

## **Protocol Version 2**

Continuous Update and Systematic Literature Review of Randomised Controlled Trials, Prospective Studies and Case-control Studies on Food, Nutrition, Physical Activity and Cancers of Mouth, Pharynx and Larynx.

Prepared by: CUP Team, Imperial College London, May 2013  
Reviewed in August 2013

### **INTRODUCTION**

#### **The Continuous Update Project.**

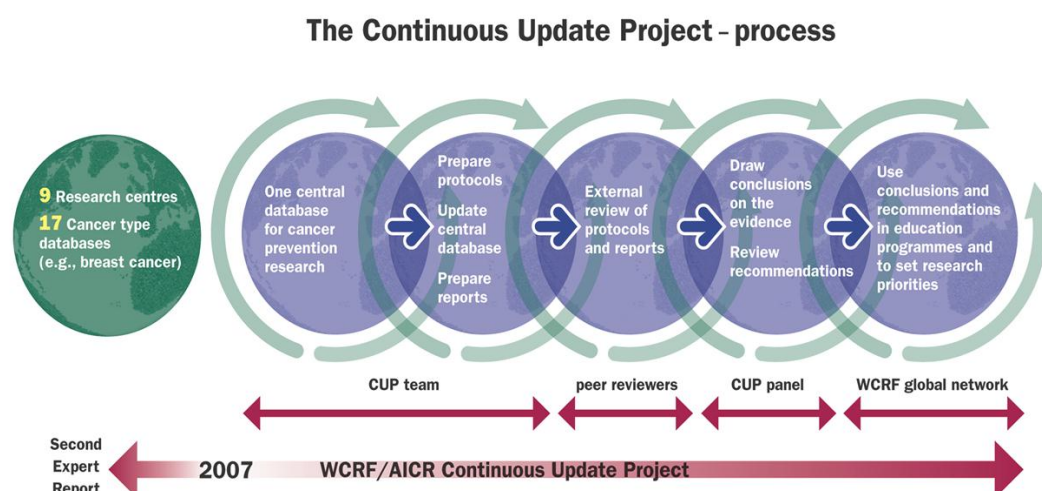
The World Cancer Research Fund/ American Institute for Cancer Research: (WCRF/AICR) has been a global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The First and Second Expert Reports (1;1;2;2) represent the most extensive analyses of the existing science on the subject to date.

The Second Expert Report features eight general and two special recommendations based on solid evidence which, when followed, will be expected to reduce the incidence of cancer. More recently, empirical evidence from a large European cohort study showed that people with lifestyle in agreement with the WCRF/AICR recommendations experienced decreased risk of cancer after an average follow-up time of ten years (3). The main risk reductions were for cancers of the colon and rectum, and oesophageal cancer, and significant associations were observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver, and oesophagus.

The Second Expert Report was informed by a process of seventeen systematic literature reviews (SLRs) all of the evidence published. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP) in collaboration with Imperial College London (ICL). The CUP [[http://www.wcrf.org/cancer\\_research/cup/index.php](http://www.wcrf.org/cancer_research/cup/index.php)] is an on-going systematic literature review on food, nutrition, physical activity and body fatness, and cancer risk. The project ensures that the evidence, on which the WCRF/AICR recommendations are based, continues to be the most-up-to-date and comprehensive available.

WCRF/AICR has convened a panel of experts for the CUP consisting of leading scientists in the field of diet, physical activity, obesity and cancer, who will consider the evidence produced by the systematic literature reviews conducted by the research team at ICL. The CUP Panel will judge the evidence, draw conclusions and make recommendations for cancer prevention. The entire CUP process will provide an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising the 2007 WCRF/AICR's cancer prevention recommendations (**Figure 1**).

**Figure 1.** The Continuous Update Process



The CUP builds on the foundations of the Second Expert Report to ensure a consistent approach to reviewing the evidence (4). A team at ICL conducts the CUP SLRs, where a central database has been created by merging the cancer-specific databases generated in the 2007 SLR's. A key step of the CUP is the update of the central database with the results of randomised controlled trials and prospective studies for most cancer sites. These study designs are considered less prone to bias and the 2007 WCRF recommendations had been mainly based on the results of randomised controlled trials and prospective cohort studies. However, the number of published cohort studies is sparse for some cancers with relative low incidence rates. For these cancers, the CUP SLR will include case-control studies.

The WCRF database has been updated at ICL in a rolling programme. The CUP started in 2007. The first cancer to be updated was breast cancer, followed by prostate and colorectal cancers. When a cancer site is included in the CUP, the team at ICL keeps updating the database for that cancer and all the other cancers already included in the CUP (**Figure 2**). Currently, the central database is updated for cancers of the breast, prostate, colon and rectum, pancreas, ovary, endometrium, bladder, kidney, gallbladder, liver and stomach.

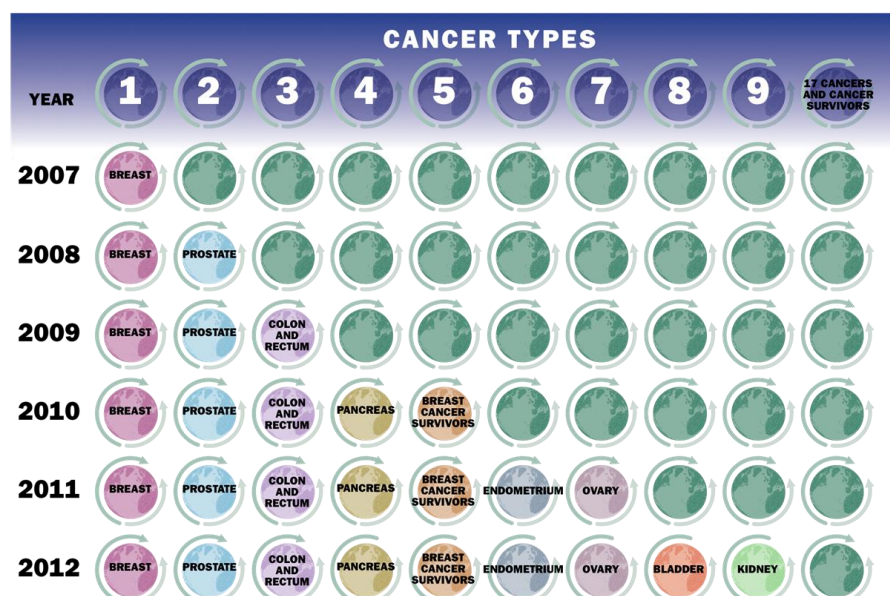
Periodically, the CUP team at ICL prepares SLR reports with updated meta-analyses by request of the CUP Panel and Secretariat. The protocols and reports of systematic literature reviews by the ICL team are available at

[http://www.dietandcancerreport.org/cancer\\_resource\\_center/continuous\\_update\\_project.php](http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php)).

The present document is the protocol for the continuous update of the WCRF database and the CUP SLR on food, nutrition, body fatness, physical activity and the risk of cancers of the mouth, pharynx and larynx. The peer-reviewed protocol will represent the agreed plan. Should departure from the agreed plan be considered necessary at a later stage, the CUP Expert Panel must agree this and the reasons be documented.

**Figure 2. The Continuous Update Project- rolling programme**

*Note: Cancer types included in the CUP rolling program in 2013: Gallbladder, Liver, Stomach, Oesophageal. Protocols in preparation: Mouth, pharynx and larynx, and nasopharyngeal cancers.*



### Epidemiology and risk factors of cancers of the mouth, pharynx and larynx.

In the year 2008, an estimated number of 263,020 new cases of cancers of the lip and oral cavity, 136, 622 new cases of pharyngeal cancer (excluding nasopharyngeal cancer) and 150, 677 of cancer of the larynx had been diagnosed worldwide, representing 1%, 2% and 1.2% respectively of the total number of cancer cases diagnosed per year (excluding nonmelanoma skin cancers) [Globocan, 2008 (5)]. The cancers of the lip and oral cavity, pharynx and larynx are two-three times more common in men than in women (**Table 1**). Over 90% of oral, pharyngeal and laryngeal cancers are squamous cell carcinomas. Risk increases with age. All together, these cancers are the seventh most frequent type of cancer worldwide. Nearly 4% of all cancer deaths were attributed to these cancers.

