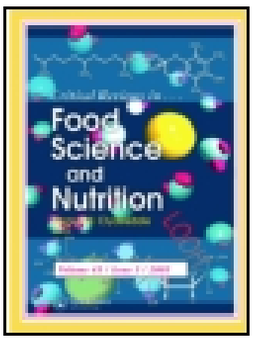

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Risks and benefits associated with infant milk

Public health risks and benefits associated with breast milk and infant formula consumption

Géraldine Boué[1,2], Enda Cummins[3], Sandrine Guillou[1,2], Jean-Philippe Antignac[4,2], Bruno Le Bizec[4] and Jeanne-Marie Membré[2,1*]

[1]LUNAM University, Oniris, UMR1014 Sécurité des Aliments et Microbiologie, F-44307 Nantes, France.

[2]INRA, F-44307 Nantes, France.

[3]UCD School of Biosystems and Food Engineering, Dublin, Ireland.

[4]LUNAM University, Oniris, USC 1329 Laboratoire d'Etude des Résidus et Contaminants dans les Aliments, F-44307 Nantes, France.

[*]Corresponding author: Jeanne-Marie Membré, Jeanne-marie.membre@oniris-nantes.fr, INRA, UMR1014, SECALIM, Oniris la Chantrerie G5, route de Gachet CS 40706, F-44307 Nantes Cedex 3.

ABSTRACT

The safety and quality of infant milk, whether it is breast milk (BM) or infant formula (IF), are a major concern for parents and public health authorities. BM is recommended as the gold standard at WHO level. However, nowadays IF appears as an essential alternative in Western countries, challenging producers to optimise nutritional quality and safety of IF. The aim of the present paper is to give an overview on the assessment and comparison of risks and benefits associated with BM and IF consumption. To date, this intensively debated subject has been mainly investigated. It has been shown that both diets could be sources of beneficial health

effects in terms of nutrition and also risks in terms of chemical safety. Moreover, microbiologists have demonstrated that IF consumption can cause illness due to product contamination or inappropriate milk preparation. The paper concludes on the bottlenecks and gaps which should be investigated to further progress the quantification of the impact of early diet on infant health. Performing a multi-disciplinary risk-benefit assessment with DALY as endpoint, might be a future option to help prioritise management options.

Keywords

risk-benefit assessment; food safety; nutrition; infant health; infant milk

INTRODUCTION

The first months of an infant's life are crucial for short and long term healthy physiological development (Horta et al., 2007; Horta and Victora, 2013). During this critical period baby size doubles and total brain weight triples (ANSES, 2014). To develop and thrive, infants have basic nutritional requirements which can be satisfied by consuming breast milk (BM) and/or infant formula (IF). The debate on the choice of "breast or bottle" (Wolf, 2013) has been ongoing for decades, and involves not only scientific aspects, but also societal, economical, personal/individual, if not ideological or spiritual/religious issues.

Breastfeeding is widely considered as the best adapted food for infant needs and is acknowledged to have beneficial health effects (Hörnell et al., 2013). However, nowadays the majority of infants in Western countries are formula fed by virtue of their parents' choice or due to medical circumstances. Indeed, about 2% of mothers are physiologically not able to breastfeed (Brown, 2015).

The World Health Organization (WHO) has defined different infant feeding diets (2008):

- *Exclusive breastfeeding:* infants are fed with breast milk but not with non-human milk such as formula, they might receive oral rehydration solution (ORS), drops and syrups
- *Predominant breastfeeding:* infant nourishment is predominantly composed of breast milk and certain liquids such as water, water-based drinks and fruit juice, and can also contain ORS, drops and syrups, but no milk formula

- *Partial breastfeeding* or *complementary feeding:* infant are fed with breast milk and other foods such as formula milk
- *Bottle feeding:* includes any food, liquid or semi-solid food, consumed with a bottle and nipple

WHO recommends to exclusively breastfeed infants under six months of age, i.e. that infants only consume BM without additional food or drink, not even water. Nevertheless, at the worldwide scale only 40% of infants are exclusively breastfed until six months of age (WHO, 2014a), however there is high variability among countries (Figure 1). In Europe, the exclusive breastfeeding rate at six months is rather low with an average of 18% (WCRF, 2009), similar to the USA rate (National Research Council, 2004). More precisely, this rate is not constant during an infant's first months of life. For instance, in France, 74% of newborns are breastfed at birth (Salanave et al., 2014), but after 48 hours, the exclusive breastfeeding rate decreases to 55.4% (Inserm, 2008) and continues to decline: 28%, 10% and 0.5% after one, three and six months, respectively (Salanave et al., 2014).

