Eco-Agri-Food Ecology and Human Health

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1 Introduction

The food system can be both a risk factor to health, or a cure for many ailments of nature and people. Alas, chronic and non-communicable diseases are rising worldwide and a deeper understanding of the role of the food system is needed in order to guide preventive efforts. 'The right to health means the right to be healthy in the first place, not the right to treatment' (Migaleddu 1952-2017). In considering factors that cause disease, epidemiologists focus on genetic susceptibility and environmental determinants: nutrition and lifestyle, as well as environmental conditions, are prime areas of investigation but seldomly, due attention is given to the role of the food system as a whole in determining health across the supply chain and for related impacts that have long latency, such as chronic diseases.

In linking food system risk factors and disease outcomes in its 2009 Global Health Risks, WHO considers under-nutrition and some nutrition-related risk factors (e.g. high blood cholesterol and glucose), as well as environmental and occupational risks (e.g. unsafe drinking water, occupational carcinogens), without however dealing with agricultural pollutants, while explicitly avoiding to cover 'broad risk factors such as diets'. The 2017 High-Level Panel of Experts on Food Security and Nutrition report on Nutrition and Food Systems highlights the role of diets and the food environment in facilitating health in a rather generic way. Chiefly, the Sustainable Development Goal 3 that aims to 'Ensure healthy lives and promote wellbeing for all at all ages' includes nine targets of which: target 3.4 refers to 'Reducing by one third premature mortality from non-communicable diseases' and target 3.9 refers to 'Reducing the number of illness from hazardous chemicals and

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R. Valentini et al. (eds.), *Achieving the Sustainable Development Goals Through Sustainable Food Systems*, Food and Health,
https://doi.org/10.1007/978-3-030-23969-5_5

air, water and soil pollution and contamination'. Interestingly, drug, alcohol and tobacco abuse are explicitly addressed but no reference is made to the crucial role of food systems, despite the fact that the health cost of the eco-agri-food system largely surpass that of the tobacco industry.

Attribution of disease causation is challenging, due to insufficient evidence regarding temporal relation, association, environmental equivalence and population equivalence. Therefore, scientific evidence is equivocal for decision-makers, leaving the ground open for overly delayed policies and public health regulations, in the face of a global emergency to act and safeguard human health and the generations to come from the non-communicable diseases epidemics. In fact, malnutrition in all its form (including under-nutrition, micronutrient deficiencies, and overweight and obesity) affects over two billion people, while the incidence of cancer is expected to increase 70% in the next two decades, neuro-degenerative diseases are doubling, and adverse developmental and reproductive effects of chemicals interfering with the endocrine systems, as well as antibiotic-resistance, are alarming concerns for present and future generations.

2 The Roles of the Eco-Agri-Food System in Disease Incidence

With a view to highlight the urgency to shift to healthier food production and consumption patterns, a brief overview follows on the major disease groups, indicating their global extent, an estimate of societal costs, and the role of different food system pathways in human health.[1]

2.1 Hunger-Related Morbidity, Obesity, Diabetes Mellitus and Metabolic Disorders

2.1.1 Extent

Hunger affects 821 million people, or 10.9% of the world population (FAO et al. 2018). Acute malnutrition is responsible for stunting 150.2 million children, while 50.5 million children are wasted, determining irreversible impacts throughout their lives. Malnutrition is responsible for mortality and acute morbidity from diarrhoeal diseases, malaria, measles, pneumonia for children under 5 years of age and perinatal conditions from maternal underweight.

[1] This preliminary literature review requires a more comprehensive review for each disease group.

In addition, two billion people have nutritional deficiencies, including both those under- and over-nourished. Overweight and obesity rates are increasing worldwide (71% of USA population, 70% in Mexico, 50% in Europe, 22% in China and 20% in India), causing millions of premature deaths, more than for people underweight. In 2017, 672 million people (or 13.2%) of adults over 18 were obese, as well as 41 million children under the age of 5. Obesity is responsible for 4.8% of deaths globally and 8.4% in high-income countries (WHO 2009b). Should current trends continue, almost half of the world population will be overweight or obese in 2030 (McKinsey Global Institute 2014).

Type 2 diabetes, which makes up 90% of diabetes cases, has increased in parallel with obesity: in 2013, there were approximately 368 million people diagnosed, as compared to 30 million in 1985, with increasing rates in young people. The risk of coronary heart disease (23%), ischaemic stroke and Type 2 Diabetes (44%) grows steadily with increasing body mass, as do the risks of cancers of breast, colon, prostate and other organs (7–41%); obesity is among the main reasons of gene mutation, causing 15–20% of all cancer deaths and is associated with a shorter life expectancy. Today, USA median life expectancy is estimated to be 8 years lower for adults aged 55–64 years (Ken Gu et al. 1998).

2.1.2 Some Societal Costs

The global cost of malnutrition to the economy could be 11% of global GDP, or USD 3.5 trillion per year (FAO 2013). Healthcare costs of overweight and obesity are expected to double each decade, reaching 16–18% of total healthcare expenditure by 2030 (Wang et al. 2008). In USA, when one person in a household is obese, the household faces additional health care costs equivalent to 8% of its annual income (IFPRI 2016). Global annual expenditure on diabetes was USD 673 billion in 2010, one third of which in USA, equivalent to 12% of global health care expenditure.

2.1.3 The Role of Diets

Food consumption depends on access to food, both in terms of quantity and quality. While under-nutrition is due to a lack of access to nutritious food, nutrient deficiencies in affluent populations is due to consumption of low-quality foods; rich in fat and sugar, poor in micronutrients. Individual food choices, although influenced by lifestyle and economic affordability, represent a model of 'expressive consumption' consistent with individual conscience (e.g. avoiding meat) but more often than not, choice is guided by centralized political decisions (e.g. sin taxes that discourage sugary drinks and labelling requirements) and in most cases, determined by food corporations in term of offer (e.g. ultra-processed food of a limited number of crops, with excess salt, sugar, fat and additives). The abundance of the so-called 'empty foods' on market shelves, coupled with cheap prices have greatly contributed to malnutrition and the prevalence of unbalanced diets. Research demonstrates that obesity is caused by increased intake of energy-dense foods that are high in fat, as well as insulin resistance related to excessive carbohydrate consumption and can best be prevented by a change of diet (WHO and FAO 2003).

