The Global Burden of Foodborne Disease: Update on the Work of the WHO's Foodborne Disease Burden Epidemiology Reference Group

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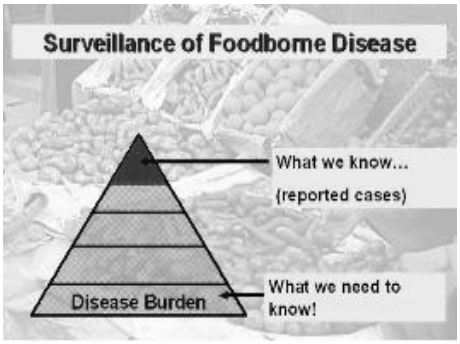
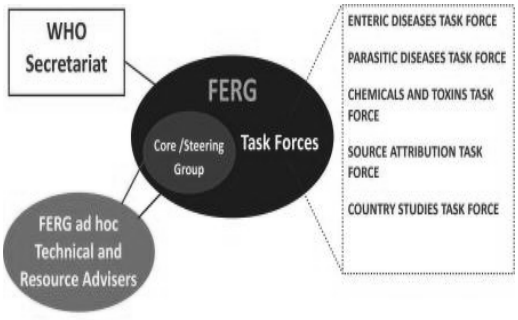
The Unknown Burden



Charge to FERG (2006)

1. Conduct epidemiologic reviews to support estimates of the global burden of foodborne diseases according to age, sex, and region for a defined list of causative agents of microbial, parasitic, and chemical origin
2. Develop causal attribution models to estimate the sources (vectors, pathways) of foodborne diseases
3. Increase awareness and commitment among Member States for the implementation of food safety policy and standards
4. Develop user-friendly tools for burden of foodborne disease studies at country level to strengthen country capacity to conduct burden of foodborne disease assessments
5. Encourage countries to use burden of foodborne disease estimates in cost-effectiveness analyses of prevention, intervention and control measures

FERG Organizational Structure



WHO Burden of Disease Portfolio

Name	Purpose
Child Health Epidemiology Reference Group (CHERG)	Estimate cause-specific morbidity and mortality in children <5 years
Monitoring and Evaluation Reference Group (MERG)	Develop monitoring and evaluation mechanisms for the Roll Back Malaria Partnership
Burden of Disease from Environmental Risks	Provide morbidity, mortality, and DALY estimates for selected diseases associated with environmental risks
WHO Steering and Technical Advisory Group on Neglected Tropical Diseases	Prevent and control NTDs and assess socio-economic impact
Leptospirosis Burden Epidemiological Reference Group (LERG)	Develop global estimates on Leptospirosis
Foodborne Disease Burden Epidemiology Reference Group (FERG)	Provide burden of disease estimates tp enable policymakers and other stakeholders to set appropriate priorities on area of food safety

Primary BoD Metric: Disability-Adjusted Life Year (DALY)

- extends concept of potential years of life lost (YLL) due to premature death to include equivalent years of "healthy" life lost (YLD) due to being in states of poor health or disability
  - YLL + YLD
- YLL: number of deaths at each age multiplied by global standard life expectancy for each age
- YLD: number of incident cases in period X average duration of disease X disability weight
- disability weight, 0 (perfect health) to 1 (death)
- 3% discounting and non-uniform age weights that give less weight to years lived at young and older ages

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- disability weight, 0 (perfect health) to 1 (death)
- 3% discounting and non-uniform age weights that give less weight to years lived at young and older ages
- burden of disease is the gap between current health status and ideal health. Where everyone lives into old age free of disease and disability

