

Introduction:

Metals and elements in food are of interest because of their potentials on human health risk. Some are known to be harmful to health (1). Lead is a known neurotoxin, particularly for young children. Its exposure during pregnancy and early childhood is harmful for neuropsychological development of the children (2). Inorganic arsenic is human carcinogen. Several non-carcinogenic adverse health effects of arsenic have also been identified (3, 4). Arsenic is not mutagenic, however affect the genes through epigenetic mechanism. While some other elements, such as copper, chromium, selenium and zinc are essential to health but they may be toxic at high levels of exposure. Heavy metals (arsenic and lead) exposure in food and also through air pollution lead to long term health effects among those exposed to these in their childhood. Lead is still the leading heavy metal with the highest global burden, especially for developing countries like Pakistan (5, 6). The underground water in Pakistan is heavy contaminated with Arsenic. The same water is used for agriculture and lead to further exposure through vegetable and fruits (7).

The health risk of heavy metals can be assessed by comparing estimates of dietary exposures with the Provisional Tolerable Weekly Intakes (PTWIs) and Provisional Maximum Tolerable Daily Intakes (PMTDIs) recommended by the FAO/WHO Joint Expert Committee on Food Additives (JECFA) as a part of the United Nations.

Malnutrition including under and over nutrition is an enormous public health problem worldwide, particularly in developing countries. Malnourished pregnant women and young children have devastating health effects in the shape of immediate and future burden of diseases. Malnutrition has several level of determinants from food production and agriculture to availability, cost and access to food, and also most importantly the choice and preparation/cooking of food. All of the above lead differential distribution of calorie intake, macro and micronutrient availability in the food.

Therefore, it is imperative to know the calorie intake, macronutrients distribution and its proportion in the local cuisine. Food frequency questionnaires (FFQ) are often used to determine the calories, macro and micronutrients in the food, based on recall. However, FFQ is subjective in nature and has its limitation in nutritional assessment (8). Food basket surveys and market basket surveys has also been done (9, 10). Also, even if the food types, amount and frequency is reliably recalled, the processing (cooking) of food itself make changes which are beyond assessment by FFQ and food basket surveys.

Therefore, it is important to have an objective assessment of calorie intake, macro and micronutrient intake, especially for pregnant women and young children. The information will not only do the objective assessment of intake of calories, macro and micronutrients among

pregnant and breastfeeding women and children in Pakistan but provide intervention options for improving nutritional status for the most vulnerable and important population subgroup where the burden of malnutrition is the largest.

Lead levels in environment and exposure is steadily decreasing in Pakistan. However, it is still very high from the health standards (11, 12). Millions of people living along river Indus are affected by arsenic through drinking groundwater. Total intake assessment of heavy metals such as arsenic in rural population and lead in urban areas among children and breastfeeding mothers in Pakistan will determine the future burden of disease among the population. All of this information may lead to policy formulation regarding food and heavy metal monitoring in Pakistan.

Materials and Methods:

Study site: The study will be conducted at two sites in Pakistan (and urban location in Karachi and a rural Gambat taluka, Khairpur, province of Sindh, Pakistan).

Karachi is a megacity and the population is exposed to high levels of lead due to air and soil pollution. The population living along River Indus is exposed to high level of arsenic through underground drinking water.

Study population: Three individuals of the same family will be recruited, including:

- Women
- Newborn (1-3 months old), and
- Young child (2-5 year old)

Sample size: A total of 100 families, 50 each from urban and rural location will be recruited for sampling. A small sample of 25-30 individuals, are appropriate for objective exposure assessment studies. Our sample of 50 at each location will also allow any subgroup analysis of high and low exposed population.

[Note: A total of 100 (50 each in Northern Japan – under Asahikawa Medical University - and Central Japan – Jichi Medical University) families will be recruited for comparative studies].

Samples and Sampling Methods:

1. Biological samples:

- Hair samples: A sample 60-100 hairs from different places from the scalp base will be collected from the women for determining arsenic and lead exposure.

Collection method: Hair samples will be collected by using gloves and will be kept in arsenic-free polyethylene bags with zip-lock before analysis.