The highest incidence rates of oral and pharyngeal cancer are seen in Melanesia, south central Asia and parts of central and western Europe (Globocan, 2008 (5) **Figure 3A**). For laryngeal cancer, the highest incidence rates are seen in parts of Europe, western Asia, Caribbean, South America and Southern Africa (Globocan, 2008 (5), **Figure 3B**).

Tobacco use (including smokeless tobacco, sometimes called “chewing tobacco” or “snuff” (6) is a well-established risk factor for cancers of the mouth, pharynx and larynx, with risk increasing with the duration and amount of use (7). Alcohol consumption is an independent risk factor for these cancers (8-10), but is also thought to interact with tobacco smoking to increase cancer risk (11;12). Betel quid use (13;14) is also a risk factor of oral cancer. Certain industrial exposures, including exposures to asbestos and synthetic fibres, have been associated with cancer of the larynx, but the increase in risk

remains controversial. People working in certain jobs in the construction, metal, textile, ceramic, logging, and food industries may have an increased risk of cancer of the larynx (15).

There is sufficient evidence in humans that HPV 16 causes cancer of the oral cavity. There is limited evidence in humans that HPV 16 causes cancer of the larynx. A positive association has been observed between infection with HPV 18 and cancer of the oral cavity, and larynx IARC (16).

**Table 1.** Estimated cancer incidence and mortality for cancers of the lip and oral cavity, pharynx and larynx. World, 2008

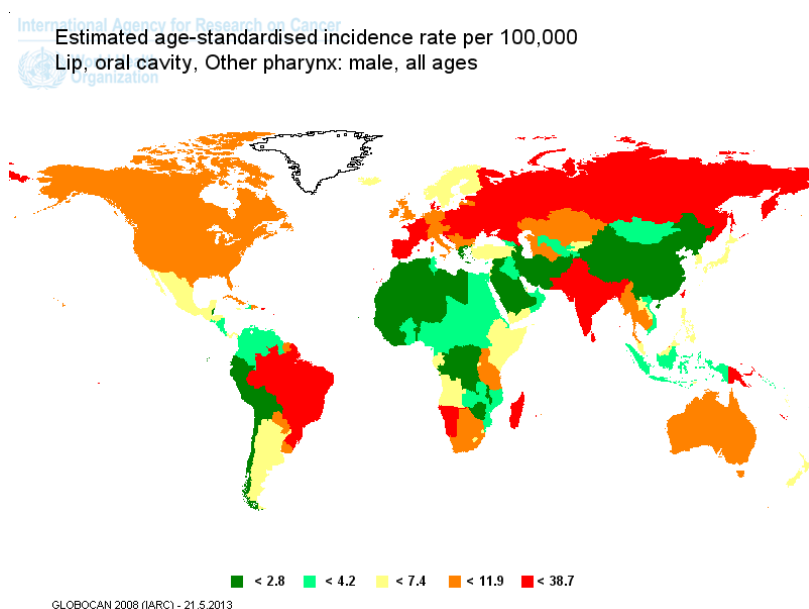
WORLD. ESTIMATED CANCER INCIDENCE, ALL AGES					
Cancer	Gender	Numbers	Crude Rate	ASR (W)	Cumulative Risk
Lip, oral cavity*	Men	170496	5	5.2	0.61
	Women	92524	2.8	2.5	0.29
Pharynx (excluding nasopharynx)	Men	108588	3.2	3.4	0.41
	Women	28034	0.8	0.8	0.09
Larynx	Men	129651	3.8	4.1	0.51
	Women	21026	0.6	0.6	0.07
WORLD. ESTIMATED CANCER MORTALITY, ALL AGES					
Cancer	Gender	Numbers	Crude Rate	ASR (W)	Cumulative Risk
Lip, oral cavity	Men	83109	2.4	2.6	0.3
	Women	44545	1.3	1.2	0.14
Pharynx (excluding nasopharynx)	Men	76458	2.2	2.4	0.28
	Women	19092	0.6	0.5	0.06
Larynx	Men	70336	2.1	2.2	0.27
	Women	11556	0.3	0.3	0.04

Source: Globocan, 2008 (5)

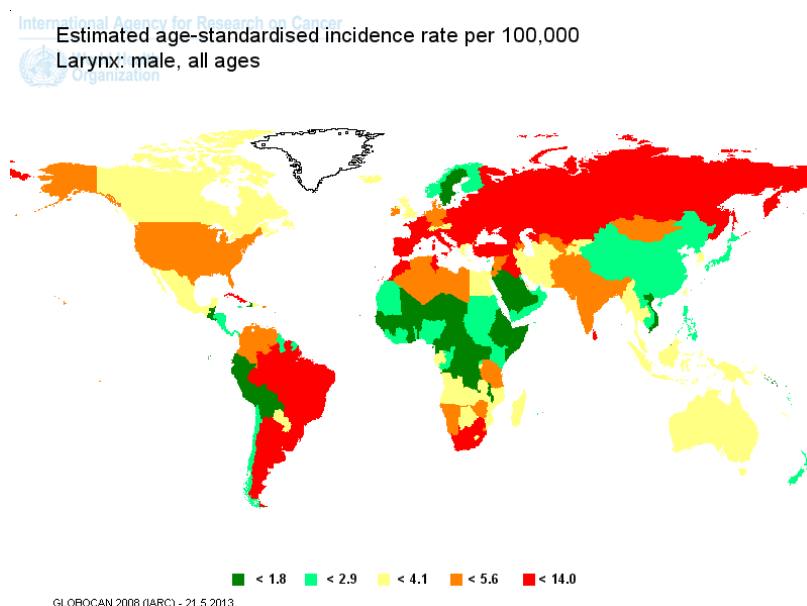
\*Note: Lips and salivary glands cancers will not be included in this review.

**Figure 3.** Incidence rates of cancers of the lip and oral cavity, pharynx and larynx by geographic area in males.

A. Lip and oral cavity



B. Larynx



Source: Globocan, 2008 (5)

## Dietary factors

In addition to alcohol, there is some evidence that dietary factors may play a role in the aetiology of cancers of the mouth, pharynx and larynx. In the 2007 WCRF/AICR second expert report (**Figure 4**), it was concluded alcohol convincingly increases the risk of cancers of the mouth, pharynx and larynx. The evidence of a potential protective effect of non-starchy vegetables and fruits was judged probable, as well as the evidence of a protective effect of carotenoids from foods. Several studies suggest that drinking maté may increase the risk of these cancers, but the evidence was judged limited. For all other exposures investigated, the associations were inconsistent or the number of studies low and no conclusion was possible.

**Figure 4.** Matrix with the judgement of the Panel of Experts in the WCRF/AICR Second Expert Report for cancers of the mouth, pharynx and larynx.

# FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE MOUTH, PHARYNX, AND LARYNX

In the judgement of the Panel, the factors listed below modify the risk of cancers of the mouth, pharynx, and larynx. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
<b>Convincing</b>		<b>Alcoholic drinks</b>
<b>Probable</b>	<b>Non-starchy vegetables<sup>1</sup></b> <b>Fruits<sup>1</sup></b> <b>Foods containing carotenoids<sup>2</sup></b>	
<b>Limited — suggestive</b>		<b>Maté<sup>3</sup></b>
<b>Limited — no conclusion</b>	Cereals (grains) and their products; starchy roots, tubers, and plantains; dietary fibre; pulses (legumes); meat; poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; coffee; tea; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; niacin; folate; vitamin C; vitamin E; calcium; iron; selenium; body fatness; energy intake	
<b>Substantial effect on risk unlikely</b>	None identified	

1

Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

2


Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).

3


As drunk traditionally in parts of South America, scalding hot through a metal straw. Any increased risk of cancer is judged to be caused by epithelial damage resulting from the heat, and not by the herb itself.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

World Cancer Research Fund



American Institute for Cancer Research



Source: WCRF/AICR Second Expert Report (1)



## 1. RESEARCH QUESTION

The research topic is:

The associations between food, nutrition and physical activity and cancers of the mouth, pharynx and larynx.

The main objective is:

To summarize the evidence from case-control studies, prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and cancers of the mouth, pharynx and larynx in men and women.