Disability Classes for BoD Analysis

Class	Severity Weights	Examples
I	0.00-0.02	stunting due to malnutrition, schistosomiasis infection
II	0.02-0.12	amputated finger, asthma, edentulism, mastectomy, severe anemia, stress incontinence
III	0.12-0.24	angina, HIV (not AIDS), infertility, alcohol dependence, low vision, rheumatoid arthritis
IV	0.24-0.36	amputated arm, congestive heart failure, deafness, Parkinson's disease, tuberculosis
V	0.36-0.50	bipolar affective disorder, mild mental retardation, neurological sequelae of malaria
VI	0.50-0.70	AIDS (not on ART), Alzheimer's and other dementias, blindness, Down Syndrome
VII	0.70-1.00	active psychosis, severe depression, severe migraine, quadriplegia, terminal stage cancer

Leading Causes of Burden of Disease (DALYs), all ages, 2004

Disease or Injury	DALYs (millions)	Percent of total DALYs
1. Lower respiratory infections	94.5	6.2
2. Diarrhoeal diseases	72.8	4.8
3. Unipolar depressive disorders	65.5	4.3
4. Ischemic heart disease	62.6	4.1
5. HIV/AIDS	58.5	3.8
6. Cerebrovascular disease	46.6	3.1
7. Prematurity and low birth weight	44.3	2.9
8. Birth asphyxia and birth trauma	41.7	2.7
9. Road traffic accidents	41.2	2,7
10. Neonatal infections	40.4	2.7
11. Tuberculosis	34.2	2.2
12. Malaria	34.0	2.2
13. COPD	30.2	2.0
14. Refractive errors	27.7	1.8

Mather et al., *The Global Burden of Disease, 2004* Update (2008)

GBoD 2004 Update: Other Findings

•Years of Life Lost (YLL) 7 times higher in Africa than in high-income countries

•South-East Asia and Africa account for 54% of total BoD, due predominantly to communicable diseases and maternal, perinatal ,and nutritional conditions

•Almost 50% of disease burden in low- and middle-income countries now from non-communicable diseases (ischemic HD, stroke)

•Disease burden in children falls almost entirely in low- and middle-income countries (36% of total burden in world)

Enteric Task Force

- Bacterial toxins (Bacillus cereus, C. perfringens, S. aureus)
- Brucella sp.
- Campylobacter sp.
- Clostridium botulinum
- Hepatitis A
- E Coli.
  - Entero-aggerative
  - Entero-pathogenic
  - Entero-toxigenic
  - Shiga-toxin producing
- Listeria monocytogenes
- Mycobacterium bovis
- Non cholera vibrio pararhemolyticus
- Non cholera vibrio vulnificus
- Vibrio cholera 01/0139
- Norovirus
- Shigella sp.
- Yersinia sp.
- Salmonella sp.
  - Non-typhoidal
  - typoid

Early Results: Child Mortality (<5) Due to Diarrheal Diseases in Developing Countries

WHO region	Average of diarrhea-proportional mortality (by mortality stratum)	Estimated diarrhea deaths (thousands)	Uncertainty (thousands)
Africa (AFR)*	MS D 17.8 MS E 17.5	402 365	346-455 315-413
America (AMR)	MS B 13.3 MS D 14.9	35 14	30-40 12-16
Eastern Mediterranean (EMR)	MS B 13.4 MS D 16.9	12 221	10-14 190-250
South-East Asia* (SEAR)	MS B 22.3 MS D 24.5	44 651	34-53 500-793
Western Pacific (WPR)	MS B 13.8	105	90-118
World	18.7	1870	1558-2193

* 78% of all diarrhea deaths in developing countries are in AFR and SEAR regions

Boschi-Pinto et al. *Bulletin of the World Health Organization* 2008;86:710-717

Parasitic Task Force

- **Intestinal protozoa** (Giardia, E. histolytica, Cryptosporidium)
- **Fasioliasis**
- **Alveolar echinococcosis**
- **Cystic echinococcosis**
- **Cysticercosis**
- **Trichinellosis**
- **Aniskiasis**
- **Toxoplasmosis**
- **Clonorchiasis and Opisthorciasis**
- **Ascariasis**