- Nail samples: All nails of both palms and soles. We will determine arsenic and lead levels for exposure assessment.
Collection method: Nail samples will be collected using gloves and kept in arsenic-free polyethylene bags with zip-lock before analysis.
- Placenta: It will be collected at the time of delivery. A sample of placenta will be cut (measuring 1x1 in diameter) from the fetal side and will be kept in polythene arsenic-free bags with zip-lock.
- Blood of pregnant women: 5ml blood will be collected by venipuncture.
- Cord blood for newborn: 8 ml blood will be collected from the cord.
- Blood of young child (sibling) (2-5 years old): 5 ml blood will be collected by venipuncture.
- Urine of breastfeeding women: Morning void urine samples of the breastfeeding women (60 ml) will be collected.
- Breast milk as newborn feed: One time breast milk sample of 30-50 ml will be collected for measurement of persistent organic pollutants (POPs), lead and arsenic.

2. Food duplicate samples:

Food duplicates for three-days for the young child (2-5 year old), breastfeeding women and one-time breast milk (as food duplicate for newborn) will be collected from the family. 'Food duplicate' means the same amount of duplicate food which is eaten by the individuals.

Collection method: Solid food will be collected for breakfast, lunch, dinner and snack in steel (arsenic and lead-free) containers separately for mother and child. Liquid food and water (total drinking water) will also be separately collected in plastic bottles for both child and mother.

3. Air and dust samples: Dust and air samples will be collected for 24 hours from the living rooms of the child (where the child spends most of his time in the home).
Collection method: Dust will be collected for one day using vacuum cleaners. Air samples will be collected using low-volume samplers on 47mm glass filters.
4. Water sample: A sample of first-run tap or well water will be collected from the drinking water source for the household.
5. Lead contents in household items: Lead levels in household utensils, paint, dust, toys and furniture will be measured using Niton handheld XRF analyzer. Spot samples will be

collected. Correlation between lead levels in household items and food lead and blood levels will be done.

Sampling procedures in a household:

A total three days will be spent and sampling will be done in one household (Day 0 to Day 2). An additional day (Day 3) will be kept for correction for any error in sampling. Sampling will be done on weekdays for three consecutive days. Sampling will not be done on any holiday.

Day 0: The sampling will start at 10:00 am in the morning. The monitoring time would be the same for each household. One-hour variation in start time is acceptable for different households. A total of 72 hours of drinks and food would be collected for the study subjects starting 10:00 am.

During the first visit, consent will be taken from the mother and assent for the child. The study objectives and sampling details will be explained to the mother. Mothers will be advised about the food diary and keeping records of food and drinks taken by her and the child. Sampling utensils will be provided to the mother with ice-box for keeping the food and drinking samples. Urine sample container will also be provided to the mother to collect it the following morning. Incentives for cooperation and for the provision of food duplicate will be explained to the mother and provided during the last visit.

Tap or well water samples (500 ml) will be collected in a separate container. Air sampling will be explained and air sampler will be installed during the first visit in the house for 24 hours.

Dietary History Questionnaire (DHQ) and Food Frequency Questionnaire (FFQ) will be administered to the mother and young child during the first visit.

Day 1: All food samples for Day 0 will be collected in the morning during the second visit and utensils will be provided for second day. Morning void urine sample will also be collected. Air samples and equipment will be collected from household. Food diary will be checked and completed with the help of the mother.

Day 2: All food samples for Day 1 will be collected in the morning during the third visit to household and utensils for Day 2 will provide. Food diary will be checked and completed with the help of the mother.

Day 3: All food samples for Day 2 will be collected in the morning during the fourth visit to the household. Food diary will be checked and completed.

Any error in sampling will be corrected by doing an additional day of sampling.

Sample measurement and processing (field and laboratory):

Weighing and measurement of food items: Solid food items will be categorized into common food groups and weighed. Liquid food intake will be measured in liters.

Food sample processing: All food samples will be brought to a hired kitchen in ice-box and will be processed daily. All solid food will be broken into small pieces with the help of food processor and will be grinded using a grinder. [Note: Only eatable parts of the solid food will be grinded and the rest will be discarded. For example bones, seeds of fruits etc. will be discarded]. All liquid food will also be mixed with the solid food and grinded together. The whole sample will be poured into big mixture tank for homogenization. A sample of 35-40 ml will be collected in duplicate in sterile arsenic-free bottles, for Japan and Pakistan, after stirring the paste to make it homogenous.