In the 2007 WCRF/AICR Systematic Literature Review (SLR) for cancers of the mouth, pharynx and larynx and in the Second Expert Report, cancers of the mouth and pharynx included those of the tongue, gums and floor and other parts of the mouth, and the pharynx. Cancers of the lip and salivary glands were not included. We will follow the same plan with this SLR. The 2007 SLR review is available at:

[http://www.dietandcancerreport.org/cancer\\_resource\\_center/downloads/SLR/Mouth\\_Pharynx\\_Larynx\\_SLR.pdf](http://www.dietandcancerreport.org/cancer_resource_center/downloads/SLR/Mouth_Pharynx_Larynx_SLR.pdf)

## 2. REVIEW TEAM

Name	Current position at ICL	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Doris Chan	Research Assistant	Supervisor of data extraction. Data analyst, SLR report preparation
Ana Rita Vieira	Research Assistant	Data analyst, SLR report preparation
Leila Abar	Research Assistant	Systematic search, article selection, data extraction
Deborah Navarro	Research Assistant	Systematic search, article selection, data extraction
Snieguole Vingeliene	Research Assistant	Systematic search, article selection, data extraction

Review coordinator, WCRF: Rachel Thompson

Statistical advisor: Darren Greenwood, Senior Research Lecturer, University of Leeds

All the reviewers have been trained in the procedures for literature search, data selection and extraction. The reviewers that will conduct the data analyses have experience in meta-analyses. Selected SLRs published by members of the ICL team are in the References Section (17-31).

### 3. TIMELINE

The SLRs for the Second Expert Report ended in December 30<sup>th</sup> 2005. The SLR centre extracted all the data from relevant articles published up to this date for the Second Expert Report.

The CUP team at ICL will search and extract data of the articles from case-control studies, prospective studies and randomised controlled trials published from January 1<sup>st</sup> 2006. The reviewers will verify that there are not duplicities in the database using a module for article search implemented in the interface for data entry.

#### **List of tasks and deadlines for the continuous update on mouth, pharynx and larynx cancer:**

Task	Deadline
Start Medline search of relevant articles published from January 1 <sup>st</sup> 2006	October 1, 2013
Start review of title and abstracts of articles identified in electronic search and select papers for complete review	October 15, 2013
Download papers and select relevant papers for data extraction	October 30, 2013
Start data extraction	November 30, 2013
Start hand search of references	November 30, 2013
Start quantitative analysis of articles included in Pubmed up to 30th May 2014*	July 1, 2014
Start writing SLR report	September 1, 2014
Send SLR report for review to CUP secretariat	November 30, 2014
Review and modify SLR report according to reviewer's comments	March-May 2015
Send reviewed SLR report to CUP secretariat	May 30, 2015
Transfer Endnote files to SLR CUP Secretariat	May 30, 2015
Panel meeting	June 2015

\*Endate of the intermediate systematic literature review to the CUP Panel



## **4. SEARCH STRATEGY**

### **4.1. Search database**

The Medline database (includes coverage from 70 countries) will be searched using PubMed as platform. The rationale for searching only in Medline is that the results of the SLR's for the Second Expert Report indicated that searching reports of prospective studies in databases other than Medline was not cost effective (32). Specifically, in the 2007 SLR for mouth, pharynx and larynx cancers, ( [http://www.dietandcancerreport.org/cancer\\_resource\\_center/downloads/SLR/Mouth\\_Pharynx\\_Larynx\\_SLR.pdf](http://www.dietandcancerreport.org/cancer_resource_center/downloads/SLR/Mouth_Pharynx_Larynx_SLR.pdf) ) 8,452 articles were identified in the electronic searches in Medline out of a total number of 9,918 references identified in all the electronic databases searched (Medline, Embase, ISI Web of Science, BIOSIS Previews, MetaRegister, LILACS, Cochrane Library, CINAHL, CAB Abstracts). Central and ClinialTrials.gov will be searched for evidence of trials relevant to this review.

### **4.2. Hand searching for cited references**

The review team will also hand search the references of reviews and meta-analyses identified during the search.

### **4.3 Search strategy for PubMed**

The CUP review team will use the search strategy established in the SLR Guidelines for the WCRF-AICR Second Expert Report (4). A first search will be conducted using as date limits January 1<sup>st</sup> 2006 to September 30<sup>th</sup> 2013 and subsequent searches will be conducted every month.

The search will be conducted in three steps:

- 1) Searching for studies relating to food, nutrition and physical activity
- 2) Searching for studies relating to cancers of mouth, pharynx and larynx
- 3) Searching for studies relating food, nutrition and physical activity, and cancers of mouth, pharynx and larynx

The full search strategy is in **Annex 1**.

## **5. STUDY SELECTION CRITERIA FOR THE UPDATE OF THE DATABASE**

### **5.1 Inclusion criteria**

The articles to be included in the review:

- Studies in men, women or both, in which cancers of the mouth, pharynx or larynx is the first cancer.
- Studies in which the exposure refers to a period before cancer diagnosis.
- Must have as exposure/intervention: patterns of diet, foods, nutrients –dietary, supplemental or both-, other dietary constituents including phytochemicals, and other bioactive compounds, energy density of the diet, glycaemic index, glycaemic load, beverages, substances in foods formed during food production or processing, food additives and contaminants, diet biomarkers,

indicators of body adiposity in early life, adolescence or adulthood, changes in body adiposity, height, breastfeeding, physical activity (Exposure list is in Annex 2)

- Must have as outcome of interest incidence or mortality of cancer of the mouth, pharynx (other than nasopharyngeal cancer) or larynx as separate outcomes, as combinations of these cancers, or for all these cancers combined<sup>¥</sup>
- Included in Medline from January 1<sup>st</sup> 2006<sup>†</sup>
- Have to present results from an epidemiologic study in men and/or women of one of the following types:
  - Randomized controlled trial
  - Group randomized controlled trial (Community trial)
  - Prospective cohort study
  - Nested case-control study
  - Case-cohort study
  - Historical cohort study
  - Population based case-control study
  - Other case-control studies

*<sup>¥</sup> Articles identified in the search with the following outcomes: “head and neck cancer”, “upper aerodigestive cancers” and other cancers groups that explicitly include mouth, pharynx or larynx cancers will also be extracted. The cancers group name will be indicated in the database under “cancer type” and the description of the cancers included in the identified groups will be indicated under “cancer type description”.*

*<sup>†</sup> January 1<sup>st</sup> 2006 is the closure date of the database for the Second Expert Report.*

## **5.2 Exclusion criteria**

- Studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders).
- Studies in which the outcome include oesophageal cancer or nasopharyngeal cancer.
- Studies in which the outcome is cancer of the lip and/or salivary glands.
- Study results in which the exposure is weight, waist circumference or hip circumference (or an index derived from any of these measures) measured at the moment of cancer diagnosis or after cancer diagnosis (e.g. in some case-control studies).
- Study results in which the exposure is a biomarker taken at or after cancer diagnosis.
- Articles written in language other than English, Chinese, French, Spanish, Portuguese or Italian, if it is not possible to obtain a translation of the article.

## 6. ARTICLE SELECTION

First, all references obtained with the searches in PubMed will be imported in a Reference Manager Database using the filter Medline.

The article selection will follow three steps:

1. An electronic search will first be undertaken within Reference Manager to facilitate the identification of irrelevant records by using the terms indicated below. Relevance will be assessed upon reading of the titles and abstracts of the articles identified by the electronic search.

### List of terms for use within Reference Manager Database

Radiotherapy  
Chemotherapy  
Cisplatin  
Docetaxel  
Cell  
Inhibitor  
Novel  
Receptor  
Antibody  
Transgenic  
Mice  
Hamster  
Rat  
Dog  
Cat  
In vitro

2. In a second step, two reviewers will assess the titles and abstracts of the remaining articles.
3. In a third step, the reviewers will assess the full manuscripts of all papers for which eligibility could not be determined by reading the title and abstract.

The reviewers will solve any disagreements about the study or exposure relevance by discussion with the principal investigator.

### 6.1 Reference Manager Files

Five user-defined fields (**Table 2**) will be created in the Reference Manager database, where the reviewers will indicate:

- 1) if the study was selected upon reading of title and abstract, or entire article
- 2) the study design of articles relevant to the review
- 3) the status of data extraction of included articles
- 4) the WCRF code assigned to the studies in the database
- 5) reasons for exclusion of articles on exposures/interventions and outcomes relevant to the review

**Table 2.** User-defined fields and terms to be used in the Reference Manager database for identification of the status of articles identified in the searches.