2.1.4 The Role of Food Quality

Industrially grown crops notably have reduced vitamins (A, C), minerals (Fe, Ca) and phenolic compounds. Generally, ionizing radiation is believed to destroy Vitamins A and K and to reduce Vitamins C, B1 and E in food (Hartwig et al. 2007; Stevenson 1994). Exposure to certain chemicals in food (e.g. Di-2-ethlylhexylphthalates), increases adult obesity and diabetes by 40–69%. Highly processed food has also its responsibility in the modern metabolic disorder epidemics, especially refined flour and sugar, as well as the high-fructose corn sugar (Goran et al. 2013) commonly used in processed food and beverages, because they trigger glycaemic peaks.

2.1.5 The Role of the Agri-Environment

Hunger is primarily an access issue, including access to means of producing or buying food; bad agricultural practices contribute to soil erosion and loss of the productive capital of the poor. Soil health is the base of the nutrition continuum (from plants, to animals and humans), as most mineral nutrients become readily available to plants when soil pH is neutral, so a correct soil pH is essential to avoid nutrient deficiencies; interestingly, the ideal pH of the soil, the body fluids and most plant fluids are all around 6.4. Compared to 50 years ago, nutrient values of fruits and vegetables have declined from 25 to 75% (Mayer 1997), partly due to the use of nitrogen fertilizers that inhibit mycorrhizal colonization of crop roots and thus nutrients flow; a properly mineralized soil is key to feeding the plant (Clark and Zeto 2000) and hence, the immune system through enzyme-rich foods. Furthermore, emerging research indicates that grass-fed animals from balanced soils have more Trans-Vasconic Acid (25%) and Conjugated Linoleic Acid (30%) (Daley et al. 2010).

Most importantly, climate change is believed to accelerate photosynthesis, resulting in more glucose than nutrient content in most plant species, due to an ionomic imbalance whereby carbon increases disproportionally to soil-based nutrients, inducing changes in the nutritional value of food, including protein, iron, calcium, zinc, vitamin E and vitamin B complex. Rising CO_2 levels, to which industrial agriculture substantially contributes, is therefore inextricably linked to a global and systemic shift in nutrition quality of human diets. On average, since the Green Revolution, and for 130 species/cultivars, it entails: 46% more total nonstructural carbohydrate concentration contributing to obesity and diabetes, equivalent to adding one spoonful of starch and sugar mixture to every 100 g of dry matter of raw plant product; 8% less of 25 important minerals (e.g. calcium, potassium, zinc, iron) contributing to more anaemia and mineral malnutrition; and reduced nitrogen concentration by 10–18%, with protein deficiencies affecting cognitive development, metabolism and the immune system (Loladze 2014). Although the (CO_2_nutrition) dynamic is still being elucidated, it is suggested the issue has potential health consequences for approximately 600 million people (Bottemiller Evich 2017; Zhu et al. 2018).

Endocrine-disrupting chemicals (EDCs) dubbed "obesogens" accumulating in the environment expose health to several metabolic disorders, including the epidemic of obesity and its related pathologies, as it is believed to modify metabolic balance at the central, hypothalamic level (Decherf and Demeneix 2011). In addition, EDCs as diabetogenic compounds are believed to have a role in disrupting insulin production and sensitivity, thus contributing to the diabetes epidemics (Neel and Sargis 2011). Prenatal bisphenol A (found in polycarbonate plastics and epoxy resins that are often used in containers that store food and beverages, such as water bottles) exposure increases childhood obesity by 20–69%; polychlorinated biphenyls and hexachlorobenzene found in the environment are recognized "obesogens" (Trasande et al. 2015) with transgenerational impacts (Decherf and Demeneix 2011).

Air pollution by particulate matter has recently been associated with increased risk of diabetes mellitus, especially when $PM_{2.5}$ is above 2.4 ug/m^3. Globally, ambient $PM_{2.5}$ contributed to about 3.2 million incident cases of diabetes, about 8.2 million DALYs[2] caused by diabetes, and 206,105 deaths from diabetes attributable to $PM_{2.5}$ exposure; the burden varied substantially among geographies and was more heavily skewed towards low-income and lower-to-middle-income countries (Bowe et al. 2018).

2.2 Cardiovascular Diseases

2.2.1 Extent

Cardiovascular diseases (CVDs) are the leading cause of death globally: 17.7 million deaths in 2015 (WHO et al. 2017), 50% of all non-communicable disease deaths and 31% of all deaths. Heart attacks and stroke account for 80% of all CVD deaths.

[2] DALYs: Daily Adjusted Life Years.

2.2.2 Some Societal Costs

By 2030, the global cost of CVDs is set to rise from approximately USD 863 billion in 2010 to USD 1044 billion, including direct healthcare costs and productivity losses (World Heart Federation 2018).

2.2.3 The Role of Diets

Unhealthy diets are an important risk factor to CVDs (WHO et al. 2011). Globally, 33% of ischemic heart disease is attributable to high blood cholesterol and 22% with raised blood sugar (WHO 2009a). Excess dietary sodium (salt) and saturated fats have historically been considered the most important factors (WHO et al. 2011), yet there now exists significant debate on these topics in the scientific literature. Recent research on salt suggests that a moderate consumption is healthier and that excessive reduction increases CVD risk. On saturated fats, a large number of rigorous review papers in recent years have found no link between these fats and heart disease (Hamley 2017). Meanwhile, high intakes of heme iron from red meat has been associated with cardiovascular diseases in USA (Etemadi et al. 2017), but there is not yet clinical trial data to confirm this hypothesis.[3] Ultimately, the dietary fat impact on health is most probably linked to the very quality of the fat (Grosso et al. 2017; Guasch-Ferré et al. 2015). An emerging risk factor for CVD are carbohydrates, with a large body of clinical trial research demonstrating improvement of most cardiovascular markers when these are reduced (Kuipers et al. 2011).