Early Results: Alveolar Echinococcosis

- **Torgerson et al., PLoS NTD 2010;4(6), e272**
  - **18,235 incident cases per year (11,900-28,200), 91% in China**
  - **Combined age and sex-specific incidence with case fatality rate and disability weight for hepatic carcinoma,**
  - **estimated DALYs: 666,434 per year (331,000-1.3 million)**

Work Initiated on Chemical Contaminants

- **Cassava cyanide**
  - **acute poisoning, konzo, tropical ataxic neuropathy**
- **Aflatoxin**
  - **acute aflatoxicosis, hepatocellular carcinoma, stunted growth**
- **Peanut allergen**
  - **anaphylaxis/death; oral allergy syndrome; skin, GI, respiratory symptoms**
- **Dioxin, dioxin-like PCBs**
  - **cancer, neurodevelopmental impairment, reduced sperm count**
- **Lead**
  - **cognitive impairment, cardiovascular morbidity**
- **Cadmium**
  - **renal disease**

Other Chemical Contaminants Under Consideration

- **Methylmercury**
- **Arsenic**
- **Organophosphate pesticides**
- **Seafood toxins** (e.g., ciguatera, scombroid, domoic acid, tetrodotoxin, paralytic shellfish poisoning, neurotoxic shellfish poisoning)
- **Phytotoxins** (e.g., aristolochic acid)
- **Manganese**
- **PBDEs**
- **Acrylamide**
- **Melamine**

Early Results: Aflatoxin

- **From:**
  - **prevalence of chronic HBV infection, by WHO region**
  - **cancer potency factors (slope of D-R curve) for HBV+, HBV-**
  - **estimated aflatoxin exposure based on maize and peanut consumption by WHO region**
- **Estimated worldwide annual incidence of aflatoxin-induced hepatocellular carcinoma (with/without HBV synergism) to be 25,200-155,000 cases (5-28% of all cases globally)**

Aflatoxin-related HCC, by WHO Region

WHO Region	HCC cases attributable to aflatoxin, HBsAg-	HCC cases attributable to aflatoxin, HBsAg+
Africa	2,150-9,300	9,230-50,600
North America	9	2-5
Central/South America	589-2,980	84-2,060
Eastern Mediterranean	446-3,720	341-13,200
SouthEast Asia	1,740-17,300	1,460-27,600
Western Pacific	2,710-6,510	6,310-21,200
Europe	99-184	62-372

Liu & Wu. *Environmental Health Perspectives* 2010;118:818-824.

Detailed Example of a BoD Analysis for a Chemical: Lead (Fewtrell et al., 2003)

Country/Region Exposure Data Requirements

- geometric mean blood lead level
- standard deviation
- sample size

- Ideally, exposure data derived from a probability sample that is representative of the entire population
  - otherwise extrapolate to population for which disease burden to be calculated (e.g., apply weighting factors)

- Sometimes cohort effect "correction factor" needed
  - e.g., adjust for significant changes in population exposure since blood lead data collected (e.g., removal of lead from gasoline)

Criteria for Selecting Key Disease Outcomes

- strength of evidence supporting causal relationship with lead
- availability of quantitative information on association between blood lead and health effect (i.e., dose-response or exposure-risk relationship)
- Outcome is a well-defined disease (i.e., ICD-10 diagnosis), or can be converted into such

Health Outcomes Selected

- IQ points lost (resulting in mild mental retardation) (children)
- Anemia (children, adults)
- Gastrointestinal symptoms (children)
- Increased blood pressure (adults)
  (resulting in ischemic heart disease, cerebrovascular disease, hypertensive disease, other cardiac diseases)

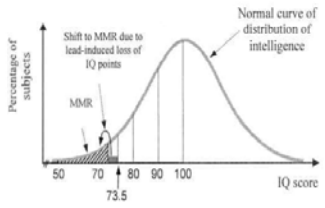
Exposure-Risk Relationships Used to Quantify Disease Burden