Field	Use	Terms	Meaning
User Def 1	For all articles retrieved in the search	Excludedabti	Excluded: exclusion based on abstract and title
		Excluded	Excluded: exclusion based on full paper text
	Indicate result of assessment for inclusion	Included	Included
User Def 2	Only for EXCLUDED studies  Indicate reasons for exclusion	Includes nasopharyngeal cancer Includes oesophageal cancer Includes other cancers sites* Inadequate study design** No measure of association No original data Commentary, letter Foreign article in [language]*** Meta-analysis Already extracted Cancer survivors MPL not primary cancer	*Other than mouth, pharynx and larynx. Only if this is the reason for exclusion **Cross-sectional studies, case-only study, ecological study, other study designs ***If the article can't be translated
User Def 3	Only for INCLUDED studies  Indicate study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other* Pooled analysis of cohort studies Pooled analysis of case-control studies	*Case-control study- other: the comparison populations are neighbors, friends, or other controls that are not population- or hospital- based.
User Def 4	WCRF code	Only for INCLUDED studies  MPL+ consecutive digits	WCRF codes are assigned automatically by the data extraction software when performing the data extraction.
User Def 5	Only for INCLUDED studies Cancer group	Indicate if the study report on a group of cancer sites such as “head and neck”, “oral and pharyngeal”, etc.	

## 7. DATA EXTRACTION

The ICL team will update the WCRF-AICR central database using an interface created for this purpose (**Figure 5**). The application will automatically check that the paper has not already been extracted to the database using author name, publication year and journal references. The data extracted will be double-checked by a second reviewer.

The data to be extracted include among others, the study design, name, characteristics of study population, age range, sex, country, recruitment year, methods of exposure assessment, definition of exposure, definition of outcome, method of outcome assessment, study size, number of cases, number of comparison subjects, length of follow up, lost to follow-up, analytical methods and whether methods for correction of measurement error were used.

The ranges, means or median values for each exposure level will be extracted as reported in the paper. The reviewer will not do any calculation during data extraction. For each result, the reviewers will extract the covariates and matching variables included in the analytical models. Measures of association, number of cases and number of comparison individuals or person years for each category of exposure will be extracted for each analytical model reported. Stratified and subgroup analyses, and results of interaction analyses will be extracted (e.g. by sex, age group, smoking status, BMI category, alcohol intake level, etc.)

Some studies present results for the cancers of interest as separate outcomes (mouth, pharynx and larynx), combinations of these cancers, or total results for these cancers. In some cases oesophageal and nasopharyngeal cases may also be included. The reviewer should extract the results for each cancer site and for the cancer groups relevant to the review.

The reviewer will also extract the results by gender, if reported, and for both gender combined when presented in the paper.

### 7.1 Study identifier

The CUP team will use the same labelling of articles used in the SLR process for the Second Expert Report: the unique identifier for an article will be constructed using a 3-letter code to represent the cancer site: MPL (mouth, pharynx, larynx), followed by a 5-digit number that will be generated sequentially by the software during data extraction.

**Figure 5. CUP interface. Example of screen for data entry**

## 7.2 Codification of exposures/interventions.

The exposures/interventions will be codified during data extraction as in the Second Expert Report. The main headings and sub-headings codes are in **Annex 2**. Wherever possible, the reviewer will use the sub-heading codes. Additional codes have been programmed in the database to facilitate the data entry (all additional codes are not shown in the Annex).

The main headings for codification of the exposure groups are:

1. **Patterns of diet**, includes regionally defined diets, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, breastfeeding and other issues
2. **Foods**, including starchy foods; fruit and (non-starchy) vegetables; pulses (legumes); nuts and seeds; meat, poultry, fish and eggs; fats, oils and sugars; milk and dairy products; and herbs, spices, and condiments, and composite foods.
3. **Beverages**, including total fluid intake, water, milk, soft drinks, fruit juices, hot drinks and alcoholic drinks.
4. **Food production** including traditional methods and chemical contaminants, food preservation, processing and preparation.

5. **Dietary constituents**, including carbohydrate, lipids, protein, alcohol, vitamins, minerals, phytochemicals, nutrient supplements and other bioactive compounds
6. **Physical activity**, including total physical activity, physical inactivity and surrogate markers for physical activity.
7. **Energy balance**, including energy intake, energy density and energy expenditure.
8. **Anthropometry**, including markers of body composition, markers of body fat distribution, height and other skeletal measures, and growth in foetal life, infancy or childhood.

The reviewer should also extract the description of the exposure/intervention definition in the free text box provided for that purpose in the data entry screen. The definition will be extracted as it appears in the paper.

### **7.2.1 Codification of biomarkers of exposure**

During the SLR for the Second Expert Report, some review centres opted for including in the review only biomarkers for which there was strong evidence on reliability or validity whereas other centres opted for including results on all the biomarkers retrieved in the search, independently of their validity. For the evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

However, since the identification and validation of other biomarkers is an expanding area in nutritional epidemiology (33), the CUP team will extract the data for all biomarkers of intake reported in the studies, independently of whether validity and reliability had been or not fully documented.

There is a growing interest in Vitamin D status in relation to cancer and increasingly, some papers are using vitamin D status estimated from a set of predictors. Results on predicted plasma 25-hydroxyvitamin D will be extracted and coded under 25-hydroxyvitamin D.

### **7.3 Codification of outcomes.**

The reviewer will indicate under “outcome type”, whether the outcome for each result is incidence or mortality and in “outcome subtype”, if the result is for outcome on mouth, pharynx (other than nasopharynx), oropharynx, hypopharynx, larynx, or any combination of these sites.

The reviewer should also extract the outcome definition in the free text box provided for that purpose in the data entry screen. The definition will be extracted as it appears in the paper, including ICD codes if reported.

### **7.4 Extraction and labelling of study results**

The reviewer will extract the measures of association (punctual estimates and confidence intervals) for the relevant exposures from all the analytical models shown in the paper, including subgroups, stratified analyses, interactions and sensitivity analyses. These results can be found in the paper in tables, in the text or as online supplemental information.



The results for each analytical model will be extracted. Potential confounders of interest include age, gender, current and past smoking status, socioeconomic status, physical activity, body mass index, total dietary energy intake, alcohol consumption, race and/or ethnicity, geographic location, dietary supplement use, use of non-steroidal inflammatory drugs, family history of the cancers of interest, pre/postmenopausal status (women), oral hygiene, consumption of mate, other dietary factors, occupational exposures and infection with HPV. From the above list, potential effect modifiers are age, gender, smoking status, body mass index, pre/post-menopausal status, race/ethnicity, and alcohol consumption.

Information on genetic polymorphisms that may interact with nutrients or other dietary factors and modify the association between dietary factors of interest and cancers of the mouth, pharynx and larynx will be noted (e.g. methylenetetrahydrofolate reductase and folic acid) and will be reported as subgroup analyses when available.

During data extraction, the reviewer should label each result as unadjusted, intermediately adjusted, or most adjusted model, as follows:

- The results of univariate models will be labelled “unadjusted”.
- The results obtained with the model including the higher number of covariables in the article will be labelled “most adjusted”.
- The results obtained using any multivariable model that is not the most adjusted model will be labelled “intermediately” adjusted.

In addition, the reviewer will indicate the “best model” for meta-analyses. This will be the “most adjusted” model. Sometimes, the researchers use models that include variables likely to be in the causal pathway with the purpose of exploring hypothetical mechanisms. When “mechanistic” models are reported by the authors, the most adjusted result that is not “mechanistic” will be indicated as “best model”. The mechanistic” models will be extracted and labelled as most adjusted model, but not as best model for meta-analysis. If there are enough results with these models, they will be used in separate analysis.

## **8. QUALITY CONTROL OF THE ARTICLE SELECTION AND DATA EXTRACTION.**

A second reviewer at ICL will check the article selection and the data extraction. If there are discrepancies between the reviewers, the discrepancy will be discussed with the Principal Investigator.

## **9. DATA ANALYSIS**

### **9.1 Meta-analysis**

The CUP team at ICL will update the meta-analyses conducted for the Second Report using studies included in the 2007 SLR and studies published after that review.

The CUP SLR will conduct dose-response meta-analysis. The results of the individual studies will be displayed graphically in forests plots of the highest vs. the lowest comparison for each study, but a

summary estimate will not be calculated, to avoid pooling different exposure levels. The only exposures in which meta-analyses for the highest vs. the lowest category will be conducted are breastfeeding (often categorised as yes vs. no), use of multivitamins (often categorised as use vs. no use) and physical activity (for which quantitative levels are often not provided and therefore, dose-response meta-analyses may not be possible). In all forest plots, the studies will be ordered by publication year, with the most recent on the top.