2.2.4 The Role of Food Quality

Excess salt intake is known to contribute to hypertension and the main source of salt comes from processed food and ready-made meals. Processed meat containing nitrate/nitrite pro-oxidants is associated with coronary heart disease and stroke, but the associations are weak, and the available clinical trial data to date does not confirm an effect of red meat on any cardiovascular disease (O'Connor et al. 2016). Regarding the responsibility of saturated fats for human health, cohort studies do not distinguish between grain-fed and grass-fed livestock and related Omega-3 to Omega-6 ratios,[4] nor different levels of trans fats, conjugated linoleic acid, vitamin

[3] The study mentions that Japan and other Asian countries have not shown such associations with red meat intake, which converges with the view related to grain-fed vs. grass-fed red meat qualities.

[4] The ratio of omega-6 to omega-3 in grass-fed beef is roughly 1.56:1, while in grain-fed beef it averages about 7.65:1; a healthy diet is believed to supply these fats in the range of 1:1 to 4:1 but diets in the West tend to have ratios in the range of 11:1 to 30:1.

E and beta-carotene of meat, which could counteract, or enhance, inflammatory effects (Daley et al. 2010; Ponnampalam et al. 2006). Dioxins (e.g. polychlorinated dibenzofurans in rice oil but also from exposure to herbicides) are associated with death from CVDs, particularly ischemic heart diseases (Brown 2008).

2.2.5 The Role of the Agri-Environment

The impact of air pollution (continuous moderate levels of exposure have greater effects than sporadic high levels of exposure) on CVDs is increasingly being recognized. Risk of stroke is twice and risk of ischemic heart disease is 1.5 times at Delhi or Beijing levels of annual exposure (Green Templeton College 2017). The incidence of infant cyanotic heart disease and meta-emoglobinemia (blue-baby syndrome) have been associated with high nitrate levels in drinking water and root crops (Fewtrell 2004).

2.3 Infectious Diseases: Food-Borne and Zoonotic Diseases

2.3.1 Extent

Over the past decade, WHO documented the under-estimated burden of food-borne diseases caused by microorganisms (e.g. Salmonella enterica, Escherichia coli), parasites (e.g. cryptosporidium, trematodes) and chemical contaminants (e.g. cassava cyanide, aflatoxins) in food. Over 30 foodborne infectious diseases encompassing a wide spectrum of illnesses caused 600 million illnesses and 420,000 deaths in 2010, and 40% of all deaths from foodborne diseases are children under the age of 5 (WHO 2015d). Diarrhoea is the acute, most common symptom of foodborne and waterborne illness in all countries, but other serious consequences include kidney and liver failure, brain and neural disorders, reactive arthritis, cancer and death.

Zoonotic diseases are a group of infectious diseases naturally transmitted between animals and humans through direct contact or though food, water and the environment. Zoonoses comprise a large percentage of all newly identified infectious diseases, as well as existing infectious diseases, such as avian, swine and other zoonotic influenza viruses, spongiform encephalopathies and variant Creutzfeldt-Jakob disease, which pandemics have been infamous in recent decades.

2.3.2 Societal Costs

The contamination of food by microbiological agents is a worldwide public health concern. The illness-related costs of 14 most common pathogens amount to USD 14 billion annually (WHO 2015c). Zoonoses are responsible for about 2.5 billion cases of human illness and 2.7 million human deaths per year (Delia et al. 2012).

2.3.3 The Role of Diets

Infectious diseases most commonly result from the ingestion of foodstuffs contaminated with microorganisms (bacteria, viruses and parasites), through consumption of raw or under-cooked food (e.g. meat, eggs, fresh produce, dairy) and food preparation with unsafe water.

2.3.4 The Role of Food Quality

The contamination of food may occur at any stage in the process from inadequate food production to poor storage conditions and post-harvest handling that promotes microbial contamination. Hygienic practices from farm to table prevent foodborne disease outbreaks.

2.3.5 The Role of the Agri-Environment

The greatest risk for zoonotic disease transmission occurs at the human-animal interface through direct or indirect human exposure to animals, their products (e.g. meat, milk, eggs) and/or their environments. Avian and other zoonotic influenza pandemics, that are associated with poor livestock raising conditions and poor food handling and cooking, can cause disease in humans ranging from a mild illness to death. The 2005 outbreak of *Streptococcus suis* in areas of China has raised concern about the risk associated with infected pork meat.

2.3.6 Occupational Hazards

Slaughtering and butchering of sick pigs are occupational risks to farmers, slaughterers, butchers as well as to those processing or preparing the meat for consumption. Human infection is most likely to occur through cuts or abrasions on the skin. Good hygiene practices are needed to avoid all infectious diseases (WHO 2018b).

2.4 *Antimicrobial-Resistant Infections*

2.4.1 Extent

Antimicrobial-resistant micro-organisms (bacteria, parasites, viruses and fungi) can develop and move between food-producing animals and humans by direct exposure, or through the food chain and the environment. Bacteria that already show concerning resistance level include: third generation cephalosporin-resistant Klebsiella pneumonia (respiratory, blood stream and urinary tract infections); third generation cephalosporin-resistant Escherichia coli (urinary tract and blood stream infections); methicillin-resistant strains of Staphylococcus aureus (skin, bone and blood stream infections); and non-typhoidal Salmonella enterica serotype Typhimurium (diarrhoea, blood stream infections and gastroenteritis) (WHO 2014).

New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. Globally, antibiotic resistance is responsible for 700,000 annual deaths and by 2050, this number could reach ten million deaths a year (Centers for Disease Control and Prevention Antibiotic/Antimicrobial Resistance 2018); a good part of this burden could be attributed to excessive antibiotic use in livestock production (Centre for Disease Control and Prevention Antibiotic Resistance, Food and Food-Producing Animals 2018). Drug resistance affects 35% of common human infections, including 230,000 people who developed multi-drug resistant tuberculosis globally, and drug resistance is starting to complicate the fight against HIV and malaria (WHO 2018a).

