), and iv) ethylmercury and methylmercury compounds used in agriculture (Bakir et al., 1973). This toxic element had long history of use in the past but most of these applications were prohibited after the adverse effects of mercury on humans and environment were recognized. Despite the known toxicity, mercury and its compounds are still used in many fields like dental amalgams, vaccines preservative, gold mining, agriculture and chlor-alkali industries (Clarkson et al., 2003a).

1.2. Chemical forms of mercury

Mercury exists in the environment in three chemical forms, elemental (metallic), inorganic (in the form of mercury salts, for example mercuric chloride, mercuric sulphide etc) and organic forms (ethylmercury, methylmercury, etc). The sources of exposure, mechanism of toxicity and health effects of all three chemical forms of mercury are different (Clarkson and Magos, 2006). Elemental mercury (Hg^0) is the volatile form of mercury, also called as metallic mercury, exist in the environment in the form of vapour. Elemental mercury is also called as liquid silver, quicksilver and hydrargyrum due to its liquid nature at room temperature and silvery appearance. This form of mercury is insoluble in water and soluble in nitric acid and sulfuric acid (Clarkson et al., 2003b).

Inorganic mercury compounds exist in the environment in the form of salts such as monovalent (mercurous Hg^+) and divalent (mercuric Hg^{++}) cationic forms. Both forms of inorganic mercury compounds (either mercurous or mercuric) exist in solid forms. Inorganic mercury salts including mercuric chloride, mercurous chloride and mercuric sulphide occur as white crystals, granules or powder form and are widely used in industries (Chan, 2011; WHO, 1991).

Mercury is also present in the environment in the form of organic mercury compounds. The organic compounds of mercury are broadly categorized into two types; i) allyl mercury, and ii) alkyl mercury compounds. Allyl mercury compounds are mostly used in the field of agriculture and medicine. Alkyl mercury compounds include ethylmercury and methylmercury compounds (ATSDR, 1999). Methylmercury is the most toxic organic form and is also named as bio-accumulative environmental toxicant (Hong et al., 2012).

1.3. Sources of mercury in the environment

Sources of mercury vary according to its chemical forms. Elemental mercury exists in the form of vapour and generates from both natural and anthropogenic sources. Natural sources from which elemental mercury vapour generates into the atmosphere include volcanoes and ores. Anthropogenic sources of mercury vapour include fossil fuels combustion, industrial emissions, dental amalgams, thermometers, sphygmomanometer, barometers, light bulbs, electric switches, medicines, medical waste incineration and mercury-based substances used in ritual and cultural practices (WHO, 1991; Carpi and Chen, 2001).

Oxidation of mercury vapour in the environment forms inorganic mercury compounds. In the past, inorganic mercury compounds have been extensively used, particularly in the field of medicine. Some of the medicinal applications of inorganic mercury compounds include; treatment of infected eczema, syphilis, psoriasis, and used as ointments (Bourgeois et al., 1986; O'Shea, 1990). Inorganic mercury compounds occur naturally in the ores. Many industrial processes including chlor-alkali plants, coke and lime production, refining of petroleum, cement manufacturing, preparation of phosphate fertilizers, metals refining and smelting release inorganic mercury in the environment. In addition, inorganic mercury present in oil, coal or natural gas are also released in the environment due to the process of volatilization. Inorganic mercury salts are also used in industries for the preparation of chemicals (WHO, 1991). Workers of industries who are exposed to inorganic mercury compounds through industrial emissions cause to contaminate their children, if clothes and shoes of those workers do not decontaminate properly (Hudson et al., 1987).

Inorganic mercury compounds are also used intentionally for the preparation of products in industries including batteries, copper foil, as a catalyst for the production of acetylene, vinyl, monomers and polymer curing (EPA, 1997). In addition, inorganic mercury salts including mercury oxide, mercury chloride, mercury sulphate, mercury nitrate, mercury iodide are used extensively in the laboratories, hospitals and schools for the chemical analysis through which people are commonly exposed. Some of the inorganic mercury salts are also used in teething powders, skin ointments for the treatment of infections, as antibacterial agents and antiseptics preservatives (WHO, 1991). So, both natural and anthropogenic sources of inorganic mercury compounds exist to which people are exposed to it.