The meta-analyses will be conducted separately for each cancer site: mouth, pharynx and larynx, and for combinations of these cancers. Studies with different cancer groups will not be pooled together, but their results will be presented in tables.

The analyses will be conducted for studies on incidence and mortality separately and combined. The meta-analysis will be conducted separately for randomized controlled trials, cohort studies and case-control studies. Nested case-control analyses will be analysed together with cohort studies.

Where an exposure is presented for all study participants, and for men and women, the analysis of all study participants will be used. Separate analyses for men and women will also be conducted if the number of studies allows it. When the number of studies allows it, meta-analyses will be conducted in smokers and non-smokers separately.

Where results from two or more studies are reported in the same paper, the results of each study will be included separately in the CUP meta-analysis instead of using the pooled result reported in the paper. The purpose is to look at heterogeneity across study results. If this is not possible, the overall result will be included and sensitivity analyses will be conducted excluding the overall results of pooling projects. The data analyst will check that the same study is not included twice in one meta-analysis.

Linear dose-response meta-analysis will be conducted to express the results of each study in the same increment unit for a given exposure. The results will be shown in a dose-response forest plots. For comparability, the increment units for the linear dose-response analyses will be those used in the meta-analyses in the previous SLRs (**Table 3**) but another increment may have to be used in the range of exposure in the identified papers is smaller than the recommended increment unit.

If most of the identified studies report servings, times, units these will be used as increment unit.

Non-linear dose-response meta-analyses will be conducted as exploratory analysis.

**Table 3. Recommended increment units for meta-analyses.**

Exposure	Increment unit
Total fruits and vegetables	100 g
Non starchy vegetables	100 g
Fruits	100 g
Citrus fruits	50 g
Red meat	100 g
Processed meat	50 g
Poultry	100 g
Fish	50 g
Eggs	25 g
Salt	1 g

Coffee	1 cup
Tea	1 cup
Alcoholic drinks	1 drink/day
Alcohol (as ethanol)	10 g
Dietary calcium	200 mg
Dietary fibre	10 g
Folate	100 µg
Blood selenium	10 µg/L
Beer	10 g/day (approx. one drink)
Wine	10 g/day (approx. one drink)
BMI	5 kg/m <sup>2</sup>
Waist	2.5 cm (1 inch)
Waist-to-hip	0.1 unit
Height	5 cm
Physical activity	5 MET-h per week

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## 9.2 Selection of studies for a dose-response meta-analysis

The meta-analysis will include studies identified during the SLR and studies identified during the CUP.

For each exposure, a dose-response meta-analysis will be conducted when:

- at least two new reports of trials or cohort studies with enough data for dose-response meta-analysis have been published after the year 2005 (end date for the SLR for the Second Expert Report) and if the total number of studies that can be included in the meta-analysis is at least of 5 in each study design
- at least 5 new reports of case-control studies have been published

The minimum number of studies was not derived statistically but it is a number of studies that can be reasonable expected to have been published after the Second Expert Report.

Where a particular study has published more than one paper on the same exposure, the analysis using the larger number of cases will be selected but if the most recent paper does not provide enough information for the dose-response meta-analysis, the previous publication with the required information will be used. The results section will indicate whether the reports of the same study are similar or not.

## 9.3 Selection of results for meta-analyses

The results based on “best” adjusted models will be used in the dose-response meta-analyses. The best adjusted model will usually be the most adjusted model. When the linear dose-response estimate is reported in an article, this will be used in the CUP dose-response meta-analysis. If the results are presented only for categorical exposures/intervention (quantiles or pre-defined categories), the slope of the dose-response relationship for each study will be derived from the categorical data.

## 9.4 Derivation of data required for meta-analyses.

The data required to derive the dose-response slope from categorical data are:

1. Number of cases for each exposure category
2. Person-years -or number of controls - for each exposure category
3. Median, mean or cut-offs of exposure categories.

The information provided in the articles is often incomplete and this may result in exclusions of results from meta-analyses. For instance, in the SLR's on oesophageal and prostate cancer for the Second Expert Report, only 64% of the cohort studies provided enough data to be included in dose-response meta-analysis, and there was empirical evidence that studies that showed an association were more likely to be usable in dose-response meta-analysis than studies that did not show any evidence (32).

The failure to include all available evidence will reduce precision of summary estimates and may lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations. To address the data incompleteness, a number of approaches will be undertaken to derive the missing data from the available data where possible (32). These approaches are summarized in **Table 4**.

For estimating the “dose-response” for each study, the means or medians of the exposure categories reported in the articles will be assigned as “dose”; if not reported, the midpoints of the exposure range in each category will be used. For lowest or highest open-ended categories the amplitude of the nearest category will be used to calculate the midpoint.

If different measurement units of exposure have been used, these will be rescaled where possible (e.g. pounds to g; kg to g, weeks to days, etc.). Where portion or serving sizes have to be rescaled, the standard portion sizes reported in the paper will be used but if not reported, the standard portion sizes used in the WCRF/AICR Second Expert Report (4) will be applied (**Table 5**). For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be estimated using the average energy intake reported in the article.

For estimating the “dose-response” for each study, the means or medians of the exposure categories reported in the articles will be assigned as “dose”; if not reported, the midpoints of the exposure range in each category will be used. For lowest or highest open-ended categories the amplitude of the nearest category will be used to calculate the midpoint.

If different measurement units of exposure have been used, these will be rescaled where possible (e.g. pounds to g; kg to g, weeks to days, etc.). Where portion or serving sizes have to be rescaled, the standard portion sizes reported in the paper will be used but if not reported, the standard portion sizes used in the WCRF/AICR Second Expert Report will be applied (4) (**Table 5**). For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be estimated using the average energy intake reported in the article.

**Table 4. Approaches to derive missing information for meta-analyses in the CUP**

Type of data	Problem	Approach
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR
	Standard error missing	The p value (either exact or the upper bound) is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Confidence interval is missing	Use raw numbers of cases and controls (or the denominator in cohort studies) to calculate confidence interval (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	This information may be estimated by using the method of Chêne and Thompson (34) with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (3-4 groups)
Category data	Numbers of controls (or the denominator in cohort studies) is missing	Derive these numbers from the numbers of cases and the reported odds ratios (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

**Table 5. List of conversion units**

Item	Conversion of one unit
Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc. soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving

## 9.5 Statistical Methods

If the dose response estimates are not reported in an article, this will be derived from categorical data using generalized least-squares for trend estimation (command GLST in Stata) (35). This method accounts for the correlation between relative risks estimates with respect to the same reference category (36). The dose-response model is forcing the fitted line to go through the origin and whenever the assigned dose corresponding to the reference group ( $RR=1$ ) is different from zero, this will be rescaled to zero and the assigned doses to the other exposure categories will be rescaled accordingly.

The study specific log odds ratios per unit increase in exposure will be combined in a random effect model using the method of DerSimonian and Laird (37), with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model.

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots and Egger's test (38). Funnel plots will be shown in the SLR when there are at least four studies included in the analysis.

Heterogeneity between studies will be quantified with the  $I^2$  statistic with cut points for  $I^2$  values of 30%, and 50% for low, moderate, and high degrees of heterogeneity (39). Heterogeneity will be assessed visually from forest plots and with statistical tests (P value <0.05 will be considered statistically significant) but the interpretation will rely mainly in the  $I^2$  values as the test has low power and the number of studies will probably be low.

Potential sources of heterogeneity will be explored by stratified analyses when the number of studies allows it (at least two studies in each stratum). The variables that will be explored as sources of heterogeneity are outcome (incidence or mortality), gender, geographic area, level of control for smoking, alcohol intake and other confounders, publication year, length of follow-up (cohort studies), type of control population (for case-control studies). Meta-regression will be conducted when the number of studies allows it.

The interpretation of stratified analysis should be cautious. If a considerable number of study characteristics are investigated in a meta-analysis containing only a small number of studies, then there is a high probability that one or more study characteristics will be found to explain heterogeneity, even in the absence of real associations.