2.4.2 Societal Costs

Antimicrobial resistance increases the cost of health care with lengthier stays in hospitals and more intensive care requirements. Antimicrobial resistance is putting the gains of the Millennium Development Goals at risk and endangers the achievement of the Sustainable Development Goal on health. In USA, it is estimated that two million resistant infections require treatment and 23,000 deaths (of which 22% are assumed to be foodborne bacteria) have direct health costs of USD 22 billion and lost productivity of USD 35 billion. This does not account for bacteria originating on farms; should data be collected from antibiotic animal use and animal infection, annual costs would increase by a factor of 10 (Centers for Disease Control and Prevention Antibiotic/Antimicrobial Resistance 2018).

2.4.3 The Role of Diets

Livestock and fish raised with antibiotics develop antibiotic-resistant bacteria which contaminate animal products; eating raw or undercooked meat, or produce contaminated with resistant bacteria, spreads antibiotic-resistance to human guts.

2.4.4 The Role of Food Quality

Recent research on glyphosate hypothesize that the selection pressure of the herbicide on bacterial resistance could lead to shifts in the gut microbiome composition, resulting in transfer of antibiotic resistance from soil to plants, animals and humans through the food web, even in urban and hospital environments. Although the link between glyphosate and antimicrobial resistance is still scarce, there is an urgent need to better understand indirect health risks for glyphosate residues in water, food and feed, through research on the associations between low-level chronic herbicide exposure, distortions in microbial communities, expansion of antibiotic resistance and the emergence of diseases (Van Bruggen et al. 2018).

2.4.5 The Role of the Agri-Environment

In the EU, 8 million kg of antimicrobial drugs were used in 2012 for food-producing animals and 3.4 million kg for humans. Worldwide, 50–80% of antibiotics are used for livestock, including macrolides and tetracyclines, penicillin, sulphonamide and bacitracin, as well as the last resort antibiotic colistin (O'Neill 2014), not only for animal treatment but also for preventive use and growth promotion purposes. Antibiotic-resistant bacteria can spread from animal feces to the environment, which can then contaminate soil and water used to grow fruits and vegetables (Centre for Disease Control and Prevention Antibiotic Resistance, Food and Food-Producing Animals 2018).

2.4.6 Occupational Hazards

Besides through spreading of resistant genes in the environment (terrestrial and aquatic), including via cow manure, slaughtering facilities present further hazards to workers through animal carcasses (mainly pork but also beef and poultry) infected, for instance, by *Clostridium difficile.*

2.5 Chronic Respiratory Diseases

2.5.1 Extent

Chronic respiratory diseases include the most common chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and pulmonary hypertension. In low-income countries, the leading cause of death is pneumonia and in high-income countries, pneumonia and chronic bronchitis are the third cause of death after coronary artery diseases and cancer.

2.5.2 Societal Costs

Globally, outdoor air pollution leads to 3.3 million premature deaths annually; after emissions from residential energy use, such as heating and cooking, agriculture is the second leading cause of outdoor air pollution, accounting to 20% of the total disease burden, or 664,100 deaths per year (Lelieveld et al. 2015), more than half of which occur in China where large cities with the highest $PM_{2.5}$ are all surrounded by intensive agriculture facilities (Gu et al. 2014).

2.5.3 The Role of Diets

While most healthy children can fight infection with their natural defences, children whose immune systems are compromised are at higher risk of developing pneumonia; a child's immune system may be weakened by undernourishment (e.g. zinc deficiency), especially in infants who are not exclusively breastfed (WHO 2016a, b).

2.5.4 The Role of the Agri-Environment

In addition to tobacco smoking (which is the main cause of lung cancer (WHO 2011), the main risk factors of lung diseases (excluding cancer) include air pollution, occupational chemicals and dusts (Calvert et al. 2008), resulting in frequent lower respiratory infections during childhood. Atmospheric pollution from factory farms and pesticide drifts from aircraft spraying are particularly associated with respiratory diseases. Atmospheric pollution from factory farms increases by 20% respiratory diseases; it is reported that exposures to large animal confinement farming produce a wide spectrum of upper and lower respiratory tract diseases, due to the complex diversity of organic dust, particulates, microbial cell wall components and gases, and resultant activation of various innate immune receptor signaling pathways (May et al. 2012).

2.5.5 Occupational Hazards

Exposure to chemicals and dusts (fine particulate matter) is estimated to cause 12% of deaths due to chronic obstructive pulmonary disease (WHO 2009b).

2.6 Neoplasms

2.6.1 Extent

Neoplasms, or cancers, figure among the leading causes of morbidity and mortality worldwide, with approximately 17.5 million new cases, and related 8.7 million deaths in 2015. The number of new cases is expected to rise by about 70% over the next 2 decades, up to 22 million.

2.6.2 Societal Costs

The financial cost of cancer is high for both the ill person, their households and society as a whole. One of the major cost is treatment. Lack of insurance and other barriers to health care leads to late cancer diagnose and more extensive and costly, and less successful treatment. In USA, the projected cost of cancer care is USD 173 billion in 2020, representing a 39% increase from 2010 (Mariotto et al. 2011). The biggest financial impact is in terms of loss of life and productivity, in which cancer accounts for 1.5% of GDP loss in USA.

2.6.3 The Role of Diets

Around one third of all cancer deaths are due to five leading behavioural and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use (WHO 2015a). Statistical and epidemiological data attribute to diets in USA 35% of human cancer mortality; on the other hand, healthy diets play a role in protecting against cancer (NRC Committee on Comparative Toxicity of Naturally Occurring Carcinogens 1996). Emerging evidence from animal studies shows some cancers respond to diets high in fat and very low in carbohydrates. Excessive animal protein intake, especially red and processed meat, creates acidifying conditions conducive to inflammation (Schwalfenberg 2012) and for instance, colorectal cancer. Mediterranean diets seem to prevent as much as 66–75% of colorectal cancer, maybe because fruits and vegetables limit the growth of IGF-1 that stimulates cancer. The American

Association for Cancer declared that 60% of cancers in USA can be avoided by simply changing diet and lifestyle.