Organic forms of mercury compounds include ethylmercury and methylmercury to which humans are mostly encountered. Ethylmercury is used as a preservative in vaccines (Dorea et al., 2013). Humans exposure to methylmercury mainly occurs via consumption of fishes, shell fishes and seafood (Mergler et al., 2007). Rice is also considered as the source of methylmercury exposure because high mercury accumulation in rice was observed in mining areas. The bioavailability of methylmercury in rice is not known yet, but translocation in rice plants has been observed in a couple of studies (Meng et al., 2010; Peng et al., 2012).

1.4. Biogeochemical cycling of mercury

The biogeochemical cycle of mercury is composed of three phases. i) terrestrial, ii) atmospheric, and iii) oceanic. Elemental mercury vapour release into atmosphere from both natural and anthropogenic sources. Natural sources include offgassing due to earth movements, volcanoes and hot springs. Anthropogenic sources include industrial activities (mining, coal combustion, emission from cement factories, etc) and disposal of waste products in which mercury is used (batteries, switches, thermometers, fluorescent lights). Mercury vapour is also oxidized in the presence of ozone, oxygen and water vapour to form mercury ions (Hg^{2+}). These mercury ions are highly water soluble and dissolve readily into rain drops. After getting dispersed and dissolved into rain water, these mercury ions are carried by rainwater to soil and sediments. Soil contains bacteria, algae, fungi and other organisms to which inorganic mercury ions incorporate. These organisms convert back this ionic mercury to elemental mercury vapour. In addition, inorganic mercury ions are converted into organic mercury compounds by the actions of bacteria, algae and fungi depending upon the environmental conditions.

Organic mercury compounds (particularly methylmercury) are lipophilic and readily penetrate through cell membranes. After penetration through cell membranes, organic mercury compounds react with proteins, amino acids, nucleic acids and accumulation of these compounds occur within organisms. Animals depending on these organisms for their food also get methylmercury that are transferred to higher trophic level of food chain. The bioaccumulation and biomagnification capacity of methylmercury is considerably high that affect the health of living organisms. This biogeochemical cycle of elemental mercury vapours, inorganic and organic mercury compounds poses adverse health effects for all living organisms (Selin, 2009).

1.5. Mercury exposure, absorption and distribution pathways in humans

There are three main exposure pathways through which humans are exposed to mercury, i) inhalation, ii) Dermal absorption and iii) Ingestion via food and water. Humans are generally exposed to mercury vapour via inhalation. Mercury vapours are readily absorbed through lungs, poorly absorbed through gastrointestinal tract and very less absorption occurs through skin. After absorption, mercury vapour is distributed to other organs of body and finally accumulation occurs in brain and kidneys (Friberg and Mottet, 1989; WHO, 1991). Oxidation of mercury vapours form inorganic mercury ions. Excretion of inorganic mercury ions in humans occurs through urine (Barregard et al., 1995). The half-life of elemental mercury vapour in blood is 1-3 days, however, urine mercury levels decrease in the body within 1-3 months (Jonsson et al., 1999).

Humans are also exposed to inorganic mercury compounds via dermal absorption or ingestion. Inorganic mercury salts are mainly absorbed within human body via dermal application. About 7 to 15 % of inorganic mercury compounds are absorbed after ingestion (Choi et al., 1999). Humans exposure to mercury salts via dermal absorption or ingestion leads to the blood absorption and finally accumulation occurs in kidneys. Most of the inorganic mercury compounds excrete from the human body via renal and faecal routes. The biological half-life of inorganic mercury compounds is 60 days within humans (Dart and Sulliva, 2004).