Non-linear dose-response relationship will be explored using fractional polynomial models (40). The best fitting second order fractional polynomial regression model defined as the one with the lowest deviance will be determined. Non-linearity will be tested using the likelihood ratio test. A program in Stata prepared by D. Greenwood, statistical advisor of the project will be used.

All analyses will be conducted in Stata/SE 12.1.

## 9.7 Sensitivity analyses

Sensitivity analyses will be carried out to investigate how robust the overall findings of the CUP are relative to key decisions and assumptions that were made in the process of conducting the update. The purpose of doing sensitivity analyses is to strengthen the confidence that can be placed in the results.

Sensitivity analysis will be done as a minimum in the following cases:

- Including and excluding studies where there is some ambiguity as to whether they meet the inclusion criteria, for example it may be unclear what cancer sites are considered in a study.
- Including and excluding studies where exposure levels were inferred by the authors (for example assigning a standard portion size when this is not provided), predicted values were used (e.g. predicted plasma 25-hydroxyvitamin D) or when other missing information was derived from the data.
- Influence-analyses where each individual study will be omitted in turn in order to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies (41).



## 10. SYSTEMATIC LITERATURE REVIEW REPORT

An updated SLR will be sent to the CUP Secretariat on May 30<sup>th</sup> 2015 for discussion in the Expert Panel.

The SLR report will include the following elements:

### 1. Modifications of the approved protocol

Any modification required during the review and its reason will be described.

### 2. Results of the search

Flowchart with number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts, number of papers included and excluded, and reasons for excluding papers.

### 3. Summary tables of studies identified in the continuous update

Number of studies by study design and publication year.

Number of studies by exposure (main heading and selected subheadings) and publication year

Number of studies by exposure and outcome subtype

### 4. Tabulation of study characteristics and main study results by study design and outcome

The tables will include the information required by the Panel to judge the quality of the studies included in the analyses (Newcastle –Ottawa quality assessment scale (42) for observational studies and the Cochrane Collaboration's tool for assessing risk of bias (43).

Example of table of study characteristics for cohort studies (in two parts below):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)
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Assessment details	Category of exposure	Subgroup	No cat	RR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

## **10. 6 Graphic presentation**

Tabular presentation will be complemented with graphic displays when two or more new reports of randomized controlled trials or cohort studies or five new reports of case-control studies have been published after December 2006. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ‘‘high versus low’’ comparisons for each study. Dose-response graphs will be given for individual studies for which the information is available. Funnel plots will be shown when there are at least four studies.

## **10.7 Results of the dose-response meta-analysis**

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.

The results of meta-analyses will be presented in tables and forest plots. The tables will include a comparison with the results of the meta-analyses undertaken during the SLR for the Second Expert Report.

All forest plots in the report will have the same format. Footnotes will provide quantified information (statistical tests and  $I^2$  statistics) on the degree of heterogeneity.

Meta-regression, stratified analyses and sensitivity analyses results will be presented in tables and, if the number of studies justifies it, in forest plots.

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Ref Type: Online Source

## **Annex 1. WCRF - PUBMED SEARCH STRATEGY**

1) Searching for all studies relating to food, nutrition and physical activity:

**#1** diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

**#2** diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient\*[tiab] OR nutrition[tiab] OR vegetarian\*[tiab] OR vegan\*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab]

**#3** food and beverages[MeSH Terms]

**#4** food\*[tiab] OR cereal\*[tiab] OR grain\*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain\*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable\*[tiab] OR fruit\*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume\*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut\*[tiab] OR groundnut\*[tiab] OR (seeds[tiab] and (diet\*[tiab] OR food\*[tiab])) OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR ((fat[tiab] OR fats[tiab] OR fatty[tiab]) AND (diet\*[tiab] or food\*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND (diet\*[tiab] or food\*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR chili[tiab] OR pepper\*[tiab] OR condiments[tiab] OR tomato\*[tiab]

**#5** fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage\*[tiab] OR (ethanol[tiab] and (drink\*[tiab] or intake[tiab] or consumption[tiab])) OR yerba mate[tiab] OR ilex paraguariensis[tiab]

**#6** pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

**#7** pesticide\*[tiab] OR herbicide\*[tiab] OR DDT[tiab] OR fertiliser\*[tiab] OR fertilizer\*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate\*[tiab] OR veterinary drug\*[tiab] OR polychlorinated dibenzofuran\*[tiab] OR PCDF\*[tiab] OR polychlorinated dibenzodioxin\*[tiab] OR PCDD\*[tiab] OR polychlorinated biphenyl\*[tiab] OR PCB\*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon\*[tiab] OR microbial contamination\*[tiab]

**#8** food preservation[MeSH Terms]

**#9** mycotoxin\*[tiab] OR aflatoxin\*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack\*[tiab] OR refrigerate\*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive\*[tiab] OR colouring\*[tiab] OR coloring\*[tiab] OR flavouring\*[tiab] OR flavoring\*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment\*[tiab] OR processed[tiab] OR antioxidant\*[tiab] OR genetic modif\*[tiab] OR genetically modif\*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

**#10** cookery[MeSH Terms]

**#11** cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol\*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR (microwave[tiab] and (diet\*[tiab] or food\*[tiab])) OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue\*[tiab] OR chargrill\*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab] OR dietary acrylamide[tiab]

**#12** ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) and (diet\*[tiab] or food\*[tiab])) OR sweetening agents[MeSH Terms]

**#13** salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide\*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate\*[tiab] OR lipid\*[tiab] OR ((linoleic acid\*[tiab] OR sterols[tiab] OR stanols[tiab]) AND (diet\*[tiab] or food\*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR sugar\*[tiab] OR sweetener\*[tiab] OR saccharin\*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

**#14** vitamins[MeSH Terms]

**#15** supplements[tiab] OR supplement[tiab] OR vitamin\*[tiab] OR retinol[tiab] OR carotenoid\*[tiab] OR tocopherol[tiab] OR folate\*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral\*[tiab] OR (sodium[tiab] AND (diet\*[tiab] or food\*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet\*[tiab] or food\*[tiab] or supplement\*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND (diet\*[tiab] or food\*[tiab] or supplement\*[tiab] or deficiency)) OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate\*[tiab] OR glucosinolate\*[tiab] OR indoles[tiab] OR polyphenol\*[tiab] OR phytoestrogen\*[tiab] OR genistein[tiab] OR saponin\*[tiab] OR coumarin\*[tiab]

**#16** physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

**#17** recreational activit\*[tiab] OR household activit\*[tiab] OR occupational activit\*[tiab] OR physical activit\*[tiab] OR physical inactivit\*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

**#18** body weight [MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms] OR obesity [MeSH Terms] OR obesity [MeSH Terms]

**#19** weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement\*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR



hip circumference[tiab] OR waist hip ratio\*[tiab] OR weight change [tiab] OR adiposity [tiab] OR abdominal fat [tiab] OR body fat distribution [tiab] OR body size [tiab] OR waist-to-hip ratio [tiab]

**#20** #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR

#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

**#21** animal[MeSH Terms] NOT human[MeSH Terms]

**#22** #20 NOT #21

2) Searching for all studies relating to cancers of mouth, pharynx and larynx:

**#23** Laryngeal Neoplasms[MeSH] OR Pharyngeal Neoplasms[MeSH] OR Mouth Neoplasms[MeSH] OR Tongue Neoplasms[MeSH] OR Oropharyngeal Neoplasms[MeSH] OR Hypopharyngeal Neoplasms[MeSH]

**#24** malign\*[tiab] OR cancer\*[tiab] OR carcinoma\*[tiab] OR tumor\*[tiab] OR tumour\*[tiab] OR adenocarcinoma\*[tiab] OR carcinoma, squamous cell\*[tiab] OR carcinoma, small cell\*[tiab]

**#25** larynx[tiab] OR pharynx[tiab] OR laryngeal[tiab] OR pharyngeal[tiab] OR hypopharyngeal[tiab] OR oropharyngeal[tiab] OR mouth[tiab] OR tongue[tiab]

**#26** #24 AND #25

**#27** Oral Leukoplakia[MeSH]

**#28** oral cancer\*[tiab] OR oral carcinoma\*[tiab] OR oral leukoplakia\*[tiab]

**#29** #23 OR #26 OR #27 OR #28

3) Searching for all studies relating mouth, pharynx and larynx cancers, and food, nutrition, anthropometry and physical activity:

**#30** #22 AND #29

## **Annex 2. LIST OF HEADINGS AND EXPOSURE CODES**

**(This list shows main headings and subheadings. Most subheadings include different food or beverage items that are not been listed for brevity).**

***\*Indicates codes added during the CUP***

### **1 Patterns of diet**

#### **1.1 Regionally defined diets**

*Include all regionally defined diets, evident in the literature. These are likely to include Mesoamerican, oriental, including Japanese and Chinese, and “western type”. Mediterranean diet will be coded separately.*

##### **\*1.1.1 Mediterranean diet**

#### **1.2 Socio-economically defined diets**

*To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).*

#### **1.3 Culturally defined diets**

*To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.*

#### **1.4 Individual level dietary patterns**

*To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes, healthy eating index, etc.) that do not fit into the headings above.*

#### **1.5 Other dietary patterns**

*Include under this heading any other dietary patterns present in the literature that are not regionally, socio-economically, culturally or individually defined.*

#### **1.6 Breastfeeding**

##### **1.6.1 Mother**

*Include here also age at first lactation, duration of breastfeeding, number of children breast-fed*

##### **1.6.2 Child**

*Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.*

#### **1.7 Other issues**

*For example, results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.*

### **2 Foods**

#### **\*2.0.1 Plant foods**

#### **2.1 Starchy foods**

##### **2.1.1 Cereals (grains)**

\* 2.1.1.0.1 Rice, pasta, noodles

\* 2.1.1.0.2 Bread

\* 2.1.1.0.3 Cereal

*\* Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

#### 2.1.1.1 Wholegrain cereals and cereal products

\* 2.1.1.1.1 Wholegrain rice, pasta, noodles

\* 2.1.1.1.2 Wholegrain bread

\* 2.1.1.1.3 Wholegrain cereal

#### 2.1.1.2 Refined cereals and cereal products

\* 2.1.1.2.1 Refined rice, pasta, noodles

\* 2.1.1.2.2 Refined bread

\* 2.1.1.2.3 Refined cereal

#### 2.1.2 Starchy roots, tubers and plantains

\* 2.1.2.1 Potatoes

#### 2.1.3 Other starchy foods

*\*Report polenta under this heading*

#### 2.2 Fruit and (non-starchy) vegetables

*Results for “fruit and vegetables” and “fruits, vegetables and fruit juices” should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.*

##### 2.2.1 Non-starchy vegetables

*This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported, they should be recorded under one of the sub-headings below or if not covered, they should be recorded under ‘2.2.1.5 other’.*

##### 2.2.1.1 Non-starchy root vegetables and tubers

\*2.2.1.1.1 Carrots

##### 2.2.1.2 Cruciferous vegetables

##### 2.2.1.3 Allium vegetables

##### 2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)

##### 2.2.1.5 Other non-starchy vegetables

\*2.2.1.5.13 Tomatoes

\*2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

*Other non-starchy vegetables’ should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition, vegetables such as French beans that do not fit into the other categories, above.*

*If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.*

#### 2.2.1.6 Raw vegetables

*This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 – 2.2.1.5.*

#### 2.2.2 Fruits

\*2.2.2.0.1 Fruit, dried

\*2.2.2.0.2 Fruit, canned

\*2.2.2.0.3 Fruit, cooked

##### 2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges

2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

##### 2.2.2.2 Other fruits

\*2.2.2.2.1 Bananas

\*2.2.2.2.4 Melon

\*2.2.2.2.5 Papaya

\*2.2.2.2.7 Blueberries, strawberries and other berries

\*2.2.2.2.8 Apples, pears

\*2.2.2.2.10 Peaches, apricots, plums

\*2.2.2.2.11 Grapes

*If results are available that consider other groups of fruit or a particular fruit please report under 'other', specifying the grouping/fruit used in the literature.*

#### 2.3 Pulses (legumes)

\*2.3.1 Soya, soya products

\*2.3.1.1 Miso, soya paste soup

\*2.3.1.2 Soya juice

\*2.3.1.4 Soya milk

\*2.3.1.5 Tofu

\*2.3.2 Dried beans, chickpeas, lentils

\*2.3.4 Peanuts, peanut products

*Where results are available for a specific pulse/legume, please report under a separate heading.*

#### 2.4 Nuts and Seeds

*To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.*

#### 2.5 Meat, poultry, fish and eggs

*Wherever possible please differentiate between farmed and wild meat, poultry and fish.*

## 2.5.1 Meat

*This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.*

*Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.*

### 2.5.1.1 Fresh Meat

#### 2.5.1.2 Processed meat

\*2.5.1.2.1 Ham

\*2.5.1.2.1.7 Burgers

\*2.5.1.2.8 Bacon

\*2.5.1.2.9 Hot dogs

\*2.5.1.2.10 Sausages

*Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.*

### 2.5.1.3 Red meat

\*2.5.1.3.1 Beef

\*2.5.1.3.2 Lamb

\*2.5.1.3.3 Pork

\*2.5.1.3.6 Horse, rabbit, wild meat (game)

*Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.*

*Show any data on wild meat (game) under this heading as a separate sub-category.*

### 2.5.1.4 Poultry

*Show any data on wild birds under this heading as a separate sub-category.*

\*2.5.1.5 Offal, offal products (organ meats)

## 2.5.2 Fish

\*2.5.2.3 Fish, processed (dried, salted, smoked)

\*2.5.2.5 Fatty Fish

\*2.5.2.7 Dried Fish

\*2.5.2.9 White fish, lean fish

## 2.5.3 Shellfish and other seafood

## 2.5.4 Eggs

## 2.6 Fats, oils and sugars

## 2.6.1 Animal fats

### \*2.6.1.1 Butter

### \*2.6.1.2 Lard

### \*2.6.1.3 Gravy

### \*2.6.1.4 Fish oil

## 2.6.2 Plant oils

## 2.6.3 Hydrogenated fats and oils

### \*2.6.3.1 Margarine

*Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2*

## Hydrogenation

## 2.6.4 Sugars

*This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.*

## 2.7 Milk and dairy products

*Results concerning milk should be reported twice, here and under 3.3 Milk*

### \*2.7.1 Milk, fresh milk, dried milk

#### \*2.7.1.1 Whole milk, full-fat milks

#### \*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

### \*2.7.2 Cheese

#### \*2.7.2.1 Cottage cheese

#### \*2.7.2.2 Cheese, low fat

### \*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

#### \*2.7.3.1 Fermented whole milk

#### \*2.7.3.2 Fermented skimmed milk

### \*2.7.7 Ice cream

## 2.8 Herbs, spices, condiments

### \*2.8.1 Ginseng

### \*2.8.2 Chili pepper, green chili pepper, red chili pepper

## 2.9 Composite foods

*E.g., snacks, crisps, desserts, pizza. Also, report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.*

### \*2.9.1 Cakes, biscuits and pastry

### \*2.9.2 Cookies

### \*2.9.3 Confectionery

### \*2.9.4 Soups

\*2.9.5 Pizza

\*2.9.6 Chocolate, candy bars

\*2.9.7 Snacks

3 Beverages

3.1 Total fluid intake

3.2 Water

3.3 Milk

*For results concerning milk, please report twice, here and under 2.7 Milk and Dairy Products.*

3.4 Soft drinks

*Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.*

3.4.1 Sugary (not carbonated)

3.4.2 Carbonated (not sugary)

*The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.*

\*3.5 Fruit and vegetable juices

\*3.5.1 Citrus fruit juice

\*3.5.2 Fruit juice

\*3.5.3 Vegetable juice

\*3.5.4 Tomato juice

3.6 Hot drinks

3.6.1 Coffee

3.6.2 Tea

*Report herbal tea as a sub-category under tea.*

3.6.2.1 Black tea

3.6.2.2 Green tea

3.6.3 Maté

3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers

3.7.1.2 Wines

3.7.1.3 Spirits

3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation



## 4.1 Production

### 4.1.1 Traditional methods (*to include 'organic'*)

### 4.1.2 Chemical contaminants

*Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:*

#### 4.1.2.1 Pesticides

#### 4.1.2.2 DDT

#### 4.1.2.3 Herbicides

#### 4.1.2.4 Fertilisers

#### 4.1.2.5 Veterinary drugs

#### 4.1.2.6 Other chemicals

##### 4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)

##### 4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)

##### 4.1.2.6.3 Polychlorinated biphenyls (PCBs)

#### 4.1.2.7 Heavy metals

##### 4.1.2.7.1 Cadmium

##### 4.1.2.7.2 Arsenic

#### 4.1.2.8 Waterborne residues

##### 4.1.2.8.1 Chlorinated hydrocarbons

#### 4.1.2.9 Other contaminants

*Please also report any results that cover the cumulative effect of low doses of contaminants in this section.*