2.6.4 The Role of Food Quality

Although the dietary contribution to cancer remains a troubling question, evidence is building-up on food system links with cancers of the digestive organs, genital organs, and haematopoietic and related tissues. Many foods on the market shelves carry pesticide residues above the acute reference dose, let alone the cumulative effects of the residues of different pesticide active ingredients and their adjuvants. In particular, toxicological evaluation of pesticides neglects the role of certain pesticides on intestinal microbes that maintain health or on enzymatic activity important to detoxification processes, resulting in unsettled debates regarding the use of certain substances, such as glyphosate's role in Non-Hodgkin's lymphomas.

Environmental exposures that damage DNA are responsible for much of the increased cancer incidence and the increased release of new chemical substances in the environment (e.g. plastics, pesticides) is paralleled with the increase of cancer; for example, polychlorinated biphenyls chemicals are known to be carcinogenic and 90% of human exposure continues to come from animal-derived foods such as milk, eggs and fish (WHO 2016a, b).

Cadmium-containing phosphate fertilizers are associated with increased pancreatic cancer rates and research has demonstrated an association with rural dietary factors, such as high consumption of rice and crawfish of fields fertilized with phosphate fertilizers (Falk et al. 1988). Naturally-occurring chemicals (such as mycotoxins produced by fungi in grains and nuts) and plant alkaloids are recognized to cause cancer in experimental animals.

Nitrosamines in processed meat, endosulphans in farmed salmon (Hites et al. 2004), preservatives and artificial sweeteners (Schernhammer et al. 2012) in processed food and beverages might also contribute to the processes leading to cancer. In particular, industrial red meat—which contains more oestrogens, sodium and Omega-6 and less Phosphorus, Iron and Calcium—is thought to increase colorectal cancer by at least 37% (World Cancer Research Fund/American Institute for Cancer Research 2007).

Combustion residues from cooking, as well as certain food preservatives and colorants, are also believed to contribute to colorectal cancer (Grandi 2008). Cooking at high temperatures produces carcinogenic compounds (e.g. heterocyclic amines, acrylamide) (EFSA 2015) and kitchenware may include carcinogenic compounds.

2.6.5 The Role of the Agri-Environment

Many approved agriculture pesticides are significant toxicants responsible for initiation and promotion in carcinogenesis, including both DNA-reactive carcinogens that can be active with a single dose and are effective at low exposure, and non-genotoxic carcinogens requiring high, sustained exposure. In USA, approximately 40 chemicals classified by the International Agency for Research on Cancer as known, probable, or possible human carcinogens, are used in EPA-registered pesticides found today on the market (IARC and WHO 2009).

Nitrogen fertilizers may increase cancer risk due to the breakdown of nitrogen by digestive enzymes (Ward 2009). Most of the nitrogen in fertilizers (both synthetic and organic) is converted to nitrate that seeps into groundwater. Ingesting nitrate contaminated drinking water (Weyer et al. 2001) leads to the body's formation of N-nitroso compounds (NOC), which have been shown to cause tumours at multiple organ sites in every animal species tested, including neurological system cancers following trans-placental exposure. It is believed that nitrates in drinking water cause colon cancer (IARC and WHO 2018). NOC formation is inhibited by dietary antioxidants found in vegetables and fruits, which may account in part for the observed protective effect of fruits and vegetables against many cancers.

2.6.6 Occupational Hazards

At least 150 chemical and biological agents are known as probable causes of cancer and many of these are found in the agricultural workplace. Greenpeace 'Toxic Load Indicator' identifies 101 pesticides that meet one of the several human toxicity cut-off criteria (e.g. carcinogenicity, mutagenicity, immunotoxicity) and which are currently authorized for use in the EU (Lars 2016). Numerous pesticides (e.g. phenoxy herbicides, carbamate insecticides, organophosphorus and organochlorine insecticides (Guyton et al. 2015)) constitute direct hazards to pesticides applicators (Schinasi and Leon 2014; De Roos et al. 2004; Alavanja et al. 2014) and their families: leukaemia rates are consistently elevated among children who grow-up on farms, among children whose parents used pesticides in the home or garden, and among children of pesticides applicators (Monge et al. 2007; Menegaux et al. 2006; Meinert et al. 2000).

Tumour viruses (e.g. herpes virus/avian sarcoma, reticoloendoteliosis, linpho-proliferative disease of turkeys) in poultry are associated with non-Hodgkin lymphoma among farmers and slaughterhouse workers.

2.7 Developmental and Reproductive Deficiencies (Endocrine Disruption)

2.7.1 Extent

Concerns are increasingly being raised for chemicals that could interact with the endocrine system (i.e. oestrogen, androgen and thyroid signalling pathways) and thus, disrupt a number of processes critical for successful development and reproduction (FAO and WHO 2009). EU expert panels achieved consensus at least for probable (over 20%) Endocrine-Disrupting Chemicals (EDCs) causation for the following conditions: Intellectual Quotient loss and associated intellectual disability, autism, attention-deficit hyperactivity disorder, childhood obesity, adult obesity, adult diabetes, cryptorchidism, male infertility, and mortality associated with reduced testosterone. EDCs induced effects on human development may be expressed through altered viability, growth, structural or functional abnormalities, due to either mutations, or biochemical/physiological disturbances, and which may be expressed immediately or delayed, especially when exposure is during the fatal period.

EDCs' trans-generational epigenetic inheritance has led to a new paradigm for non-communicable disease referred to as the Developmental Origins of Health and Disease (DOHaD) (Street et al. 2018). Precaution suggests not to wait for conclusive evidence of harm to human health in order to ban certain pesticides (e.g. organochlorine, organophosphates and pyrethroids) and certain foodware additives (e.g. phthalates, BPA).

2.7.2 Societal Costs

Simulations produced a median EDC-related health cost of €157 billion annually in the European Union, or USD 217 billion, corresponding to 1.28% of EU gross domestic product (GDP) (Trasande et al. 2015). In USA, EDCs disease costs are much higher than in Europe, or USD 340 billion annually (of which USD 42 billion from pesticides alone) corresponding to 2.33% of GDP, due to poly-brominated diphenyl ethers (used as flame retardant) impacts on IQ and intellectual disability—while in the EU the largest contributor to health costs are organophosphate pesticides (Attina et al. 2016).