Sample for freezing and dispatch: All samples will be kept frozen at -20 °C in a refrigerator before dispatch.

Laboratory analysis:

Laboratory analysis for As and Pb levels for all the samples will be conducted at Jichi Medical University in Japan.

Exposure measurement for arsenic (As) and lead (Pb) will be conducted using atomic absorption spectrophotometry (AAS) Non-radioactive isotope profiles of Pb in house dust and food duplicates and the biological samples from some subjects will also be analyzed for Pb source apportionment.

To assess body burden of As and Pb will be conducted by measuring the metal concentrations in the biological samples such as hairs, nails, blood, breast milk and urine. Whole blood and placenta samples will be processed to extract DNA using Qiagen kits.

Urine samples will also be analyzed for 8-OHdG concentration and Delta aminolevulinic acid concentration.

Statistical analysis:

The analysis will be done based on the following objectives:

- To determine the health effects due to arsenic and lead exposure
- To determine correlation between surma use of mother and child and blood lead levels of mother and child.

- To determine correlation between utensils, household dust, paint, toys and blood lead levels of mother and child.
- To determine the effect of arsenic and lead on child development (follow-up of the cohort using Bayley's scale).
- To determine the total sodium intake of young child, newborn and pregnant women.

References:

1. Domingo JL, Perelló G, Giné Bordonaba J. Dietary Intake of Metals by the Population of Tarragona County (Catalonia, Spain): Results from a Duplicate Diet Study. *Biol Trace Elem Res.* 2012;146(3):420-5.
2. Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. *J Pediatr.* 2002;140(1):40-7.
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4. Schuhmacher-Wolz U, Dieter HH, Klein D, Schneider K. Oral exposure to inorganic arsenic: evaluation of its carcinogenic and non-carcinogenic effects. *Crit Rev Toxicol.* 2009;39(4):271-98.
5. Kadir MM, Janjua NZ, Kristensen S, Fatmi Z, Sathiakumar N. Status of children's blood lead levels in Pakistan: implications for research and policy. *Public Health.* 2008;122 (7):708-15.
6. Iqbal MP. Lead pollution – A risk factor for cardiovascular disease in Asian developing countries. *Pak J Pharm Sci.* 2012;25(1):289-94.
7. Fatmi Z, Abbasi IN, Ahmed M, Kazi A, Kayama F. Burden of skin lesions of arsenicosis at higher exposure through groundwater of taluka Gambat district Khairpur, Pakistan: a cross-sectional survey. *Environ Geochem Health.* 2013;35(3):341-6.
8. Hedrick VE, Dietrich AM, Estabrooks PA, Savla J, Serrano E, Davy BM. Dietary biomarkers: advances, limitations and future directions. *Nutrition Journal.* 2012;11(109).
9. Schechter A, Pöpke O, Harris TR, Tung KC, Musumba A, Olson J, et al. Polybrominated diphenyl ether (PBDE) levels in an expanded market basket survey of U.S. food and estimated PBDE dietary intake by age and sex. *Environ Health Perspect.* 2006;114(10):1515-20.
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11. Rahbar MH, White F, Agboatwalla M, Hozhabri S, Luby S. Factors associated with elevated blood lead concentrations in children in Karachi, Pakistan. *Bull World Health Organ.* 2002;80:769-75.
12. Kadir MM, Janjua NZ, Kristensen S, Fatmi Z, Sathiakumar N. Status of children's blood lead levels in Pakistan: implications for research and policy. *Public Health.* 2008;122(7):708-15.

Sub-Agreement

**(Health Science Research Grant from Ministry of Health, Labor and Welfare Japan:
Grant Title; Health risk assessment of dietary intake of lead and arsenic)**

This Sub-Grant Agreement ("Sub-Agreement") is made on a collaborative research project between **Jichi Medical University**, (Jichi Medical University is a private university in Shimotsuke, Tochigi, Japan, **Address:** 3311-1 Yakushiji, Shimotsuke, Tochigi Prefecture 329-0498, Japan. **Phone:** +81 285-44-2111) (hereinafter referred to as "JMU") of the one part and Aga Khan university, a body corporate, established under the laws of Pakistan by virtue of President Order No. 3 of 1983, having a campus at Stadium Road, Karachi, Pakistan (hereinafter referred to as "the AKU") of the other part.