Outcome	Blood lead threshold[a] (µg/dl) Children	Adults	Relationship
IQ reduction[b]	5	ND	Linear relationship between 5–20 µg/dl BPb[c] (loss of 1.3 IQ points per 5 µg/dl BPb); loss of 3.5 IQ points above 20 µg/dl.
Increased systolic blood Pressure[d]	ND	5	Linear relationship assumed between 5–20 µg/dl (increase of 1.25 mmHg per increase of 5 µg/dl BPb for males, and 0.8 mmHg for females); above 20 µg/dl, an increase of 3.75 mmHg for males, and 2.4 mmHg for females.
Gastrointestinal effects	60	ND	20% of children are affected above these rates[e].
Anaemia	70	80	20% of people are affected above these rates[e].

[a] Thresholds for gastrointestinal effects and anaemia are levels "at risk", as defined by ATSDR (1999).
[b] The disease burden is always estimated for one particular year and the effects of previous exposures are not accounted for in the year of assessment. As a result, only children aged 0–1 year old were considered in the calculations, since the effects of lead on previous cohorts were considered in previous years.
[c] BPb: blood lead level (in µg/dl).
[d] Adults aged 20–79 years only.
[e] Based on Schwartz et al. (1990); see section 4.1.
ND No documented effects or insufficient evidence.

IQ Loss and Mild Mental Retardation (MMR)

- IQ loss not a disease per se, so burden is incurred *only* when IQ loss results in MMR (i.e., IQ<70)
- To attribute a disease burden to loss of IQ points, calculated number of children who are pushed into MMR range as a result of lead exposure



IQ Loss and MMR: Adjustment Ratio

- background risk of MMR differs in developed and developing regions because distributions of other MMR risk factors differ (e.g., meningitis, pertussis, encephalitis, ascariasis, iodine deficiency, etc.)
- Apply region-specific adjustment ratio:

$$AR = (P_R - P_{baseline} + P_{MR\ standard})/P_{MR\ standard}$$

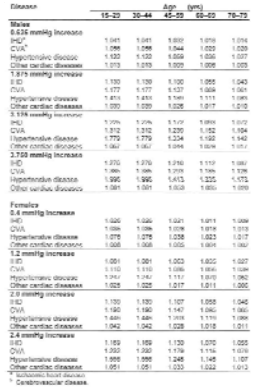
P_R=region-specific prevalence of MR from known causes
$P_{baseline}$=prevalence of MMR from known causes in developed countries
$P_{MR\ standard}$=prevalence of MMR according to standard distribution of IQ score

Region*:	AfrD	AmrA	AmrB	EurA	EurB	SearB	SearD	WprA	WprB
AR	2.05	1.00	2.71	1.00	1.53	3.25	2.06	1.00	3.03

*classification depending on child and adult mortality

Foundation for Estimating Lead-Associated CVD Morbidity

relative risks for different forms of CVD for defined increases in blood pressure, by age and sex



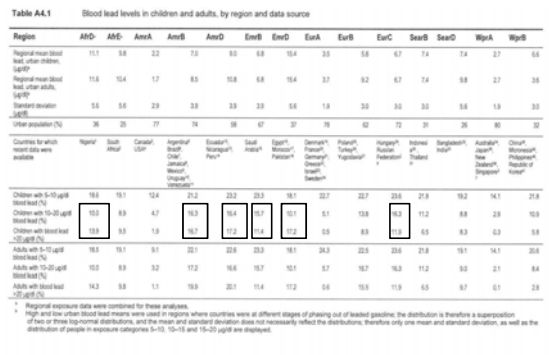
Blood Pressure (BP) and Cardiovascular Disease