Infants are more sensitive to infections during the first few months of life because their immune system is under developed and even though breastfed infants receive antibodies through breast milk they remain a particular at risk population. Sanitary issues have occurred in the last few decades due to the consumption of powder infant milk contaminated by *Cronobacter sakazakii*, causing a dozen of illnesses, with some fatalities (European Commission, 2015b). More recently, in China a scandal occurred regarding melamine adulteration that caused about 300,000 clinical

cases, including six deaths (Gossner et al., 2009). Furthermore, infant health might be influenced by the consumption of milk contaminated by chemicals, whether it be BM or IF. BM might contain chemical contaminants due to a mother's exposure through food consumption, dermal contact or inhalation (e.g. persistent organic pollutants like PCBs). IF is also subject to chemical contamination due to cow's milk or even during powder processing. It could be also contaminated during the milk preparation by for instance the addition of tap water or the use of unappropriated materials (e.g. bottle containing bisphenols or phthalates).

Consequently, for years, breast milk and infant formula have captured public and scientific attention regarding, on the one hand, the BM diet and the balance of beneficial health effects with potential adverse effects due to chemical contaminants; and on the other hand, the IF diet and the assessment of its potential chemical and microbiological risks. In this context, the present review aims to i) sum up the current legislation and nutritional requirements, ii) give an overview of adverse and beneficial health effects of both diets with regard to microbiology, chemistry and nutrition fields; and then iii) summarise current advances in the risk-benefit assessment of infant milk, with a specific focus on infants from birth to six months of age from European countries.

INFANT MILK : CURRENT LESGISLATION AND NUTRITIONAL REQUIREMENTS

Infant diets have historically evolved over time and can also be differentially examined across various cultural and/or anthropological issues. The first infant food substitute was developed and commercialized in the 1860s. The Codex Alimentarius Commission (CAC) has defined the IF as a "breast-milk substitute specially manufactured to satisfy, by itself, the nutritional requirements

of infants during the first months of life up to the introduction of appropriate complementary feeding" (1981).

Definitions of different infant diets

Infants and young children's nutritional requirements vary from zero to three years. As described in Figure 2, infants can consume different kinds of milk: BM or IF. From a regulatory point of view, there are different formula intended for three different age categories: infants from zero to six months (also called starter or IF), from six months to one year (also called follow-on formula) and from one year to three years of age (also called growing-up formula). Additionally, the food transition that corresponds to the progressive introduction of solid food in the diet is advised to start from the age of six months by WHO (2004) and between four and six months in Europe (EFSA, 2009). This review specifically focuses on IF and BM consumed by infants from zero to six months of age, without integrating the potential consumption of solid food.

European infant formula legislation

In Europe, IF composition has evolved over years according to the scientific progress and discoveries (National Research Council, 2004). Nowadays, even if the main ingredients are strictly regulated, there is a lot of different IF brands available on the market offering a large range of products with different protein and fat sources and novel ingredients intending to offer beneficial health effects (Tijhuis et al., 2014). For example in France in 2012 there were about 300 IF recorded (AFPA, 2012). However, the industrial's margin is thin regarding composition and safety of IF that is regulated. Indeed, at the European level, food safety is governed by the General Food Law (European Commission, 2002) and regulated "from farm to fork", i.e.

including feed and primary production, food processing, storage, transport and retail sale. The laws regulating IF composition and safety, with microbiological, chemical and nutritional criteria, are presented in Table 1. The laws are based on the assessment made by the European Food Safety Authority (EFSA), the independent agency in charge of the risk assessment of food and feed. EFSA has recently published an opinion paper on IF (EFSA, 2014) updating the evaluation made by the Scientific Committee on Food (2003). The EFSA opinion (2014) suggests new reference values for nutrients (Table 2), which can be expected to be implemented at the legislation level in the near future (European Commission, 2015a). The Member States of the European Union then implement the European legislation, at their national level.

In parallel, from international perspectives, the CAC established by the FAO (the Food and Agriculture Organization of the United Nations) and WHO, develops food standards that are not legally mandatory norms, but are often used by national and regional legislations. For example, in Europe, the Codex standards have often served as the basis for European legislation (Luning et al., 2006). This harmonisation facilitates the trade between countries at the global level, encouraged by the World Trade Organization (WTO, 1995, 1998). In 1981, the CAC published the food standard for IF that sets levels of nutrients (Codex Alimentarius Commission, 1981). This standard was reviewed and updated by a group of experts, namely the Committee on Nutrition of the "European Society for Paediatric Gastroenterology, Hepatology, and Nutrition" (ESPGHN) and "the international scientific committee", their work has been published (Koletzko et al., 2005).

How to fulfil infant requirements?

Infant nutritional needs

Humans, and then infants, need energy to perform and regulate all biochemical processes that maintain body structures (e.g. synthesis of growing tissues) and functions (e.g. basic metabolism, thermoregulatory needs) and to perform physical activities (EFSA, 2013; FAO/WHO, 2001). The energy requirement mainly comes from carbohydrate and lipid intakes.

Infants also need macro- and micro-nutrients. Schematically, proteins help to maintain and build tissues, essential fatty acids to regulate cell membrane fluidity, water to assure the transport of nutrient and metabolic waste. Vitamins and minerals participate to all main biochemical processes. More details on the functions are provided in Table 2.

