4. regional estimates of the proportion of diarrhoea episodes and deaths caused by the 11 named foodborne hazards in children under 5 years;
5. country-level estimates of the proportion of diarrhoea episodes and deaths caused by the 11 named foodborne hazards in the population aged 5 years and over (to be delivered to the CTF);
6. regional estimates of the proportion of diarrhoea episodes and deaths caused by the 11 named foodborne hazards in the population aged 5 years and over;
7. a list of references and extracted information on the duration of diarrhoea episodes (to be discussed by the EDTF).

4.2 Meeting between the EDTF and the CTF

A meeting was held between the EDTF and the CTF, during which the EDTF explained the five categories of calculation for the enteric agents (Table 1).

- The first category concerns typhoid, for which existing GBD estimates will be used. The GBD 2010 study calculated DALYs based on prevalence data. However, FERG will base its DALY estimates on incidence data. As a result, GBD prevalence estimates will need to be converted to incidence estimates, and the EDTF will determine the best approach to convert prevalence DALYs to incidence DALYs. Furthermore, GBD information on deaths and the age distribution of death will be used. It is expected that IHME will have information on the latter.
- The second category concerns STEC, Listeria and invasive *Salmonella*. For these agents, hierarchal models are constructed on the basis of a systematic review, to arrive at estimates for each of the 14 WHO subregions. Case-fatality ratios will be derived from the systematic reviews. The age distribution of death is also needed; the ETDF will discuss this further.
- For brucellosis, *Clostridium perfringens, C. botulinum, Bacillus cereus and Staphylococcus aureus,* systematic reviews are not available, and there are only a few data points. The available data will be shared with the CTF, to see if it is possible to impute these data. If imputation is not possible for the toxins, they may not be included in the final FERG estimates. Toxin deaths may be derived from the estimates of GBD and CHERG based on hospital patients. As regards brucellosis, countries that are free of the disease will need to be taken into account. Mortality due to brucellosis will be assessed using case-fatality ratios.
- For *Shigella*, cholera, EPEC, ETEC, *Campylobacter*, norovirus, other diarrhoeal diseases and maybe *Salmonella*, the point of departure for the calculations is the CHERG estimates for diarrhoea episodes. These estimates will be portioned out by etiology for patients aged under and over 5 years. Estimates of disease duration for these pathogens and age distribution of deaths are still needed; estimates of duration of illness will be provided by reviewers currently working on STEC, norovirus and diarrhoeal diseases.
- The fifth category concerns hepatitis A virus and *M. bovis*. For hepatitis A virus, the WHO Hepatitis Group will provide incidence and mortality estimates by region. For *M. bovis*, the WHO Tuberculosis Group will provide estimates of human tuberculosis incidence and mortality by country.

Table 1. Overview of the five approaches to calculation of DALYs for enteric agents

Category	Agent or disease	Approach to arrive at DALY estimates
1	Typhoid fever	Use existing GBD 2010 estimates and convert prevalence to incidence
2	STEC, *Listeria*, invasive *Salmonella*	Use data from systematic reviews and hierarchal modelling
3	Brucellosis, *Clostridium perfringens, C. botulinum, Bacillus cereus, Staphylococcus aureus.*	No systematic review available; use available data points and imputation if possible
4	Non-invasive *Salmonella, Shigella*, cholera, EPEC, ETEC, *Campylobacter*, norovirus and other diarrhoeal diseases	Use CHERG estimates for diarrhoea and portion out by etiology for patients under and over 5 years
5	Hepatitis A virus, M. *bovis*	Use WHO estimates of incidence and mortality for hepatitis A and human tuberculosis

4.3 Meeting between the EDTF and the Source Attribution Task Force (SATF)

4.3.1 Expert panel make-up

The EDTF prefers the expert panels on source attribution to be global rather than regional. These global panels will focus on enhanced regional representation. Also it was pointed out that subpanels would be needed for developed and developing countries.

The following panels were agreed upon:

- a global panel on brucellosis;
- a global panel on hepatitis A;
- a global panel on all other diarrhoeal diseases – developed countries (no typhoid fever); and
- a global panel on all other diarrhoeal diseases – developing countries.