- **blood lead level divided into intervals**
- **estimate BP increase associated with each blood lead interval (sex-specific)**
- **population distribution of blood lead level is combined with the relative risk for each BP interval to calculate the impact fraction:**

$$IF = (\Sigma P_i RR_i - 1)/\Sigma P_i RR_i$$

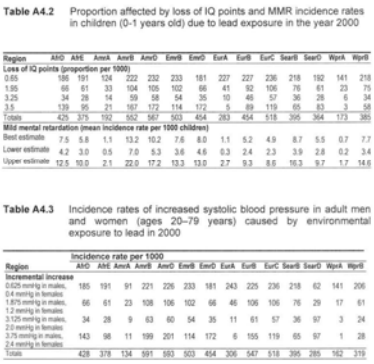
IF=impact fraction
P_i=proportion of population at exposure interval i
Rr_i=RR at exposure interval i, compared to reference level

Estimated Blood Lead Levels, by WHO Region



In 2000, <10% of children had BLL >20, but *99%* were in developing countries

Estimation of Incidence Rates, by Region, for Mild Mental Retardation and Increased Systolic Blood Pressure Attributable to Lead Exposure



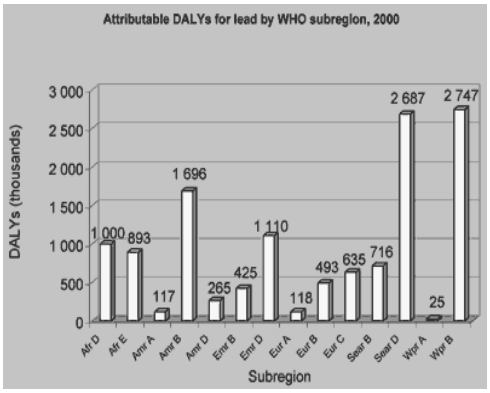
Lead-Associated DALYs, by WHO Region

Table A4.4 DALYs and deaths caused by lead-induced MMR and cardiovascular disease (CVD)

Region	AfrD	AfrE	AmrA	AmrB	AmrD	EmrB	EmrD	EurA	EurB	EurC	SearB	SearD	WprA	WprB	World
DALYs due to MMR (in thousands)															
	871	768	82	1393	225	334	868	55	212	153	582	1912	16	2361	9813
DALYs due to CVD (in thousands)															
IHD[1]	44	38	19	112	12	51	125	30	125	249	49	447	3	86	1391
CVA[2]	58	60	10	134	16	19	70	25	111	196	54	250	6	256	1266
HTD[3]	16	17	4	46	10	16	34	3	33	22	25	46	0	57	329
OCD[4]	10	9	2	12	2	4	11	4	11	15	5	32	0	8	126
Totals[5]	128	124	35	304	40	90	241	63	280	482	133	775	9	407	3112
CVD mortality (deaths in thousands)															
Totals	8	8	2	20	3	6	17	5	22	39	9	57	1	31	229

[1] ischaemic heart disease [2] cerebrovascular disease [3] hypertensive disease
[4] other cardiac diseases [5] total cardiac diseases

Bottom line: **MMR accounts for 9.8 million DALYs. CVD diseases 3 millions DALYs; together account for *almost 1%* of global burden of disease**



Limitations

- **Uncertainties inherent in data available**
  - **accuracy of blood lead measurements in sample**
  - **degree to which sample representative of population as a whole**
- **Uncertainties associated with method used to adjust exposure data (e.g., cohort effects associated with lead reduction measures)**
  - **distribution of effect modifiers (e.g., genetics, nutritional status, health status) might differ between populations and so affect risk of disease**
- **Uncertainties in model parameters (e.g., exposure-response relationships derived from literature)**
- **Likelihood that some disease burden is associated with outcomes for which no ICD-10 diagnosis**

Blood Lead Levels and Performance on End-of-Grade Reading Achievement Test, 2000-2004, NC 4th graders (N=8,600)

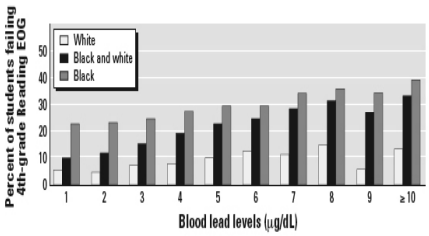


Figure 4. Percent of students failing 4th-grade Reading EOG.