For Europe, the reference intake for energy and nutrients are listed in Table 2, using the EFSA assessment (EFSA, 2014).

The sum of these energy costs should be met by milk intake. Prediction of the energy required according to age, gender, weight and height has been estimated in the EFSA opinion on nutrient requirements and dietary intakes of infants (EFSA, 2013). Combining these needs, it varies from zero to six months for boys between 78 and 109 kcal/kg per day and between 78 and 103 kcal/kg per day for girls.

Comparison of breast milk and infant formula composition

To comply with nutritional requirements, in terms of energy and nutrients, infants from zero to six months consume two kinds of products: BM and/or IF, whose different compositions are highlighted in Table 2. Regarding IF composition, two figures are presented, one from the current EU legislation and another one from EFSA recommendation (EFSA, 2014). Indeed, the

essential IF composition for nutrients and energy content was assessed by EFSA after the publication of a systematic review by Tijhuis *et al*. (2014) that compared the nutrient status and health effects of different IF compositions. Nonetheless, the comparison between IF and BM cannot be based exclusively on quantitative indicators, it has to take also into account the nature and quality of nutrients. For instance, BM contains smaller micelles of casein and about 60% of soluble proteins that do not precipitate with casein; both these properties lead to a more efficient absorption of BM in the stomach compared with IF (Turck, 2010). Another difference is the lower content of Vitamin D in BM, requiring a supplementation for breastfed infants. In addition, human milk composition is not standardised and might change depending on the lactating woman. For example, fats and fatty acids in BM composition depends on the mothers food intake (VKM, 2013).

Infant food intake recommendations

Exclusive breastfeeding is recommended by the United Nations Children's Fund (UNICEF, 2014) and WHO (2014a) until six months of age, meaning that infants during this period should only consume BM and no other food, not even water. UNICEF and WHO support the fact that breastfeeding is better for child survival and health (WHO/UNICEF, 2015), particularly in countries where population has no access to safe water. The European recommendation is more nuanced and varies among countries between four and six months of exclusive breastfeeding (Yngve and Sjöström, 2001).

AN ATTEMPT TO DEFINE HEALTH, HEALTH EFFECT, RISK AND BENEFIT

Health is defined here as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). A **health status** of an individual is the location on the "Illness-Wellness continuum" (Dever, 1997; Travis and Ryan, 1988), going from serious illness causing premature death to high level of wellness, schematised in Figure 3. More precisely, the high level of wellness corresponds to the "optimal level of functioning or capacity in all the important dimensions of health, and from any type of illness or disease" (Goodacre et al., 2010), it is not only associated with the absence or presence of disease.

Health effect can be defined as any change in the Illness-Wellness scale of the health status represented in Figure 3 resulting from the exposure to a microbiological factor (e.g. *Cronobacter sakazakii*), a chemical factor (e.g. methyl mercury) or a nutritional factor (e.g. fatty acids), named a **HECF** (Health Effect Contributing Factor) in a previous study (Boué et al., 2015). A HECF is an agent that causes a change of the health status on the "Illness-Wellness continuum" of an individual. An **adverse health effect** is a decrease of the health status in the direction of illness/premature death and a **beneficial health effect** is an increase of the health level in the direction of the high level of wellness.

Risk/benefit can be then defined as the probability of having a consequent health effect following exposure to a HECF in food.

Based on the Illness-Wellness concept, the probability of location on the wellness part of the scheme can be associated with the term **benefit** if the health effect is not linked to the absence of disease but to an improvement of the capacity to compensate for additional stress (e.g.

development of the immune and digestive system or intellectual quotient improvement). Similarly, the probability of location on the illness part of the scheme can be related to **risk** associated with illness (e.g. Listeriosis, obesity or cancer). In this context, a decrease of a risk will not be considered a benefit. For example, the adjunction of a preservative in food can simultaneously introduce a chemical risk and decrease a microbiological risk; the risk of illness in this case is not located on the superior part of illness-wellness scale and therefore will not be named a benefit. In such a case, the output should be analysed in a risk-risk assessment.

HEALTH EFFECTS ASSOCIATED WITH INFANT MILK CONSUMPTION

Health effects associated with the consumption of breast milk and/or infant formula with regard to nutritional, microbiological and chemical components has been an important research topic from the 1990s and around which a lot of studies have been published and reviewed in the last ten years. The scientific literature on this subject is then very extensive. Consequently, this section does not aim to be exhaustive. Instead, it intends to give an overview of the main adverse/beneficial health effects associated with infant milk consumption.