2.7.3 The Role of Diets

Neonatal development may be influenced by chemicals or their metabolites that are present in the maternal diet and subsequently transferred into maternal milk, or via consumption of infant formula containing certain additives, phytoestrogens (in soy-based formula) or migrants from infant feeding bottles. In particular, exposure to

EDCs (e.g. phthalates, bisphenols and per-fluoro-otanoic acid) used in plastic bottles, tins, cans, foodware and non-stick cookware (European Food Safety Authority 2014) is associated with 40–69% of anomalies of male reproductive hormone balance (infertility, cryptorchidism, hypospadias) and 0–19% incidence of testicular cancer (Trasande et al. 2015).

2.7.4 The Role of Food Quality

Long-term and low-level exposure to a wide range of pesticide residues over recommended levels in conventional fruit and vegetable (Chiu et al. 2016) has been reported to cause male reproductive disorders. Also, artificial colorants (i.e. E102, E104, E110, E122, E124) in food have been linked to Attention Deficiency and Hyper-activity syndrome (McCann et al. 2007).

2.7.5 The Role of the Agri-Environment

Globally, close to 800 chemicals are known or suspected to interfere with hormone receptors, synthesis or conversion but only a small fraction of these chemicals has been investigated for endocrine effects. No systematic neurotoxicity testing is required for the registration process of substances, despite the fact that at least 100 different pesticides cause adverse neurological effects. The European Union is taking the lead on regulating EDCs, including regulations on pesticides and biocides: 194 of the 432 candidate substances listed by the EU have evidence of endocrine-disrupting properties in at least one living organism.

Some EDCs produce effects that can cross generations, suggesting that the increase in current disease rates may be due to exposure of our grandparents to EDCs; transgenerational transmission and continued exposure are likely to increase effects over each generation. Despise knowledge gaps hampering progress to better protect public health, what is certain is that the increase of endocrine disease incidence over the recent decades rules-out genetic factors as the sole plausible explanation (WHO and UNEP 2013).

2.7.6 Occupational Hazards

Undescended testes in young boys, thus risk of subfertility and testicular cancer in adult life, are linked with exposure to diethylstibestrol (DES) and poly-brominated diphenyl ethers (PBDEs) and with occupational pesticide exposure during pregnancy. The incidence of genital malformations (e.g. cryptorchidisms, hypospadias) in baby boys has increased over time and levelled-off at unfavourably high rates (WHO and UNEP 2013).

2.8 *Neuro-Degenerative Diseases*

2.8.1 Extent

The cause of neuro-degenerative diseases, such as Alzheimer's Disease (AD), Parkinson disease, dementia, amyotrophic lateral sclerosis and Huntington disease, is generally unknown. Although these diseases are significantly influenced by gene susceptibility factors, underlying environmental risk factors have pronounced effect size on certain conditions, such as AD. An increased risk has been recorded in people with hypertension and those exposed to certain pesticides (Plassman et al. 2016). In 2015, there were approximately 48 million people worldwide with Alzheimer's, especially in industrialized countries. In 2013, Parkinson's disease was present in 53 million people and resulted in about 103,000 deaths globally (WHO 2015b). Deaths due to dementia more than doubled from 2000 to 2015, making it the seventh leading cause of global deaths in 2015 (WHO Mortality and Global Health Estimates 2018). The incidence of neuro-degenerative diseases is expected to double every 20 years, as the world's population ages (JPND Research 2018).

2.8.2 Societal Costs

The current costs of dementia are staggering. The global cost of Alzheimer's disease in 2010 was USD 604 billion, or 1% of the global GDP. In USA, people suffering from Alzheimer's and Parkinson's diseases cost the nation nearly USD 200 billion annually in patient care and lost productivity and is estimated to increase to USD 1.1 trillion by 2050 (Institute for Neurodegenerative Diseases 2018). To meet the coming crisis in neurological care, an army of caretakers will be needed.

2.8.3 The Role of Diets

Alzheimer's disease (AD) is highly associated with atherosclerosis and high blood pressure, thus cardiovascular disease risk factors. Diets rich of fibres and anti-oxidants (polyphenols) are believed to prevent strokes that lead to dementia (Barnard et al. 2014). High levels of Advanced Glycation End-products (AGEs) from (over)cooking animal-derived foods rich in fat and protein (e.g. grilled meat) is linked to increased oxidant stress and AD (Uribarri et al. 2010). Other studies speculate that elevated insulin caused by excessive carbohydrates is linked to AD (Li and Hölscher 2007).

2.8.4 The Role of the Agri-Environment

Monosodium glutamate additive (E621) (FAO 2013)[5] in excessive quantity is associated with brain damage and neuro-pathologies, including AD, as well as Parkinson's and Huntington's diseases (Lau and Tymianski 2010). While diets rich in flavonoids from fruits and vegetables may prevent degenerative diseases by protecting neurons, certain pollutants in food, such as heavy metals in poultry and tuna (Arsenic), dairy products (Lead) and fish (Mercury) and dioxins in animal feed, may accelerate neuro-degenerative processes.

2.8.5 Occupational Hazards

In France, neuro-degenerative diseases are recognized as professional diseases of agricultural pesticide users, especially of viticulture workers (Bolis 2012). In particular, pesticides of strongest association with parkinsonism are: 2,4-dichlorophenoxyacetic acid, paraquat, permethrin, dieldrin, mancozeb, rotenone, maneb, and diquat (Tanner et al. 2009).

2.9 Auto-Immune System Disorders: Celiac Disease and Allergies

2.9.1 Extent

Allergic diseases refer to a hyper-sensitivity of the immune system to something in the environment that usually causes little or no problem in most people, including food allergies (6% of developed world population), atopic dermatitis (20%), allergic asthma (1–18%) and anaphylaxis (Stenius et al. 2011). Although nearly any food is capable of causing an allergic reaction, the majority of reactions is caused by 8 foods: peanuts, tree nuts, milk, egg, wheat, soy, fish and shellfish. Food allergy (i.e. IgE-mediated food allergy, such as asthma) and other food hyper-sensitivities (i.e. non-IgE-mediated hypersensitivity, such as coeliac disease) are adverse reactions to specific foods or food ingredients occurring in sensitive individuals.