WHEREAS, under the Ministry of Health, Labor and Welfare, Japan (hereinafter referred to as "MHLW") a grant was awarded to JMU in pursuance of a proposal and JMU is further awarding a grant to AKU in this regard to do work as defined in the scope of work attached as Annexure A.

AND WHEREAS, the AKU has agreed to perform the work required to be performed by the AKU for the purposes of the Project and as specified and described in the proposal.

NOW THEREFORE the parties agree to enter into this Grant Agreement on the following terms and conditions:

1. Scope of Work and Remuneration

1.1 The AKU shall perform work as specified and particularly described in the annexure A and for performing such work JMU will pay to the AKU a maximum amount of ¥714,600 (hereinafter referred to as the "Grant Funds"). AKU shall carry out work between the period 01 January, 2014 to 31st March, 2014 and Grant Funds to be disbursed by JMU to the AKU shall be in line with the Budget Annexed herewith and marked as Annexure "B". It is agreed that the AKU shall ensure that all the work required to be performed by the Sub recipient as per the proposal, shall be performed in a manner as set out in the proposal and/or under this Agreement.

Deliverables receiving date	Payment Schedule	Contingent Upon
	¥714,600	100% within 30 days of signing of the agreement and upon submission of an invoice by the AKU
TOTAL	714,600	

AKU to fill the Bank Wire Transfer Information form (Annexure "D") attached along with this Agreement and send to JMU.

2. Reporting

AKU is required to submit brief technical reports to JMU specifying the work done upto the point of that deliverable and submitting an invoice of the amount due. Reports should be submitted electronically to the attention of Dr. Fujio Kayama via email (kayamaf@jichi.ac.jp) and (Mrs. Kyoko Isaoka) via email (keiri3@jichi.ac.jp) as per above deliverables table.

AKU also agrees to submit such other reports as JMU may reasonably request from time to time.

3. Record Maintenance and Inspection:

The AKU agrees to maintain adequate records for the Project (both technical and financial) and shall make them available to JMU (physically or electronically), as and when required, to enable it to easily determine how the Grant Funds were expended. All expenses should be based on the approved budget. The Foundation and/or JMU reserve the right to disallow inappropriate expenses or those not relevant to the Project. All records and systems should be maintained on generally accepted International Accounting Standards prevailing in the country of AKU.

4. Indemnity:

a. AKU will indemnify JMU, its directors, trustees, officers, employees, contractors, staff, and agents for any and all damages, costs, expenses and other liabilities, including reasonable attorney's fees and court costs, arising out of the AKU's performance of the Services to the extent that any such claim is caused by its negligence, recklessness, willful misconduct, failure in performing its obligations, or any breach of any warranty or representation under this agreement.

b. JMU will indemnify the AKU, its directors, trustees, officers, employees, contractors, and agents for any and all damages, costs, expenses and other liabilities, including reasonable attorney's fees and court costs, to the extent that any such claim is caused by JMU's negligence, recklessness, willful misconduct, failure in performing its obligations, or any breach of any warranty or representation under this Sub-agreement. JMU also agrees to indemnify AKU for any defects in any sample as mentioned in the Materials Transfer Agreement. The material is of an experimental nature and is provided without warranty of fitness for any purpose, or any other warranty or representation, whether express or implied.

5. Approvals and standards:

AKU will obtain all the necessary approvals from its relevant Governing Body and its ethical review committee. JMU also warrants that it has obtained approvals from its necessary Governing bodies regarding this project and grant.

6. Use of Grant Funds:

Grant Funds shall be used for the purposes of the scope of work stipulated under this Agreement. JMU will pay fixed amounts at the completion of each deliverable and this amount of (state amount) will not be exceeded in any circumstances except by written consent of JMU.