Microbiology: type of microorganisms and identification of potential adverse/beneficial health effects

Sources of bacteria in infant milk

Intrinsic contaminants **of powder infant formula:** The first IF commercialised was responsible for many deaths due to microbiological contaminants of the milk or cross-contaminations during preparation. Nowadays, the ready to feed formula are safe because they are sterilized (FAO/WHO, 2004), while contrary to many beliefs, powder infant formula (PIF) might present a risk as it is not a sterile product. In PIF, microorganisms have been identified and classified (Table 3) according to the level of evidence (FAO/WHO, 2004). The level of evidence attributed to each microorganism depends on the causal relation established between PIF contaminated and cases reported of infant illness. The evidence is classified into three classes: clear evidence and causality (Grade A), causality plausible, not yet demonstrated (Grade B) and causality less plausible or not yet demonstrated (Grade C). The most incriminated bacteria are *Cronobacter sakazakii* (also named *Enterobacter sakazakii* until 2008) and *Salmonella* spp. which are also the

only two microorganisms classified with clear evidence and causality. However, some grading C microorganisms have been found in PIF. More precisely, among the 18 alerts recorded on the Rapid Alert System for Food and Feed (European Commission, 2015b) between 1988 and May 2015, nine reported PIF were contaminated by *Cronobacter sakazakii*, four by *Salmonella* spp. and one by *Clostridium botulinum*. In parallel, there were infant botulism cases identified in Europe, seven in France (Brett et al., 2005) and one in UK potentially linked to PIF consumption (King et al., 2010).

Contaminants of infant formula introduced during preparation: The list previously given only takes into account milk supply contamination whereas infants can be infected by cross-contamination occurring during preparation. Indeed, PIF preparation requires different steps with potential cross-contamination and growing phases: water addition, warm-up, storage, bottle and nipple cleaning, etc. Formula milk preparation might be contaminated by extrinsic sources like inappropriate handling or ineffective disinfection of bottle and nipple. The WHO has published a guide on PIF preparation at home (FAO/WHO, 2007a) and in a care settings (FAO/WHO, 2007b) that gives hygiene recommendations. Nevertheless these guidelines are not yet exactly applied and there are a lot of different possible scenarios, highlighting potential different points of contamination and microbial growth (Sani et al., 2013).

Inadequate handling and temperature abuse during storage might expose infants to *Bacillus cereus* toxin (Buchanan and Oni, 2012; Haughton et al., 2010; Kim et al., 2011; Shaheen et al., 2006). In a study, about 5% of bottles were contaminated by *Staphylococcus aureus* just after use (Buchanan and Oni, 2012; Redmond et al., 2009) and other enterobacteriaceae were identified in

rehydrated powder milk (Buchanan and Oni, 2012; Sani et al., 2013). Reusing bottles also constitutes a potential source of contamination due to inefficient cleaning methods, *Staphyloccocus aureus* was detected in 12% of unclean bottles in a UK experiment (Redmond and Griffith, 2009a; Redmond and Griffith, 2009b; Redmond et al., 2009) although this bacterium is classified as C by the FAO/WHO (2004) considering only intrinsic factors.

Water added to powder is a pathway of contamination. Illness due to contaminated water is responsible for about 1.7 million deaths world-wide every year with a higher prevalence in developing countries (Ashbolt, 2004; Marino, 2007; ten Veldhuis et al., 2010). Bacteria incriminated in these illnesses are *Pseudomonas aeruginosa*, *Aeromonas* spp., *Cryptosporidium parvum*, *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli* O:157 (Fawell and Nieuwenhuijsen, 2003). More precisely, in France, hazards incriminated are *Campylobacter* spp., *Cryptosporidum parvum* and norovirus (ANSES, 2013a).

Havelaar *et al*. estimated in 2004 that the burden of disease associated with drinking water due to *Cryptosporidium parvum*, *Escherichia coli* and *Campylobacter* spp. contamination was about 60 years of perfect health lost per 1,000 people per year. (Havelaar and Melse, 2003).

Pre- and pro- biotics in breast milk and powder infant formula: Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Sanders, 2008). On the other hand, a prebiotic is an ingredient, not a microorganism. It induces changes in the gastrointestinal microflora composition and/or activity that confers "benefits upon host wellbeing and health" (Gibson et al., 2004). Both, pre- and pro- biotics (named synbiotics when added conjointly) are recognised as having an impact on the infant

microbiota establishment (also called the gut microbiota). The gut microbiota plays a role in different beneficial health effects highlighted by Pender *et al.* (2006) such as the establishment of a barrier limiting the colonisation by pathogens, the participation in metabolic functions like the fermentation of non-digestible fibers, the salvation of energy as short-chain fatty acids, the production of vitamin K and also the stimulation of the development of the immune system. It is also involved in the reduction of infections by competitive exclusion and production of antimicrobial compounds (Fernandez et al., 2013). Those benefits are mainly associated with the presence in the gut microbiota of probiotic bacteria from species of *Bifidobacteria* spp. and *Lactobacilli* spp.; and their growth are promoted by prebiotics such as galacto-oligosaccharides and fructo-oligosaccharides transmitted through BM.