## 4.2 Preservation

### 4.2.1 Drying

### 4.2.2 Storage

#### 4.2.2.1 Mycotoxins

##### 4.2.2.1.1 Aflatoxins

##### 4.2.2.1.2 Others

### 4.2.3 Bottling, canning, vacuum packing

### 4.2.4 Refrigeration

### 4.2.5 Salt, salting

#### 4.2.5.1 Salt

#### 4.2.5.2 Salting

#### 4.2.5.3 Salted foods

##### 4.2.5.3.1 Salted animal food

##### 4.2.5.3.2 Salted plant food

#### 4.2.6 Pickling

#### 4.2.7 Curing and smoking

##### 4.2.7.1 Cured foods

##### 4.2.7.1.1 Cured meats

##### 4.2.7.1.2 Smoked foods

*For some cancers e.g. colon, rectum, oesophageal and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-nitrosamines should also be covered here.*

#### 4.3 Processing

##### 4.3.1 Refining

*Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.*

##### 4.3.2 Hydrogenation

*Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils*

##### 4.3.3 Fermenting

##### 4.3.4 Compositional manipulation

##### 4.3.4.1 Fortification

##### 4.3.4.2 Genetic modification

##### 4.3.4.3 Other methods

##### 4.3.5 Food additives

##### 4.3.5.1 Flavours

*Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.*

##### 4.3.5.2 Sweeteners (non-caloric)

##### 4.3.5.3 Colours

##### 4.3.5.4 Preservatives

##### 4.3.5.4.1 Nitrites and nitrates

##### 4.3.5.5 Solvents

##### 4.3.5.6 Fat substitutes

##### 4.3.5.7 Other food additives

*Please also report any results that cover the cumulative effect of low doses of additives.*

*Please also report any results that cover synthetic antioxidants*

##### 4.3.6 Packaging

##### 4.3.6.1 Vinyl chloride

##### 4.3.6.2 Phthalates

#### 4.4 Preparation

#### 4.4.1 Fresh food

##### 4.4.1.1 Raw

*Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).*

##### 4.4.1.2 Juiced

#### 4.4.2 Cooked food

##### 4.4.2.1 Steaming, boiling, poaching

##### 4.4.2.2 Stewing, casseroling

##### 4.4.2.3 Baking, roasting

##### 4.4.2.4 Microwaving

##### 4.4.2.5 Frying

##### 4.4.2.6 Grilling (broiling) and barbecuing

##### 4.4.2.7 Heating, re-heating

*Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.*

*Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.*

## 1 5 Dietary constituents

*Food constituents' relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.*

### 5.1 Carbohydrate

#### 5.1.1 Total carbohydrate

#### 5.1.2 Non-starch polysaccharides/dietary fibre

##### 5.1.2.1 Cereal fibre

##### 5.1.2.2 Vegetable fibre

##### 5.1.2.3 Fruit fibre

#### 5.1.3 Starch

##### 5.1.3.1 Resistant starch

#### 5.1.4 Sugars

##### \*5.1.5 Glycaemic index, glycaemic load

*This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices*

*as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.*

## 5.2 Lipids

### 5.2.1 Total fat

### 5.2.2 Saturated fatty acids

### 5.2.3 Monounsaturated fatty acids

### 5.2.4 Polyunsaturated fatty acids

#### 5.2.4.1 n-3 fatty acids

*Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.*

#### 5.2.4.2 n-6 fatty acids

#### 5.2.4.3 Conjugated linoleic acid

### 5.2.5 Trans fatty acids

### 5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

*For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.*

## 5.3 Protein

### 5.3.1 Total protein

### 5.3.2 Plant protein

### 5.3.3 Animal protein

## 5.4 Alcohol

*This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.*

### \*5.4.1 Total Alcohol (as ethanol)

#### \*5.4.1.1 Alcohol (as ethanol) from beer

#### \*5.4.1.2 Alcohol (as ethanol) from wine

#### \*5.4.1.3 Alcohol (as ethanol) from spirits

#### \*5.4.1.4 Alcohol (as ethanol) from other alcoholic drinks

#### \* 5.4.1.5 Total alcohol (as ethanol), lifetime exposure

#### \* 5.4.1.6 Total alcohol (as ethanol), past

## 5.5 Vitamins

### \*5.5.0 Vitamin supplements

#### \*5.5.0.1 Vitamin and mineral supplements

#### \*5.5.0.2 Vitamin B supplement

### 5.5.1 Vitamin A

#### 5.5.1.1 Retinol

5.5.1.2 Provitamin A carotenoids

5.5.2 Non-provitamin A carotenoids

*Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.*

5.5.3 Folates and associated compounds

\*5.5.3.1 Total folate

\*5.5.3.2 Dietary folate

\*5.5.3.3 Folate from supplements

*Examples of the associated compounds are lipotropes, methionine and other methyl donors.*

5.5.4 Riboflavin

5.5.5 Thiamin (vitamin B1)

5.5.6 Niacin

5.5.7 Pyridoxine (vitamin B6)

5.5.8 Cobalamin (vitamin B12)

5.5.9 Vitamin C

5.5.10 Vitamin D (and calcium)

5.5.11 Vitamin E

5.5.12 Vitamin K

5.5.13 Other

*If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under 'other'.*

5.6 Minerals

5.6.1 Sodium

5.6.2 Iron

5.6.3 Calcium (and Vitamin D)

5.6.4 Selenium

5.6.5 Iodine

5.6.6 Other

*Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under 'other'.*

5.7 Phytochemicals

5.7.1 Allium compounds

5.7.2 Isothiocyanates

5.7.3 Glucosinolates and indoles

- 5.7.4 Polyphenols
- 5.7.5 Phytoestrogens eg genistein
- 5.7.6 Caffeine
- 5.7.7 Other

*Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.*

## 5.8 Other bioactive compounds

## 6 Physical activity

### 6.1 Total physical activity (overall summary measures)

#### 6.1.1 Type of activity

##### 6.1.1.1 Occupational

##### 6.1.1.2 Recreational

##### 6.1.1.3 Household

##### 6.1.1.4 Transportation

#### 6.1.2 Frequency of physical activity

##### \*6.1.2.1 Frequency of occupational physical activity

##### \*6.1.2.2 Frequency of recreational physical activity

#### 6.1.3 Intensity of physical activity

##### \*6.1.3.1 Intensity of occupational physical activity

##### \*6.1.3.2 Intensity of recreational physical activity

#### 6.1.4 Duration of physical activity

##### \*6.1.4.1 Duration of occupational physical activity

##### \*6.1.4.2 Duration of recreational physical activity

### 6.2 Physical inactivity (eg sitting time, TV watching, other sedentary habits)

### 6.3 Surrogate markers for physical activity e.g. occupation

## 7 Energy balance

### 7.1 Energy intake

#### \*7.1.0.1 Energy from fats

#### \*7.1.0.2 Energy from protein

#### \*7.1.0.3 Energy from carbohydrates

#### \*7.1.0.4 Energy from alcohol

#### \*7.1.0.5 Energy from all other sources

### 7.1.1 Energy density of diet

- 7.2 Energy expenditure
- 8 Anthropometry
  - 8.1 Markers of body composition
    - 8.1.1 BMI
    - 8.1.2 Other weight adjusted for height measures
    - 8.1.3 Weight
    - 8.1.4 Skinfold measurements
    - 8.1.5 Other (e.g. DEXA, bio- impedance, etc)
    - 8.1.6 Change in body composition (including weight gain)
  - 8.2 Markers of distribution of fat
    - 8.2.1 Waist circumference
    - 8.2.2 Hips circumference
    - 8.2.3 Waist to hip ratio
    - 8.2.4 Skinfolks ratio
    - 8.2.5 Other e.g. CT, ultrasound
  - 8.3 Skeletal size
    - 8.3.1 Height (and proxy measures)
    - 8.3.2 Other (e.g. leg length)
  - 8.4 Growth in foetal life, infancy or childhood
    - 8.4.1 Birthweight
    - 8.4.2 Weight at one year