Miranda et al., *Environmental Health Perspectives* 2007;115:1242-1247

Blood Lead Level and ADHD (physician-diagnosed, on meds)

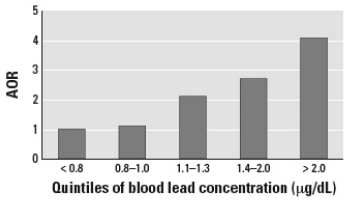
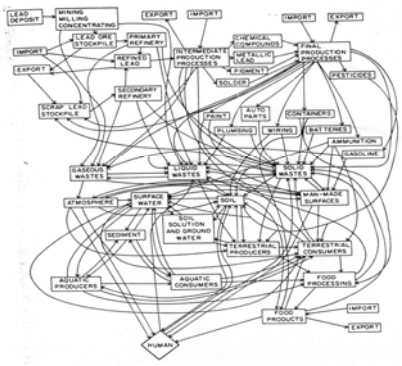
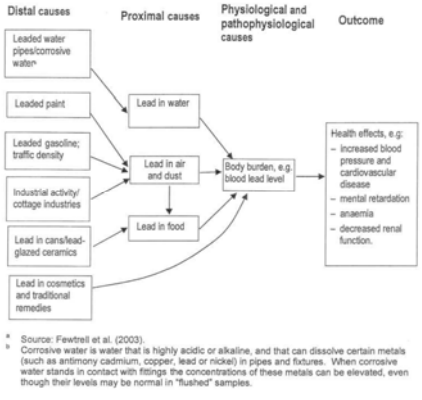


Figure 1. AOR for ADHD among U.S. children, NHANES 1999–2002, by blood lead concentration (µg/dL). The model was adjusted for child's age, sex, race/ethnicity, preschool attendance, serum ferritin, prenatal ETS exposure, smoker in the household, and insurance status.
p-value for trend = 0.012.

Braun et al. *Environmental Health Perspectives* 2006;114:1904-1909

Source Attribution is a Major Problem for FERG: How Much Lead-Associated Morbidity is Food-Related?





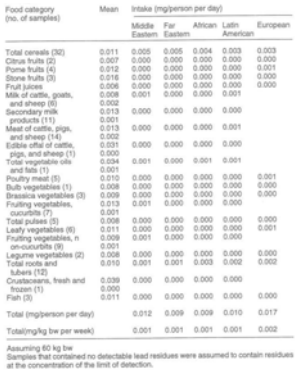
[a] Source: Fewtrell et al. (2003).
[b] Corrosive water is water that is highly acidic or alkaline, and that can dissolve certain metals (such as antimony cadmium, copper, lead or nickel) in pipes and fixtures. When corrosive water stands in contact with fittings the concentrations of these metals can be elevated, even though their levels may be normal in "flushed" samples.

Approach 1: Generic Estimation of Daily Lead Absorption

	Weight (kg)	Water consumption (litres/day)	Air intake (m^3/day)	Dust (µg/day)	Digestive absorption (%)	Respiratory absorption (%)	Food consumption[b] (g/day)	Indoor-outdoor ratio
Infants, 6 months	5.0	0.5	2.5	10	50	40	1000	
Children, 2 years	13.6	0.5	5.0	50	40	40	1500	0.7
Adults	60.0	1.0	20.0	20	10	40	3300	

[a] Sources: WHO (1995); INSERM (1999); FAO (1989).
[b] Food consumption includes drinks.