4.3.2 List of pathogens and type of questions for attribution

The list of pathogens for attribution was finalized. The ETDF recommended eliminating the second-level expert attribution because of the change to global panels. It is not likely that it will be possible at this level to tease out specific foods, with an awareness of production systems in specific regions. If second-level attribution cannot be eliminated, then simpler versions of the questions that will be submitted to the expert panels need to be developed; for example, a more general question related to point of contamination for food would be preferable. A potential question is: If you had to eliminate this pathogen in food, what percentage of your effort would you invest in interventions at reservoir, processing, food service and home levels?

It was decided that the second-level attribution would be done for *Campylobacter, Salmonella*, STEC and brucellosis. The specific food types and the point in the chain of contamination are likely to be important.

5. Chemicals and Toxins Task Force

5.1 Cadmium

Exposure to cadmium will be estimated using urinary cadmium levels as biomarker, with a focus on the general population rather than groups from highly contaminated regions. Where such biomarker data are not available, the intake information from the WHO Global Environment Monitoring System (GEMS) database might be used. Cadmium exposure has been associated with several disease outcomes; adverse renal and bone effects were selected for the burden of disease estimates.

- *Renal effects*. Although efforts have been made quantitatively to associate cadmium exposure to biomarkers for tubular dysfunction and albuminuria, there is no disability weight available for these adverse effects. Current scientific understanding of these biomarkers is inadequate to link them quantitatively with ESRD. To estimate the incidence of cadmium-related ESRD, it is feasible to use the dose–response relationship between cadmium exposure and the resulting decrease in the estimated glomerular filtration rate (eGFR) (9). Using the country-specific distribution of eGFR, the incidence rate of stage 4/5 ESRD due to cadmium exposure can be estimated using the distributional shift of GFR.
- *Bone effects (osteoporosis/fractures)*. The relationship between cadmium exposure and osteoporosis has been established. However, there is no disability weight for osteoporosis. Since osteoporosis is a risk factor for fractures, which have disability weights, attempts will be made to estimate the cadmium-attributable incidence of fractures. The dose–response relationship between urinary cadmium levels and bone mass density can be used to obtain country-specific bone mass loss and, where available, the WHO FRAX fracture prediction parameters can be used to link bone mass density with the risk of fracture. WHO FRAX is a tool developed by WHO to evaluate fracture risk (10). Thus, urinary cadmium levels can be used to estimate the risk of fracture. Where such data are not available, an alternative method using the dose–response relationship between cadmium exposure and the risk ratio of fractures will be considered.

5.2 Methylmercury

Mercury intoxication results in many disease outcomes, but the most sensitive is considered to be impaired neurological development of children exposed prenatally, with loss of intelligence quotient (IQ) as endpoint. To estimate the number of methylmercury-induced cases of intellectual disability in the population, an exposure-based approach will be used, with mercury levels in hair or blood as biomarker and a focus on the general population rather than highly exposed subpopulations.

The systematic review identified over 1300 articles from a range of countries and regions with data on mercury levels in hair or blood collated in table format. One study was selected for each country, using the following criteria: a nationally representative study, general population data, preferably with distribution of values (not a mining community or clinical cases, but a control group in a "hotspot" study could be included), recent survey, preferably measurements on hair, but some studies with blood measures were included (a conversion factor was applied to estimate hair mercury levels).

There is the option to include data from subpopulations in hotspots close to mining or fishing communities; however, exposure in a mining community affects predominantly males and may not be relevant to fetal exposure. In addition, exposure is likely to be to ingested or inhaled elemental mercury, not methylmercury.

Two options for filling data gaps on biomarkers were discussed: (a) using a regression model to link total fish consumption to levels of mercury in hair, using national survey data; or (b) using revised GEMS/Food cluster diets to assign known levels of mercury in hair to other countries in the same cluster for which no data are available.