A clear difference has been shown in the composition of the gut microbiota of formula fed compared with breastfed infants, with a higher level of *Bifidobacteria* spp. and *Lactobacilli* spp. for breastfed infants and of *Clostridium difficile* for formula fed infants (Francino, 2014). The gut microbiota is considered to evolve until the age of three to five years and then would remain relatively stable, susceptible to vary if there is a bacterial infection, antibiotic treatment, surgical, lifestyle or significant change in diet (Rodríguez et al., 2015). During this first critical period the diet is a major factor that regulates its composition, given the opportunity to supplement IF in order to manipulate the microbiota profile. As a result, commercialised IF are more and more supplemented by pre- and/or pro- biotics by industrials intending to promote beneficial intestinal microbiota. However, even though the addition of pre- and/or pro- biotics in PIF has been judged to be not a “safety concern with regard to growth and adverse effects” by the Committee on Nutrition of the ESPGHAN, they could not recommend its supplementation due to a lack of

convincing evidence (Braegger et al., 2011). Moreover, EFSA does not consider pre- or pro-biotics as essential in infant milk composition (EFSA, 2014).

Microorganisms associated with breast milk: BM is not sterile and can be a source of microbiological contaminations (Fernandez et al., 2013) by bacteria, viruses, fungi and parasites, depending on the associated transmission rate. Among them, *Escherichia coli*, and *Staphylococcus aureus* were identified as responsible for several infections (Jones, 2001; May, 2012) as well as *Brucella* (MacDonald, 2006), *Listeria monocytogenes* (Jones, 2001), *Streptococci* (Jones, 2001), *Salmonella* (Jones, 2001) and *Coxiella burnetti* (Jones, 2001).

Potential adverse and beneficial health effects

The main microorganisms associated with infant milk (both rehydrated IF and BM) are listed in Table 4 with the sources of human exposure and potential health effects.

Chemistry: type of chemical hazards and identification of potential adverse health effects

Chemical contaminants of BM and IF have been investigated for decades and a large list of substances has been established (Massart et al., 2008; Sonawane, 1995). However, this list can evolve over time according to regulatory dispositions or changes in human exposure.

Most contaminants are produced by humans as a response to technological purposes (e.g. pesticides for agriculture, food packaging, paintings, fuel car, etc.) and another part results from industrial processes (e.g. waste incineration, cement manufacturing, etc.) (Cattaneo, 2013). Food is one of the main sources of human chemical contaminations (natural or synthetic) through substances found in the diet; they are present in raw materials and/or introduced during production and processing steps. The number of deaths attributable worldwide to diseases due to

chemical exposure was estimated to 4.9 million per year in 2011 which corresponds to a loss of 86 million years of perfect life per year integrating the quality of life lost due to disease (Pruss-Ustun et al., 2011). This estimation was judged as an underestimation (Fulcher and Gibb, 2014) partly due to unknown dose-response relationships.

Sources of infant milk contamination

Breast milk chemical contaminations: Mothers are unavoidably exposed to environmental chemical compounds during basic activities and through different media such as food, water, air, or manufactured products (Cattaneo, 2013). The main routes of exposure are then ingestion, inhalation, and/or cutaneous contact. Some of these contaminants (the lipophilic and persistent ones) can accumulate in their fatty tissues and can be released during secretion of milk which represents one route of excretion for mammals (in addition of urine or faeces) (Marseglia et al., 2014). As a consequence, the levels of some contaminants in human milk are influenced by the number of infant breastfed. BM can also be contaminated as a consequence of other occupational and lifestyle factors (professional activity, drug usage, active or passive smoking, geographical living area, etc.). The temporal evolution of these environmental and lifestyle factors (human exposure is variable across the entire lifetime) also contributes to this complex problem, as emphasised by Solomon *et al.* (2002). Monitoring of historical persistent environmental contaminants (dioxins, PCBs, DDT, etc.) has highlighted a significant decrease in some countries in the past decades, due to regulation decisions banning or regulating them. Conversely, other emerging substances such as food contact materials (bisphenols, phthalates) are presenting a reverse temporal trend.

Infant Formula chemical contaminations: Cow's milk can be basically contaminated in the same way as BM. The observed levels of contamination in cow milk are, however, usually lower than those reported in human milk (VKM, 2013). The existing regulatory dispositions imposed at European levels (and other countries) in the field of food safety, but also the differences in terms of diet and environmental exposure level *versus* volume of milk produced ratio, explains this observation. Cow milk can also contain veterinary drugs administrated to animals. On the other hand, powdered IF is obtained from milk dehydration by a high thermal process. This step first affects milk nutritional properties, destroying vitamins, minerals and amino acids like lysine which are essential for growth and development. These controlled industrial processes ensure reduced levels of most environmental chemical contaminants, even if this step may also produce harmful molecules, like those produced during the Maillard reaction. Then, PIF is rehydrated with water potentially chemically contaminated and served with a bottle and a nipple that could also contaminate milk through chemical migration from materials. Such water contaminants can have severe effects on health. Havelaar *et al.* have estimated that in 2004 the worldwide burden of disease associated with drinking water contaminated with arsenic and bromate at about 64,900 years of life in perfect health lost per 1,000 people per year (Havelaar and Melse, 2003). Finally, the levels of some contaminants may be found more elevated in IF compared to BM. For example, contaminations by arsenic, cadmium, lead and uranium have been assessed to be higher in IF than in BM (Ljung et al., 2011).