Approach 2: Estimated Dietary Lead Intake Based on WHO Regional Diets and Average Residues from U.S. Total Diet Study (JECFA, 2000)

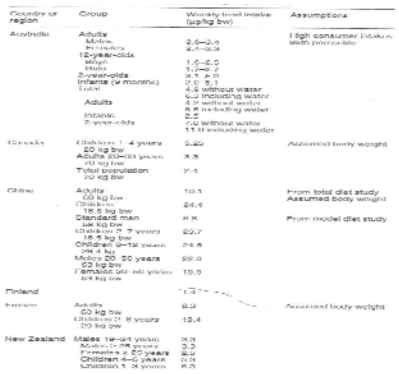


Food category (no. of samples)	Mean	Intake (mg/person per day)				
		Middle Eastern	Far Eastern	African	Latin American	European
Total cereals (32)	0.011	0.005	0.005	0.004	0.003	0.003
Citrus fruits (2)	0.007	0.000	0.000	0.000	0.000	0.000
Pome fruits (4)	0.012	0.000	0.000	0.000	0.000	0.001
Stone fruits (3)	0.016	0.000	0.000	0.000	0.000	0.000
Fruit juices	0.006	0.000	0.000	0.000	0.000	0.000
Milk of cattle, goats, and sheep (6)	0.008	0.001	0.000	0.000	0.001	
Secondary milk products (11)	0.002 0.013 0.001	0.000	0.000	0.000	0.000	
Meat of cattle, pigs, and sheep (14)	0.013 0.002	0.000	0.000	0.000	0.001	
Edible offal of cattle, pigs, and sheep (1)	0.031 0.000	0.000	0.000	0.000	0.000	
Total vegetable oils and fats (1)	0.034 0.001	0.001	0.000	0.001	0.001	
Poultry meat (5)	0.010	0.000	0.000	0.000	0.000	0.001
Bulb vegetables (1)	0.008	0.000	0.000	0.000	0.000	0.000
Brassica vegetables (3)	0.009	0.000	0.000	0.000	0.000	0.000
Fruiting vegetables, cucurbits (7)	0.013 0.001	0.001	0.000	0.000	0.000	
Total pulses (5)	0.008	0.000	0.000	0.000	0.000	0.000
Leafy vegetables (6)	0.011	0.000	0.000	0.000	0.000	0.001
Fruiting vegetables, n on-cucurbits (9)	0.009 0.001	0.001	0.000	0.000	0.000	
Legume vegetables (2)	0.008	0.000	0.000	0.000	0.000	0.000
Total roots and tubers (12)	0.010	0.001	0.001	0.003	0.002	0.002
Crustaceans, fresh and frozen (1)	0.039 0.000	0.000	0.000	0.000	0.000	
Fish (3)	0.011	0.000	0.000	0.000	0.000	0.000
Total (mg/person per day)		0.012	0.009	0.009	0.010	0.017
Total(mg/kg bw per week)		0.001	0.001	0.001	0.001	0.002

Assuming 60 kg bw
Samples that contained no detectable lead residues were assumed to contain residues at the concentration of the limit of detection.

- <u>Assumption</u>: levels of lead in U.S. foods accurately estimate levels elsewhere

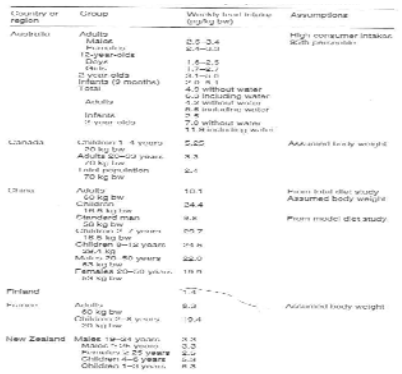
Approach 3: Estimate Dietary Lead Intake Based on Country-Specific Data (diverse methodologies) (JECFA, 2000)