7. Political Campaign / Lobbying Activity:

Grant funds shall not be used by the AKU to influence the outcome of any election for public office or to carry on any voter registration drive. There is no agreement, oral or written, permitting the Grant funds to be directed to or earmarked for lobbying activity or other attempts to influence local, state, federal, or foreign legislation. AKU's strategies and activities, and any materials produced with grant funds, will comply with applicable local, state, federal, or foreign lobbying law. AKU agree to comply with lobbying, gift and ethics rules applicable to the Project under local, state, federal or foreign law.

8. Assignment:

This Agreement or any of the rights or obligations under this Agreement shall not be assigned without JMU's prior written consent. An assignment includes (a) any transfer of the Project or any part thereof; (b) an assignment by operation of law, including a merger or consolidation, or (c) the sale or transfer of all or substantially all of AKU's assets. This assignment does not include outsourcing non-research related activities to third parties eg. Transportation related to the project.

9. Force Majeur:

Both parties understand and agree not to hold any other party responsible and accountable in case either party fails to fulfill its obligations and responsibilities because of reasons including Acts of God, war, floods, terrorism, riots, government restriction or such other reason being beyond the control of either Party.

12. Disputes:

In the event of any controversy or claim arising out of or relating to any provision of this Sub-Agreement or any breach thereof, the parties will try to settle such conflict amicably between themselves. Further they may resort to arbitration if things are not settled bilaterally.

13. Intellectual Property Rights:

Both AKU and JMU will promptly disclose to each other all inventions, discoveries, improvements, designs, processes, formulations, products, computer programs, works of authorship, databases, mask works, trade secrets, and know how (whether or not patentable or subject to copyright or trade secret protection) first conceived or reduced to practice during the performance of the services under this Sub-Agreement. The ownership of any of the aforesaid intellectual property rights created jointly during the performance of this Agreement, shall vest jointly between JMU and AKU. The parties will jointly file application for the purposes of seeking protection and/or registration of the intellectual property rights created during the performance of this Sub-Agreement and the cost for seeking such protection and/or registration shall be borne jointly by the parties in equal proportion. The ownership of any of the aforesaid intellectual property rights created solely by AKU during the performance of this Sub-Agreement, shall vest in the AKU. The ownership of any of the aforesaid intellectual property rights created solely by JMU during the performance of this Sub-Agreement, shall vest in JMU.

14. Publication

AKU and its investigators shall be free to publish, present or use any of the results arising from the performance of the Research under this Sub-Agreement for their own instructional, research or publication objectives, provided that such use does not disclose any of JMU's Confidential Information as described in ARTICLE 15 hereof other than as required to communicate an scientifically appropriate description of the methods and results of the Research. This publication also allows identification of JMU as a part of the publication process. At least thirty (30) days prior to submission of any publication or presentation the

AKU and the Investigator shall submit any proposed publication or presentation to JMU for review and comment. Expedited reviews for abstract presentations may be arranged if mutually agreeable to the parties. Upon notice of JMU to the AKU that JMU reasonably believes that patent applications should be filed prior to any publication, then publication will be delayed until such applications have been filed the delay not to exceed 90 days unless by mutual agreement of JMU, the AKU and the AKU's Project Director. Except as specifically agreed to in this Agreement, neither party will use the other party's name in for advertising, for other commercial purposes, or otherwise, without appropriate written permission, unless required by law or government regulation.

15. Confidentiality:

Except with the prior written consent of JMU, the AKU shall ensure that it will not at any time communicate to any third party any confidential information disclosed to the AKU for the purposes of this Sub-Agreement or discovered by the AKU in the course of the work performed under this Sub-Agreement nor shall the AKU make public any information as to the recommendation formulated in the course of or as a result of work performed under this Sub-Agreement. The information required to be kept confidential includes amongst others the information pertaining to JMU, Foundation and their respective staff, employees, faculty etc as well as well as any data relating to the subjects or their medical tests or their results thereof that the AKU may come across during the completion of its activities under this Sub-Agreement.

Since the services involve substances or materials supplied by AKU (hereinafter referred to as "AKU's Materials"), the JMU agrees to treat AKU's Materials and all information concerning AKU's Materials as Information. JMU will return all unused AKU's Materials to AKU at the completion of the Services, except samples which it can destroy as per mutual agreement between AKU and JMU. AKU agrees to provide the JMU all Information in its possession concerning AKU's Materials that is reasonably necessary for safe and proper handling of AKU's Materials for performance of the Services.