Ingestion is the most common route to which humans are exposed to organic forms of mercury, mainly methylmercury. After ingestion, about 95 % of methylmercury get absorbed through gastrointestinal system (Clarkson, 2002). Absorbed amount of methylmercury in human body reacts with cysteine, binds to red blood cells and flows inside the blood (Davis et al., 1994). In comparison with other forms of mercury compounds, methylmercury compounds are highly lipophilic and have high affinity for sulfhydryl group of proteins. Methylmercury easily crosses through the blood placental barrier of pregnant women and affects the fetus. Accumulation of methylmercury in humans poses risk to central nervous system, lungs, kidneys and cardiovascular system (NRC, 2000).

1.6. Biomarkers

Urine, blood, hair and nails samples are most commonly used for the assessment of mercury exposure in humans. However, selection of particular sample must be done depending on the chemical forms of mercury to which humans are exposed in the particular environment. For instance, urine samples are considered useful for the assessment of mercury vapour and inorganic mercury compounds because these forms of mercury finally accumulate in kidneys (ATSDR, 1999). Hair and blood samples are most commonly used for the assessment of methylmercury exposure of humans (Groth, 2010). Other samples like nails, meconium, placenta and umbilical cord are also considered appropriate for methylmercury exposure assessment (Gundacker et al., 2010). Moreover, blood and urine samples are mainly used for the assessment of recent exposures to inorganic and methylmercury compounds, but urine is considered as a most reliable for long term exposure as compared to blood samples (Risher et al., 2002). Hair samples are considered useful for the assessment of methylmercury exposure in humans in the past years, because information is preserved in the hair samples for the long time (Dakeishi et al., 2005).

1.7. Toxic effects of mercury species

Health effects of mercury depend on its chemical forms to which humans are mainly exposed in the particular environment. In addition, toxicity and adverse health effects of mercury and its compounds also depend on its concentration, magnitude, time of exposure and susceptibility of individuals. Human exposure to mercury vapour exerts both acute and chronic health effects. Acute effects include respiratory illnesses; asthma, pneumonitis and lungs damage. Chronic effects due to the mercury vapour exposure include bronchitis, renal failure and even death (ATSDR, 1999). Exposure to mercury vapour for a long time may cause severe neurological disorders including tremors, hypertension, nervous system dysfunctioning and psychological disturbances (Liu et al., 2008). In addition, chronic health effects like acrodynia and erethism (psychological disease) have been observed in children after inhalation of mercury vapour (Dangwal, 1993).

Studies showed that immune system of workers in chlor-alkali plants are highly affected after exposure to elemental mercury vapour for a long time. In some of the previous studies, it has been observed that exposure to elemental mercury vapour may weaken the immune system and decrease the resistance against chronic diseases including cancer, severe skin infections and also induce allergies in humans (Moszczynski, 1999; Park et al., 2000). Adverse health effects due to mercury vapour exposure via the dental amalgam fillings among the general population were studied. In one study, positive correlation was observed among number of dental fillings and mercury concentrations in tissues and organs including brain (Bjorkman et al., 2007). One of the epidemiological studies showed severe neurological symptoms among dental professionals due to mercury vapour exposure. These symptoms include memory loss, fatigue and disturbance in sleep (Moen et al., 2008). In addition, it was observed in one study that urine mercury concentrations were increased among the individuals as the number of amalgam fillings increased (Kingman et al., 1998). Moreover, in another study, the decrease of blood and urine mercury concentrations was observed after the removal of dental amalgam fillings (Sandborgh-Englund et al., 1998c). Chronic symptoms among people were also observed after exposure to mercury vapour for a long time particularly pulmonary system was severely affected (Haddad and Stenberg, 1963). Reproductive system was affected due to inhalation of elemental mercury vapour, however, in another study, no association among mercury vapour exposure and reproductive system of humans was observed (ATSDR, 1999).