Country or region	Group	Weekly lead intake (µg/kg bw)	Assumptions
Australia	Adults Males Females 12-year-olds Boys Girls 2-year-olds Infants (9 months) Total Adults Infants 5 year olds	2.6–3.4 2.4–3.0 1.6–2.5 1.7–2.7 3.1 to 6 2.0, 5.1 4.9 without water 6.0 including water 5.2 without water 6.5 including water 3.4 7.0 without water 11.9 including water	High consumer intakes, 95th percentile
Canada	Children 1–4 years 20 kg bw Adults 20–(>) 70 kg bw Total population 70 kg bw	5.25 3.3 2.1	Assumed body weight
China	Adults 60 kg bw Children 16.5 kg bw Standard man bw Children 2–7 years 16.5 kg bw Children 8–12 years 29.4 kg Males 20–50 years 63 kg bw Females 20–(>) 54 kg bw	10.1 24.4 9.8 20.7 24.8 29.0 19.6	From total diet study Assumed body weight From model diet study
Finland		1.4	
France	Adults 60 kg bw Children 2–5 years 20 kg bw	6.0 10.4	Assumed body weight
New Zealand	Males 14–64 years Males 7–14 years Females ≥ 25 years Children 4–6 years Children 1–3 years	4.8 3.3 2.0 3.4 4.3	

Sources :
- **GEMS/Food database**
- **market basket surveys**
- **national nutrition surveys**
- **total diet studies**

Approach 3: Estimate Dietary Lead Intake Based on Country-Specific Data (diverse methodologies) (JECFA, 2000)



Country or region	Group	Weekly lead intake (µg/kg bw)	Assumptions
Australia	Adults Males Females 12-year-olds Boys Girls 2-year-olds Infants (9 months) Total Adults Infants 5 year olds	2.6–3.4 2.4–3.0 1.6–2.5 1.7–2.7 3.1 to 6 2.0, 5.1 4.9 without water 6.0 including water 5.2 without water 6.5 including water 3.4 7.0 without water 11.9 including water	High consumer intakes, 95th percentile
Canada	Children 1–4 years 20 kg bw Adults 20–(>) 70 kg bw Total population 70 kg bw	5.25 3.3 2.1	Assumed body weight
China	Adults 60 kg bw Children 16.5 kg bw Standard man bw Children 2–7 years 16.5 kg bw Children 8–12 years 29.4 kg Males 20–50 years 63 kg bw Females 20–(>) 54 kg bw	10.1 24.4 9.8 20.7 24.8 29.0 19.6	From total diet study Assumed body weight From model diet study
Finland		1.4	
France	Adults 60 kg bw Children 2–5 years 20 kg bw	6.0 10.4	Assumed body weight
New Zealand	Males 14–64 years Males 7–14 years Females ≥ 25 years Children 4–6 years Children 1–3 years	4.8 3.3 2.0 3.4 4.3	

Sources :
- **GEMS/Food database**
- **market basket surveys**
- **national nutrition surveys**
- **total diet studies**

Problem: Data not available for most developing countries

- **Whichever approach, use estimated dietary intake to calculate contribution of foodborne lead to blood lead level (empirically, PK model), by age and region, as an estimate of fraction of disease burden attributable to it**

- **Whichever approach, use estimated dietary intake to calculate contribution of foodborne lead to blood lead level (empirically, PK model), by age and region, as an estimate of fraction of disease burden attributable to it**
  - **e.g., if 20% of blood lead level in a region can be attributed to dietary lead intake, 20% of disease burden is assumed to be due to this pathway for purpose of calculating DALYs**
  - **If so, 12.9 million total DALYs for lead X 0.2 = 2.6 million DALYs**

Future of FERG

- **FERG originally designed as a 5-year project (2007-2012)**
- **Will take longer**
- **Funding a major issue**
  - **US CDC, European CDC, RIVM (Netherlands), USDA, governments of UK, Japan, Germany, Ireland, Sri Lanka, as well as in-kind contributions (US FDA)**