5.2.1 Prediction of level of intellectual disability from IQ loss

Loss of IQ is not a disease as such; thus, an estimate is needed of the shift in the distribution of people with different degrees of intellectual disability (mild (IQ 50–70); moderate (35–50); severe (20–35); or profound (<20)). There are disability weights for the various degrees of intellectual disability.

To link IQ loss due to methylmercury exposure to the stage of intellectual disability requires data on the percentage of population in each IQ range, and a slope factor linking mercury levels in the hair of pregnant women to IQ loss in their offspring, taking into account the beneficial effects of eating fish as well as the risks, and the uncertainty around hair data. The mercury-associated shift in mild intellectual disability rates can then be predicted using birth rate data, estimating the number of children in each stratum of maternal mercury hair values, and converting these to increments of IQ loss using the slope factor of Axelrad et al. (11). Because decrements in intellectual disability may be compounded by diet, medical care, etc., the CTTF will use WHO adjustment factors for the WHO regions to make regional estimates (12).

5.3 Lead

For lead, an exposure-based approach is used, similar to that for methylmercury. Lead levels in blood will be used as biomarker for young children, and systolic blood pressure for adults. Again, the focus is on the general population rather than highly exposed subpopulations. Lead exposure may result in many disease outcomes, but the most sensitive is considered to be impaired neurological development in children, with IQ loss as endpoint. In adults, the endpoint is cardiovascular disease.

The main sources of lead exposure are soil and dust, paint chips, tapwater and diet. Other potential exposures are from dietary supplements, clay, lime, and cooking pots. For dietary exposure, total diet studies are considered to be the best information source.

There are three such studies that include information on children, in China, Europe and the USA (13, 14). New data on consumption and exposure in Europe are also available from the European Food Safety Authority (EFSA) (14).

To predict intellectual disability from IQ loss in young children, the shift in degrees of intellectual disability will be estimated (see the discussion on methylmercury, section 5.2). Because the estimates are largely independent of non-dietary exposures to lead, a bilinear dose–response model is best for converting lead levels in blood to IQ loss.

To predict cardiovascular disease from biomarker data for adults, lead levels in blood will be converted to systolic blood pressure using known slope factors. Using data on blood pressure, the relative risk slopes for three types of cardiovascular disease – ischaemic heart disease, cerebrovascular disease (stroke) and hypertensive disease – can be calculated for four age groups (15–44, 45–59, 60–69 and 70–79 years). Death rates from cardiovascular disease are needed to convert current relative risk to incidence of cardiovascular disease due to lead exposure, and to identify relevant disability weights for the three cardiovascular disease types.

5.4 Peanut allergens

There are three types of data on peanut allergy: self-reported, IgE prick test results and food challenge data. It was agreed to use self-reported data to estimate prevalence, since these are available for more countries.

Incidence rates will be derived for countries with data, on the assumption that incidence rates are equivalent to prevalence rates (once peanut allergy occurs in a young child it is expected to be lifelong). The CTTF discussed how data could be extrapolated to countries and regions with no data. One option is to refer to the International Study of Asthma and Allergies in Childhood (ISAAC) (which covers over 100 countries) (15). There is not sufficient time or resources to do additional analytical work on serum samples to determine the proportion with peanut allergy. However, it would be possible to use the ISAAC figures for the proportion that were deemed to be sensitized (which would include other allergies, asthma, rhinitis and eczema) and apply a standard proportion to derive an estimate of the percentage with peanut allergy.

There are disability weights that could be used for peanut allergy and anaphylactic shock.

5.5 Dioxins

A body burden approach will be taken for dioxins. Dioxin levels in breast milk will be used as a marker of body burden. The approach will focus on women of childbearing age. Dioxin exposure may have many adverse outcomes, but the most sensitive are changes in thyroid function and reproductive toxicity (prenatal effect on development of male reproductive organs and postnatal disturbances of sperm count). Exposure to high levels of dioxin may result in an increased risk of cancer, but this will not be covered in the burden of disease estimates, since dioxin exposure through the food supply is believed to be below the level associated with an increased risk of cancer.