Potential adverse health effects

The main substances investigated in the literature are presented in Table 5, with their potential health effects, following three different sections:

- Raw milk contamination concerning both IF and BM that can be contaminated by the same substances.

- IF can be contaminated by the manufacturing process steps and also by water addition in case of rehydration.

- Packaging used can contaminate IF and pumped BM.

Several classes of environmental chemical contaminants have been pointed out with regard to their role in apparition and/or development of various human health outcomes: reproductive and developmental functions, hormono-dependant cancers, immune system, and, metabolic syndrome / obesity. The recent International Agency for Research on Cancer monography on PCBs (IARC, 2015) states that "there is *sufficient evidence* in humans for the carcinogenicity of polychlorinated biphenyls (PCBs). PCBs cause malignant melanoma. Positive associations have been observed for non-Hodgkin lymphoma and cancer of the breast." The link between a perinatal chemical exposure and neurodevelopmental outcomes (IQ, autism, etc.) is also a very strong emerging concern. In spite of extensive scientific literature and existing evidential base, the unequivocal demonstration of causality between chemical exposure and deleterious health impact however still remains extremely challenging at the population scale in humans and animals. The cumulative and/or mixture effect of these substances is also a major issue that remains largely unknown (Pohl et al., 2004).

Another important issue to be considered is whether the relative impact is caused by in-utero versus ex-utero exposure. Indeed in-utero infant exposure to chemical contaminants (i.e. the fetal exposure during the nine months of gestation due to the mother-fetus transfer from cord blood or

amniotic fluid) could have a higher impact on health than ex-utero exposure through several weeks or months of breast or IF based feeding (Pronczuk et al., 2002).

Nutrition: relative health effects of breast milk / infant formula

The approach undertaken in nutrition to identify health effects associated with BM and IF consumption is different from those used in microbiology and chemistry. Indeed, health effects are identified by comparison of health status of breastfed infants with those who are formula fed (epidemiological studies). Generally, in epidemiological studies enable to link specific health effects to diets (e.g. BF vs IF) but they cannot always back to the causing agent in the food element involved in the health effect. The health effects associated with BM compared with IF consumption have been classified into two categories by WHO: short and long term effects. In the short term, BM consumption could reduce the prevalence of gastro intestinal infection and respiratory tract infection (Horta and Victora, 2013) and in the long term it could decrease the prevalence of obesity, blood pressure, total cholesterol, type 2 diabetes and increases infant intellectual quotient (Horta et al., 2007). Recently, the National Institute for Public Health and the Environment of Netherlands (RIVM, 2015) have undertaken a systematic literature review and have integrated the new findings to identify the list of health effects, associated with both diets, and classify them according to their grade of evidence (Table 6). Each grade of evidence depends on the kind of study investigated: the number and type of studies (randomised controlled trial, prospective cohort, case-control studies), result consistency, study quality, biological gradient, experimental evidence, biological plausibility, etc. The evidence is classified in five grades: Convincing, Probable, Possible, Insufficient, No evidence and Conflicting for health

effects investigated in different studies of sufficient power that demonstrated an opposite effect. Main health effects and hypothetical mechanisms were summarised in Table 7.

Finally, BM is also recognized as having immunological properties associated with certain identified components of the milk (VKM, 2013). These properties have not been fully demonstrated yet. An infant's mother transmits immunological components through BM such as: antibodies, lactoferrin, α-lactalbumine, lysozyme, carbohydrate components, fats and fatty acids, cytokines, hormones, growth factors, immune cells, prebiotics and probiotics. It is not transposable to IF consumption because cows' milk composition is different. For example, cow's milk contains ten times less lactoferrin than BM. Some BM's components protect infants against microbial infection:

- Antibodies protect infants from infectious diseases and act in the mucosal microbiota development. Among them immunoglobulin A (IgA) and secretory IgA named SIgA are well known.

- Lactoferin is a bactericidal BM protein which has antiviral effects. This protein survives in the gut and acts as an intestinal barrier.

- α-Lactalbumine is an antimicrobial efficient against bacteria, fungi and also malignant cells.

- Lysosyme is an anti-microbial component against gram positive and negative bacteria and against viruses.

- Carbohydrate components act as competitive components, binding to the mucosal surface that avoids bacteria adhesion. It has been demonstrated to protect infants against *E.coli*, *Campylobacter* spp., *S. pneumonia* and *V. cholerae*.