16. Termination:

If (a) JMU is not reasonably satisfied with AKU's performance under this Agreement or the content of any written report from AKU as required under this Grant Agreement, or (b) AKU fails to comply with any term or condition of this Agreement, JMU has the right at its discretion to terminate this Agreement. Due intimation will be provided by JMU to AKU and proportionate payment will be made for deliverables already provided by AKU.

18. Entire Agreement; Amendment.

This Sub-agreement constitutes the entire agreement and supersedes any prior oral or written agreements or communication between the two parties regarding its subject matter. The provisions of this Sub-agreement are severable so that if any terms or provision is found for any reason to be invalid, illegal, or unenforceable, such finding shall not affect the validity, construction, or enforceability of any remaining terms or provision. This Sub-agreement may be amended or modified only by a mutual written agreement (modification) of the parties.

21. Warranty Disclaimer and Limitation of Liability

Except for a party's indemnification obligations above and obligations regarding Information, in no event will either party's liability to the other for any costs, expenses, or damages, regardless of the form of action, whether based on contract, tort, negligence, strict liability, products liability or otherwise, ever exceed the amount paid to the AKU hereunder. Under no circumstances will either party be liable to the other for loss of use or profits or other collateral, special, consequential or other damages, losses, or expenses.

IN WITNESS WHEREOF, the Parties have signed and subscribed to this Sub-agreement through their authorized representatives.

FOR AND ON BEHALF OF AKU
UNIVERSITY

FOR AND ON BEHALF OF JMU

{Name of Authorized Signatory}
{Title}

{Name of Authorized Signatory}
{Title}

AKU'S INVESTIGATOR

JMU'S INVESTGATOR

Dr Zafar Fatmi
Associate Professor

Dr Fujio Kayama
Professor

Department of Community Health Sciences

Department of Environmental &
Preventive Medicine, School of Medicine

ANNEXURE A

Following is a brief outline of the scope of work of the AKU:

- Provide technical and logistic support on ground in Pakistan for facilitation of the overall study objectives.
- Collect process and store specimens before shipping to JMU, of food for three days from 50 households each from urban and rural location (for women, her newborn and young child under-5 years) (as described in the proposal).
- Collect process and store specimens before shipping to JMU, of blood, placenta, cord blood, hairs and nails samples from above study participants.
- Ship the specimens through mail in appropriate condition.

ANNEXURE B

BUDGET

ANNEXURE

BANK ACCOUNT INFORMATION

Request for Payment via Wire Transfer

INSTRUCTIONS:

1. Please complete this form and returned.

Bank information for fund transfer.

Account Title : _____

Account No : _____

Currency Account: _____

Name of Bank: _____

Bank Address : _____

Swift Code: _____

ABA Chips: _____

Any other information that facilitates the funds transfer: _____

Intermediary Bank if any: _____

Swift Code: _____

ABA Chips: _____

Any other information that facilitates the funds transfer: _____

19. 研究成果の刊行に関する一覧表

○この期間の調査自体の研究成果刊行物はなし。

○これまでの調査に関連する刊行物の一覧（平成25年度）

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2. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, Yamagata Z, Kayama F, Kishi R, Ohya Y, Saito H, Sago H, Okuyama M, Ogata T, Yokoya S, Koresawa Y, Shibata Y, Nakayama S, Michikawa T, Takeuchi A, Satoh H. Rationale and study design of the Japan environment and children's study (JECS).; Working Group of the Epidemiological Research for Children's Environmental Health. *BMC Public Health*. 2014 Jan 10;14:25. doi: 10.1186/1471-2458-14-25. PMID: 24410977 [PubMed - in process] Free PMC Article
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4. Fatmi Z, Abbasi IN, Ahmed M, Kazi A, Kayama F. Burden of skin lesions of arsenicosis at higher exposure through groundwater of taluka Gambat district Khairpur, Pakistan: a cross-sectional survey. *Environ Geochem Health*. 2013 Jun;35(3):341-6. doi: 10.1007/s10653-012-9498-3. Epub 2012 Oct 31. PMID: 23111830 [PubMed - indexed for MEDLINE]