Results of surveys of dioxin levels in breast milk are available from WHO for many countries for 2000–2010, but these data represent pooled samples. Data from European countries suggest that dioxin levels in breast milk may have decreased with time. It was decided to estimate the body burden for various countries on the basis of the geometric mean for breast milk ± 1.5 standard deviations (SD) and the geometric mean for blood ± 2.0 SD (actual body burden). The estimations of standard deviation are based on individual breast milk and blood data from various countries.

An estimate of the human dioxin body burden that results in a 5% loss of sperm count following prenatal exposure was derived from dose–response modelling of animal data with extrapolation to humans (reference body burden). The reference body burden was then compared with the actual body burden to estimate the percentage of pregnant women with a body burden that would result in a 5% sperm count reduction in their offspring. However, a 5% reduction in sperm count is of clinical importance only if it reduces the sperm count below the cut-off point for impaired fertility (taken as 20 million per ml). The percentage of pregnant women with a body burden that would result in impaired fertility in their offspring was then calculated (P_{if}). This probability serves as the starting-point for the DALY calculation, assuming that impaired fertility leads to primary infertility.

Similarly, an estimate of the human dioxin body burden resulting in a 5% loss of total T4 (TT4) hormone in the blood of women of reproductive age was derived from dose–response modelling of animal data with extrapolation to humans. This reference body burden was compared with the actual body burden that results in a 5% reduction in TT4 level. However, a 5% reduction in TT4 level is of clinical importance only if it reduces the TT4 level below the cut-off point for impaired thyroid functioning (taken as the $P_{0.05}$ of the human TT4 blood level). The percentage of the population of women of reproductive age with a body burden that would result in impaired thyroid functioning was calculated (P_{thy}). This probability serves as the starting-point for the DALY calculation, assuming that impaired thyroid functioning leads to hypothyroidism.

The calculated percentages, P_{if} and P_{thy}, will be combined with demographic data to estimate country-specific prevalence and incidence rates for impaired fertility and hypothyroidism.

5.6 Arsenic

Biomarkers of arsenic typically include urinary arsenic (adjusted for urinary creatinine), and toenail arsenic. Urinary arsenic level is a biomarker of recent arsenic exposure, while toenail arsenic levels reflect exposure to arsenic over a longer duration (usually months). Since single doses of arsenic are rapidly and extensively cleared from the blood via the kidneys, blood arsenic concentrations have been considered to reflect only recent exposure. However, arsenic concentration in blood can be used as a biomarker to measure the steady-state concentrations produced by chronic and continuing exposure.

An exposure-based approach will be taken to assess the number of cases of arsenic poisoning. Selected disease outcomes are bladder, lung and skin cancers. These three cancer endpoints are the health effects that are best documented in the scientific literature. Although there is growing evidence of an association between arsenic exposure and an increased risk of liver cancer, this is not included in the current assessment. Cardiovascular disease has also been linked to arsenic exposure (16), but including cardiovascular disease as outcome would require additional work.

The main pathways of exposure to arsenic are via water and food, with systemic accumulation of arsenic from soil and from water used in food preparation. There are many effects on body functions. Some studies have reported an interaction between smoking and arsenic exposure, leading to bladder and lung cancers. Folate deficiency is also a cofactor in the incidence of cancers. As the level of deficiency increases, adverse health effects increase, but there is not enough information to quantify the relationship with arsenic. Increased selenium in the diet tends to decrease the incidence of skin lesions, but this effect has also not been quantified.

Dietary exposure to inorganic arsenic will be estimated using the 13 GEMS/Food cluster diets, together with lower and upper bound concentration levels reported by EFSA; conversion factors for different foods will be taken from the literature.

Cancer prevalence rates will be estimated by combining exposure to arsenic in food with a cancer slope factor. Cancer slope factors may be used to estimate the risk of cancer associated with exposure to a carcinogenic. For each cancer, age-specific incidence rates will be calculated for males and females. It was noted that arsenic exposure increases the risk of reaction to other potential carcinogens, and that the incidence of related cancers increases with age.