RISK AND BENEFIT ASSESSMENT OF INFANT MILK CONSUMPTION

A set of beneficial and adverse health effects associated with BM and IF consumption have already been identified in the nutrition, microbiology and chemistry fields. Then, ideally, to estimate the overall impact of the infant diet on health, a multidisciplinary approach comparing all risks and benefits is required. However, so far, such risk-benefit, or risk-risk assessment of infant milk (both BM and IF) has not yet been carried out. Nevertheless, three recent scientific studies have paved the way towards a comprehensive and multidisciplinary assessment.

Presentation of the risk-benefit assessment approach

The risk-benefit assessment (RBA) is the scientific evaluation of known or potential health effects resulting from human exposure to a factor contributing to health effects in food (adapted from the WHO definition of the risk assessment (WHO)). It is one of the three interconnected parts of the risk-benefit analysis that includes also the risk-benefit communication and management. The objective of the risk-benefit management is to set up public health actions which are based on the RBA results, to improve the level of health of the population.

The RBA is not the sum of a risk assessment and a benefit assessment. It is a more complex approach that includes a comparison of the evaluated risks and benefits (Tijhuis et al., 2012). This comparison introduces the notion of scenarios: reference (or baseline) and alternatives. The baseline scenario is the current exposure of consumers or zero exposure. This scenario serves as

a reference for the first RBA. Alternative scenarios are hypothetical consumer exposures which are used to test the levels of exposure that are likely to improve public health. These alternative scenarios are designed to target potential management options. Although management options are designed by managers and not by assessors, the RBA assessment is done in close collaboration between them and the assessment is oriented towards targeted and initially defined management options.

The approach undertaken to compare risks and benefits from different fields is detailed in the review of RBA associated with food consumption (Boué et al., 2015) and generally follows these steps:

- 0 -- Problem definition
- 1 -- Identification of Health Effect Contributing Factor (HECF)
- 2 -- Exposure assessment
- 3 -- Characterisation of HECF
- 4 -- Health impact (HI) characterisation
- 5 -- Harmonisation of HI
- 6 -- Assessment of different scenarios of consumer exposure

The main case study in RBA concerned the assessment of fish consumption with more than 33 papers published on this issue, as detailed in Boué *et al.* (2015). Different beneficial and adverse health effects were associated with fish consumption (e.g. neurodevelopment, cancer, Listeriosis, coronary heart disease, etc.) and have been linked to nutritional (DHA and EPA), chemical (methyl mercury and dioxins) and microbiological (Listeria *monocytogenes*) HECF. The main recommendation resulting from these assessments was to consume two fish dishes per week, including one with fatty fish and alternating fish species, type of production and location of production (ANSES, 2013b; FAO/WHO, 2010). Other assessments were conducted for specific countries (Norway, Netherlands, Poland, France, China, USA, Portugal and Bermuda), different fish species or type of farming. Finally two studies have illustrated how a multidisciplinary and quantitative RBA could be conducted using the Disability Adjusted Life Year (DALY, number of years of life lost in a perfect health state (Gold et al., 2002)) as a single public health indicator. Berjia *et al*. (2012) have performed a RBA in the fields of microbiology and nutrition balancing the beneficial health effect due to omega-3 intake with the risk of listeriosis due to cold-smoked salmon consumption; and Hoekstra *et al*. (2013) in the fields of chemistry and nutrition balancing the risks and benefits of fish consumption, in Denmark and the Netherlands.

Studies reporting risk and/or benefit assessment of infant formula and breast milk consumption

Quantitative microbiological risk assessment of Cronobacter sakazakii in powdered infant formula by WHO and FAO

The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) performed a quantitative microbiological risk assessment of *Cronobacter sakazakii* in powdered infant formula (FAO/WHO, 2004, 2006; Paoli and Hartnett, 2006) and developed an interactive website (FAO/WHO, 2011). Different scenarios of milk preparation and sampling plans were evaluated regarding the potential intrinsic contamination of manufactured PIF with *Cronobacter sakazakii*. The following sets of scenarios of milk preparation were assessed:

- Room ambient temperature during preparation: cool, warm and very warm.
- Water temperature of reconstitution: 10°, 20°, 30°, 40°, 50°, 60° and 70°C.
- Cooling step: by refrigeration at 4°C or holding at room temperature.
- Re-warm action: no re-warm or re-warm with a bottle warmer.
- Feeding duration: short or long period.

The model developed enables an estimate of the risk of illness associated with each scenario of preparation and the potential number of illnesses per million infant per day. The output is expressed as a relative risk which is the risk estimated for a given scenario divided by the risk of a baseline scenario (specified for each five sets of scenario listed above). This expression allows analysis of an increase or decrease of the risk compared with the baseline scenario. The main conclusion was that the risk is lower if milk is reconstituted with water at 60° and 70°C and higher if milk is reconstituted with water at 40° and 50°C. Based on scenario analysis, one of the main potential management options was the recommendation of reconstitution of the milk by

adding water at 60 to 70°C to the powder. This quantitative microbiological assessment represents a key progress toward the comprehensive and multidisciplinary assessment of infant milk consumption. Indeed, the individual risk assessment of *Cronobacter sakazakii* has been undertaken from the 'Identification of Health Effect Contributing Factor' (step 1 in RBA presented before) up to the 'Health impact characterisation' (step 4 in RBA); that gives the substantive information to assess the main concern identified from the microbiology field in this complex issue.