Use of inorganic mercury salts exerts both acute and chronic health effects. Acute adverse effects due to exposure to inorganic mercury salts include damage to kidneys, intestines and liver. Researches showed that exposure to mercuric chloride induces hypertension, increased heart rate and also heart failure in humans. In some of the previous animal studies, association of mercuric chloride exposure and adverse effects on cardiovascular system were also noticed (Rossoni et al., 1999; Raymond and Ralston, 2004). In one of the previous studies, exposure to inorganic mercury salts induces severe abnormalities in women including nephrotic syndrome, hypersalivation, and insomnia (Tlacuilo-Parra et al., 2001; Tang et al., 2006). In one study, use of mercurous chloride for medicinal purposes induces severe abnormalities in a person including nausea, abdominal pain, vomiting and consequently death due to renal failure (Kang-Yum and Oransky, 1992). Chronic toxicity of inorganic mercury salts may cause tubular necrosis (Warkany and Hubbard, 1951). In addition, studies found that nervous system is severely affected due to exposure to both inorganic and organic mercury compounds because both forms of mercury accumulate within the body organs with the passage of time (Friberg and Mottet, 1989).

Methylmercury is the organic form of mercury that exerts more toxic effects on humans as compared to other forms of mercury. In the past, the most common disaster occurred due to methylmercury exposure was Minamata disaster of Japan. The severe abnormalities were observed in Minamata disaster that include ataxia, deafness, visual constriction, drowsiness and coma. Cerebral palsy and neurological abnormalities were also observed in infants (Tokuomi et al., 1982). In some of the previous epidemiological studies, it was found that prenatal exposure to methylmercury affects the cognitive development of children by decreasing the number of neurons (Grandjean et al., 1997; Cox et al., 1989). In 1970s, one incident happened in Iraq where chronic exposure to methylmercury occurred by eating bread made of methylmercury contaminated grains affect more than 6000 people. Children were also exposed to chronic mercury levels and more than 400 people died in this incident (WHO, 1990). In addition, methylmercury exposure also induces severe developmental disorders, carcinogenicity, reproductive and cardiovascular effects (EPA, 2009). In one of the previous studies, it was found that exposure to methylmercury induced the production of free radicals and decreased the function of antioxidant enzymes that affected cardiovascular system (Choi et al., 2009). Methylmercury exposure affects the reproductive system by reducing the number of sperms, survival rate and deformation of fetus (NRC, 2000; EPA, 2009). In addition, high concentrations of methylmercury in humans increased the production of antinuclear antibodies and infection of malaria (Crompton et al., 2002; Gardner et al., 2010). Other epidemiological studies showed the harmful effects of methylmercury exposure to children during prenatal and postnatal development (Lee et al., 2007; Vahter et al., 2000).

1.8. Minamata Convention

Due to the above-mentioned adverse effects of mercury and its compounds on humans and environment, Governing council of United Nations Environmental Programme (UNEP), in 2003, warranted to take actions internationally to reduce the mercury levels from the environment. As discussed earlier, mercury and its compounds are well known for the adverse health effects on people, particularly women and children are mainly exposed to it. Due to long range transport of mercury and its biogeochemical cycling, a mercury programme was established by the governments to address these concerns. In 2007, Governing council decided that measures for reducing the levels of mercury from the environment must be taken. In addition, old strategies and measures must be reviewed for addressing the mercury issues. After extensive review of the measures that had been taken in the previous years, in 2009, Governing council agreed that actions that had been taken in the past was not sufficient and decided to take actions globally for mercury levels reduction, particularly emission due to anthropogenic activities. For this purpose, intergovernmental negotiating committee (INC) was established in 2010 and concluded its session in 2013 by the agreement on the Minamata convention on Mercury.

The INC held five sessions for the negotiation of global agreement on mercury, and afterwards, held two sessions more for the discussion of financial, technical as well as administrative aspects. The text of the convention was adopted by the conference held in Japan in 2013. Afterwards, it was opened for signature for one year until 2014. There are 128 countries who are signatories of the Minamata convention and 92 ratified it. The two main objectives of the convention are; a) to protect the human health from the release of mercury and its compounds, particularly due to man-made activities, b) to set out the range of measures for the mercury levels reduction from the environment. These also include measures to control the supply and trade of mercury, set limitations to control the mercury emissions from the specific source such as mining, and control the intentional use of mercury compounds in the products preparation. After implementation of the Minamata convention, it is expected that mercury levels will be reduced globally with the passage of time, thus objectives of the convention will be achieved (Minamata convention on mercury, 2013).