5.7 Cyanogenic glycosides

An exposure-based approach is taken for cyanogenic glycosides. The selected disease outcome is paraparesis occurring in konzo-affected populations. Evidence is available for only five countries in sub-Saharan Africa. Some acute cyanide poisoning has been reported for other regions, but the information is not sufficient for assessment. The CTTF discussed whether impaired neurocognitive function should be included as a disease outcome. However, the one study that provided some evidence for this link in one country (17) had an inadequate sampling frame. It was therefore agreed not to include incidence of impaired neurocognitive function in the burden of disease estimates.

Linamarin is a cyanogenic glycoside found mainly in cassava, with high levels in bitter cassava and very low levels in sweet cassava. Three factors are likely to result in a high rate of konzo: dependence on bitter cassava in the diet, a lack of legumes and meat in the diet, and living conditions that increase the probability of incorrect preparation of cassava, especially bitter cassava. The available data for five African countries will be extrapolated to other African countries that have similar consumption levels of cassava, legumes and meat, to estimate the incidence of konzo-related paraparesis. It was noted that the consumption levels used in the extrapolation exercise are national per capita levels. It is therefore possible that specific groups in other African and non-African countries may have similar dietary patterns that are not reflected in the national figures.

See Table 2 for an overview of biomarkers and selected disease outcomes for each agent.

Table 2. Overview of biomarkers and selected disease outcomes for each agent

Agent	Biomarker	Disease outcomes
Cadmium	Urinary cadmium levels	Renal dysfunction and bone effects (osteoporosis, fractures)
Methylmercury	Hair/blood mercury levels	IQ loss
Lead	In children: blood lead levels In adults: systolic blood pressure	In children: IQ loss In adults: cardiovascular disease
Peanut allergens	-	Peanut allergy and anaphylactic shock
Dioxin	Breast milk dioxin levels	Thyroid dysfunction and reduced sperm count
Arsenic	Urinary and toenail arsenic levels	Bladder, lung and skin cancers. Possibly cardiovascular disease
Cyanogenic glycosides	-	Konzo

6. Parasitic Diseases Task Force

The list of parasites examined by the Parasitic Diseases Task Force (PDTF) was reviewed and the need for additional commissioned work was discussed. For the parasites for which the work has been completed, the PDTF discussed what data had to be extracted for the CTF database templates. A review of the available data revealed a conflict between the FERG data and the GBD 2010 data for some of the parasites.

6.1 Foodborne trematodes

The results of the GBD 2010 study (2) will be used for foodborne trematodes (*Fasciola, Clonorchis, Opisthorchis*). The work for GBD 2010 was undertaken in collaboration with FERG. The paper by Fürst et al. reports 665 000 DALYs, whereas GBD 2010 reports 1.8 million DALYs, despite being based on the same dataset (18). The reasons for this discrepancy are not clear. The results of the paper need to be discussed and the data carefully analysed; the PDTF will contact the authors of the paper to obtain the raw data.

6.2 Echinococcosis

A report on echinococcosis estimates provided by IHME was reviewed by the PDTF. Many of the figures, such as the incidence totals for Eastern and Western Europe, are questionable. For alveolar echinococcosis, raw data are available from work commissioned by FERG. These data include public health data (published and unpublished), data from hospital records and published data from, for example, Russian government records and Chinese surveillance. There are also surveillance data of 20 000–30 000 Tibetans in highly endemic areas and natural history models.

The PDTF recommends that these commissioned data be used rather than the GBD 2010 data for alveolar echinococcosis. The data will be provided to the CTF.

A review of cystic echinococcosis by Budke et al. has been published (19). The data from this review are reasonably complete, although it is not clear what the data gaps are, i.e., which countries have no cases and which countries have no data. PDTF will contact Dr Budke to request the data on cystic echinococcosis in order to complete the CTF template.

6.3 Cysticercosis

The commissioned work on cysticercosis has resulted in the publication of two papers (20, 21). The first deals with the sequelae of cysticercosis, while the second addresses neurocysticercosis-induced epilepsy. The latter showed that 29% of epilepsy is induced by neurocysticercosis. There are no WHO figures for epilepsy, so this percentage will be