2.9.2 Societal Costs

Living with Celiac disease is relatively expensive, including medical costs and lost productivity at work after consuming gluten-containing food and often, procuring and buying gluten-free alternatives to wheat-based foods.

[5]E621 additive is considered safe by US/FDA but is subject to quantitative limits in the European Union.

2.9.3 The Role of Diets

Allergy develops through the process of sensitization (exposure to food allergen) so eating habits may influence its development (FAO and WHO 2009). Celiac disease (distinct from wheat allergy) is an auto-immune disorder of an estimated 1% of the global population that is caused by a reaction in genetically predisposed people to gluten found in wheat, rye, barley and hybrids products made from these grains. Celiac disease also starts with early introduction of gluten-containing cereals in diets, with an increased incidence when babies are not breastfed when gluten is introduced in the diet. Celiac changes gut permeability, leading to poor absorption of nutrients in the intestine, anemia, poor absorption of Vitamin B12 (leading to dementia) and poor absorption of Vitamin D and calcium; it is further found in connection with other diseases, such as type 1 diabetes and rheumatoid arthritis (FAO and WHO 2009).

2.9.4 The Role of Food Quality

Alterations in immune system responses also arise as a result of exposure to chemical contaminants (e.g. persistent organochlorine compounds) in foods. Celiac disease starts with early introduction of gluten-containing cereals in diets but also by consuming cereals with altered gluten levels by the agrifood industry. Food irradiation (with gamma rays of Caesium 137) is used to preserve food, to prevent the spread of invasive pests and delay, or to eliminate sprouting or ripening; wheat irradiation, that increases the level of gluten, is thought to alter non-gliadin components that can lead to damage of intestinal wall and increased autoimmune diseases, such as Celiac disease (Kucek et al. 2015; Parisani 2018; Robson 2018).

2.10 Gastro-Intestinal Tract Disorders

2.10.1 Extent

Digestive disorders and diseases (of the oesophagus, stomach, liver, pancreas, kidneys, gallbladder or intestines), range from mild (gastritis) to serious (cancer), and affect millions of people worldwide. Besides alcohol-related diseases, the main chronic liver diseases are closely related with diabetes and obesity. Gastro-oesophageal reflux disease, functional constipation, and irritable bowel syndrome are highly prevalent diseases, affecting each of them 1 out of every 6 persons all over the world (Guarner et al. 2009).

2.10.2 The Role of Diets

Adequate diets, including enzymes that support metabolic processes, are key to improving metabolic functions, including both prevention and treatment of several disorders. Chronic metabolic acidification is due to the sulphur content of meat amino-acids. Non-Alcoholic Fatty Liver Diseases (NAFLD) are caused by excess intake of saturated fats and soft drinks. Hypertension caused by excess salt in diets may cause renal failure. Some data suggest that chronic kidney disease is mainly due to hyper-filtration of animal proteins, while kidney stones may be induced by excess uric acid (Ambühl 2011).

2.10.3 The Role of the Food Quality

Mineral phosphorus fertilizers introduce Cadmium in the food chain (especially in barley, wheat and vegetables) which contributes to kidney disease (EFSA 2015). Kidney insufficiency is partly due to phosphate additives (pyrophosphate and sodium polyphosphate) in meat and soft drinks (Amato et al. 1998). Crohn disease, colitis and other metabolic syndromes, sometimes leading to lethal cardio-vascular problems, are associated with emulsifiers (i.e. E433 and E466) used in ice creams, ready-made meals, gluten-free products and artificial vitamins (Chassaing et al. 2015).

2.10.4 The Role of the Agri-Environment

Herbicides (i.e. atrazine, metolachlor, alachlor, paraquat and pendimethalin) and insecticides (i.e. permethrin) are associated with high risk of kidney disease (Lebov et al. 2016), as well as with exposure to environmental pollutants, especially overloads of toxins from heavy metals. Glyphosate-based herbicides are associated with NAFLD and its progression to non-alcoholic steatohepatitis (NASH) (Mesnage et al. 2017). In USA, increased kidney diseases for the young, elderly and immune-compromised, are associated with factory farm pollution of water by pathogens such as E. coli (Hribar 2010). Calcium phosphate fertilizers contaminated with polonium phosphates have detrimental effects on gut health by enhancing intestinal colonization of Gram-positive pathogens and subsequent pathogenesis, especially in diets containing corn oil (Sprong et al. 2002).

2.10.5 Occupational Hazards

Climate change-caused dehydration of field workers has been reported to cause chronic kidney disease (one fifth of the sugarcane field harvesters in El Salvador (Wallace-Wells 2017)).

2.11 Poisoning, Injury and Certain Other Consequences of External Causes

2.11.1 Extent

Millions of acute poisoning cases are reported for pesticide handlers (formulators, manufacturers, applicators), of which 300,000 deaths are estimated to occur annually at the global level (Schafer et al. 2004). The farming, fishing and forestry industries have a suicide rate consistently higher than the rate of the general population, five times as high in USA, twice as high in Australia and UK and 18% as high in India (IPES-Food/Global Alliance for the Future of Food 2017).

2.11.2 Societal Costs

Statistics from many countries or regions show that agriculture consistently has one of the highest accidents and injury rates of the industrial sectors (Litchfield 1999). In USA, the annual costs of occupational morbidity across the economy is USD 250 billion and the agricultural sector, including food manufacturing and food preparation industries, is the biggest contributor (Newman et al. 2015).

2.11.3 The Role of Food Quality

Acute toxicity may also be caused by veterinary drug and pesticides residues in food, as well as microbiological contaminants (mycotoxins and marine biotoxins) or low-digestible carbohydrates (such as polyol sweeteners) (FAO and WHO 2009). Substances that can give rise to acute health effects in short periods of intake include certain metals, mycotoxins, veterinary drug residues, pesticide residues or low-digestible carbohydrates.