1.9. Mercury in Pakistani population

Pakistan is one of the signatories of the Minamata convention on mercury. Assessment of human mercury exposure levels, identification of particular mercury species among the exposed individuals, and evaluation of major exposure sources are essential for the reduction of mercury levels from the environment. In this study, assessment of current human exposure to mercury levels and its forms among Pakistani people will be the initiative for the fulfilment of convention. The adverse effects of mercury and its compounds on humans and environment are well recognized, however, data are still limited in Pakistani population in terms of environmental exposure levels. A couple of studies had been carried out for the assessment of mercury exposure levels among the general population of Pakistan in the past years (Ashraf et al., 1995; Anwar et al., 2007; Ali et al., 2014). However, the results of previous Pakistani studies (Ashraf et al., 1995; Ali et al., 2014) did not provide reliable information about mercury concentrations because of the lack of quality assurance and quality control information during the analytical process except in one study conducted in Lahore city by Anwar et al. (2007). These studies also do not provide sufficient information regarding exact mercury exposure source in the particular environment or concentration of mercury species in the samples to which people are mainly exposed.

1.10. Objectives of study

The studies on mercury levels in the hairs of Pakistani population are quite limited. Therefore, the objectives of the present study are;

1. Assessment of current mercury exposure status of Pakistani city dwellers to check mercury contamination levels using hair samples by well-validated analytical method.
2. Characterization of high concentration of mercury in excessively exposed Pakistani subjects by speciation analysis and stable isotope analysis.
3. Assessment of health risks of general Pakistani people due to use of mercury containing products.

Chapter 2, 3 and 4

Chapter 2, 3 and 4 of thesis cannot be disclosed because some parts of thesis have been accepted for publication in the journal, and other parts have to submit in the journal for publication. Therefore, these chapters cannot be disclosed due to copyrights of journals.

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Appendix

Questionnaire

(Please fill in the accurate information)

Id-no:

1. General Information

i. Age ________(years) **ii. Weight ________ (kg)**

iii. Height ________ (cm) **iv. Gender** a) Male b) Female

v. Present residence (city)

vi. Education (in years):

a) 1-5 years b) 6-10 years c) 11-14 years d) 14+ years

vii. Types of work (occupation):

a) Jobless b) Farmer c) Student d) Factory worker e) Others

2. Life Style

i. Smoking?
a) Never smoked b) Ex-smoker c) Current smoker

ii. Do you do passive smoking?
a) Yes b) No
If yes, please fill in part (iii)

iii. Who is the source of passive smoking for you?
a) Family or friends b) Workplace c) Both a and b d) any other

iv. Do you have any skin problem?
a) Yes b) No
If yes, please mention in part (v)

v. Mention the name of skin problem

3. Fish consumption

If you eat fish, please mention the name of fish and consumption frequency of the particular fish in the table given below. Fill check mark?

Name of fish usually eat	Every day	4 or 5 times a week	2 or 3 times a week	less than 1 time a week	2 or 3 times a month	2 or 3 times a year	Once a year	Never	Amount of fish eating at a time
1)									Little・Regular・Much
2)									Little・Regular・Much
3)									Little・Regular・Much
4)									Little・Regular・Much
5)									Little・Regular・Much
6)									Little・Regular・Much

3. Use of Personal care products (PCPs)

PCPs		Do you use	Name of product	Frequency of use
Bathroom	Facial wash	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	Body soap	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	Shampoo	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	Hand soap	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
Hair care	Hair dye	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
Skin care	Body cream	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	Skin fairness cream	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	a. Fair and lovely cream	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	b. Faiza beauty cream	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	c. Still man's bleach cream	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week
	d. Due whitening cream	1. Yes 2. No		① More than twice a day ② Once a day ③ Two or three times a week ④ Once a week

Thanks for your kind cooperation