2.11.4 Occupational Hazards

Agricultural workers suffer a wide variety of disorders as a result of their occupation. These range from minor (cuts, bruises) to more severe (deep wounds, fractures), permanent (amputation, spinal cord injury) and fatal injury. Ill-health as a result of contact with animals, micro-organisms, plant material dusts or chemicals are associated with certain types of agriculture. There is also an underlying but unquantified incidence of pain, stress and injury as a result of ergonomic problems due to poor working procedures and conditions that vary from benign lower back pain due to physical workload, through various musculoskeletal diseases, to

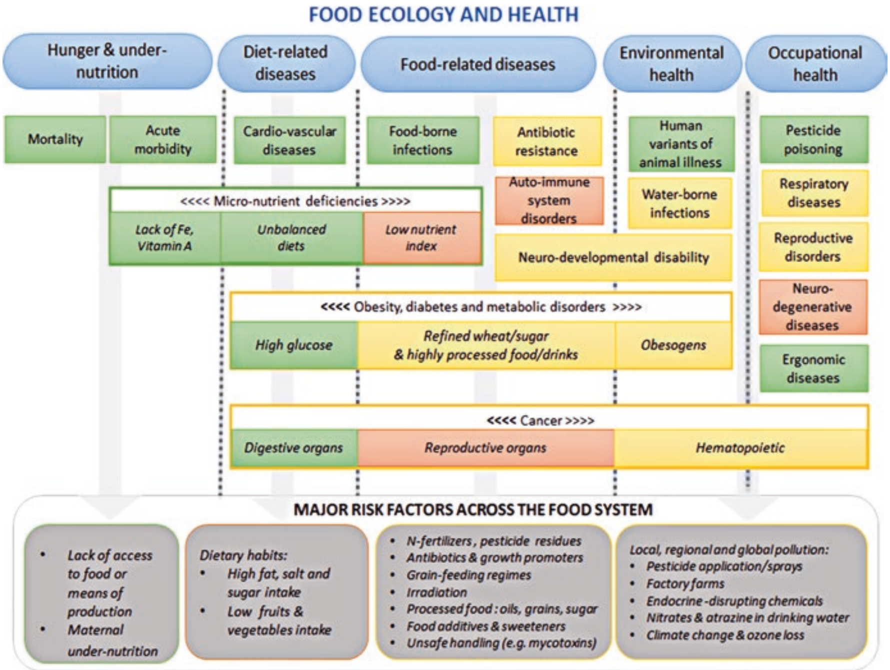

Fig. 1 Food Ecology and Health. The food-health nexus requires considering the entire eco-agri-system. The green coloured boxes refer to areas with sufficient scientific evidence, orange boxes refer to emerging evidence, while red boxes represent poorly understood or insufficiently documented links between health and the food and agriculture system

severe carpal injury in food processing industries (notably poultry in USA) (Gottfried 2016).

3 Addressing Eco-Agri-Food Ecology and Health

3.1 *Food Ecology*

A preliminary representation of the main disease groups related to eco-agri-food systems, grouped according to major exposure routes, is presented in the Fig. 1. It brings together knowledge from nutrition science, environmental health and epidemiological, toxicological and clinical medicine under the common umbrella of food ecology. Clearly, Fig. 1 over-simplifies the complexity in real life, as no disease can be defined according to strict boundaries. Such representation is a first step towards building a more consistent framework for understanding eco-agri-food system-related health. It highlights the fact that disease outcomes follow different pathways and often respond to multiple risk factors within eco-agri-food systems, in addition to lifestyle and other factors.

3.2 The Way Forward

Healthy food is the cornerstone of good health. As described above, disease outcomes are highly influenced by the food system, from seed breeding, fertilization and irradiation that maximize calorie yields at the expense of vitamins, minerals and polyphenols, to factory farm products low in Omega 3 and other anti-oxidants, pesticides and veterinary drugs that cumulate chemicals in our bodies, additives and sweeteners in processed food, endocrine-disrupting chemicals in packaging, coating cans and non-stick cookware, poor handling practices resulting in aflatoxin or microbiological contamination, or cooking at high temperatures that further adulterate our meals with acrylamide or other toxins. In addition, industrial agricultural practices substantially contribute to unhealthiness through air pollution, climate change and drinking water contamination. Thus, addressing health cannot but take a system thinking in order to consider the eco-agri-system as a functional whole, with inter-connected and self-reinforcing impacts on health.

Implementing SDG 3 will require the concerted efforts from policy-makers, researchers and practitioners involved in: SDG 2 (zero hunger) in order to undertake multi-disciplinary food research among agriculturists, nutritionists, environmentalists and health providers, away from the single nutrient focus; SDGs 6 (water), 7 (energy), 13 (climate change), 14 (life below water), 15 (life on land) in order to minimize ecological drivers through precautionary policies that restrict agricultural chemicals with cut-off criteria for human health and that phase-out chemical agricultural substances in the longer-term; SDG 12 to incentivize responsible production and consumption systems (such as organic and regenerative agriculture), that safeguard public goods, namely public health and ecosystem services; and SDG 17 (partnerships) for framing the nutrition and health debate around food democracy and access to diverse nutritious food. The SDGs provide the aspirational holistic perspective for policy coherence in addressing human health and in particular, all the eco-agri-food system pathways that affect health outcomes.

Acknowledgments The author wishes to thank the following colleagues for having provided insights to an earlier version of this paper, including: Barbara Gemmill-Herren (Biovision Foundation), Bruce Hirsch (Clarence Heller Foundation), Bernhard Johannes Kahl (University of Copenhagen), Peter Kenmore (Santa Clara University), André Leu (International Federation of Organic Agriculture Movements), Alexander Mueller (TMG Think Tank on Sustainability), Nina Teicholz (New York Times), Domenico Scanu (International Society of Doctors for the Environment), Cristina Tirado (International Union for Nutritional Sciences) and Kevin Gallagher (Future of Agriculture Think Tank). Thanks are also due to Isabella and Daniele Scialabba for having checked and organized the list of references.

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