Benefit and risk assessment of breast milk consumption in Norway by VKM

The Norwegian Scientific Committee for Food Safety (VKM) undertook a benefit and risk assessment of BM for infant health in Norway (VKM, 2013). This population is particularly of interest because it is among the highest breastfeeding rates compared with European rates, with about 84% of infants exclusively breastfed at zero month, 10% at six months and 80% partially breastfed at six months. The objective of the study was to assess risks and benefits of BM consumption in Norway considering the current level of contaminants. The alternative of breastfeeding, IF, was discussed for comparison and it was out of scope to perform an integrative RBA of both diets.

The approach carried out in the study was to identify, the main adverse and beneficial health effects of BM consumption and to compare, using health outcomes, the grade of evidence attributing to each health effect. Beneficial health effects associated with breastfeeding were challenged by chemical contamination of BM. For example, nutritional epidemiological studies have highlighted that the improvement of infant neurodevelopment supported by breastfeeding was impaired by persistent organic pollutants (POPs) contaminating BM. A grade of evidence

was associated with each one, based on the WCRF guidance report (2007). Grades of evidence were classified as followed: Grade 1 - Convincing (high), Grade 2 -- Probable (moderate), Grade 3 -- Limited suggestive (low), Grade 4 -- Limited no conclusion (insufficient). Each grade of evidence depends on the studies used: type and number of studies, result homogeneity, study quality, biological gradient, experiment evidence and biological plausibility. For chemicals, the exposure of the Norwegian infants was estimated by calculating the level of contaminants in BM in Norway and the daily intake of BM by infants. This exposure was compared with safety reference values, when available, like tolerable intakes defined by WHO or JECFA and it was combined with studies on the potential health effect to estimate the grade of evidence attributed. Based on this approach, the main findings were:

- **Neurodevelopment**: evidence is convincing that breastfeeding improves the infant neurodevelopment whereas the risk associated with POPs exposure is judged “limited suggestive” and to mercury “limited and no conclusion.”

- **Immune response-associated disease**: evidence is convincing that BM protects infants against infections as long as they are breastfed. The evidence of negative effect on vaccine antibody titer, middle ear infections, thymus weight, asthma and wheezing associated with POPs contaminations is “limited and inconclusive” (based on studies of other countries that are 3 to 100 times more exposed to POPs).

- **Growth, overweight and obesity**: evidence is convincing that BM protects infants against obesity and being overweight in childhood. The evidence of negative effects of

POPs are “limited and inconclusive” (based on studies with populations with higher level of chemical contamination).

VKM concluded that infants currently breastfed (exclusively or partially) in Norway up to six or 12 months of age, have nutritional beneficial health effects that outweigh the risk of impaired neurodevelopment, reduced resistance to infection, overweight and obesity associated with chemical contaminants considering the current level of contaminants (n.b. those considered in the study) in BM. This semi-quantitative risk and benefit assessment constitutes another key progress toward the comprehensive and multidisciplinary assessment of infant milk consumption. It gives a valuable summary of the literature regarding potential risks and benefits associated with both diets mainly from the nutritional and chemical sides. Through this report, a list of Health Effect Contributing Factors associated with the consumption of both infant milk has been identified (step 1 in RBA presented before), the exposure of the Norwegian population has been evaluated (step 2 in RBA) and materials to advance on the characterisation of health effect contributing factors were given (step 3 in RBA); it contributes to the first steps of the RBA of both diets in chemistry and nutrition.

Quantification of health effects of breastfeeding by the RIVM

The National Institute for Public Health and the Environment (RIVM) quantified the relative health effects of breastfeeding both for the mothers and their infants at first in 2005 (Büchner et al., 2007). These relative health effects were based on relative risks and odd ratios estimated through nutritional epidemiological studies comparing the occurrence of various health effects in

the population of breastfed infants versus the formula fed population. It combined at the same time the potential adverse and beneficial health effects.

The current rate of mothers partially breastfeeding for six months or more, with no distinction between exclusive and mixed lactation, is about 35% for the Dutch population. The remaining partially breastfeeding five (3%), four (4%), three (8%), two (9%°) or one month (19%) or did not breastfeed at all (22%) (Büchner et al., 2007). This assessment has been refined in 2007 (Van Rossum et al., 2005) integrating new data and also the health care cost of diseases for different potential policy scenarios depending on the rate of breastfed infants and breastfeeding duration. The economic gain associated with the decrease of diagnostic and treatment of diseases enabled by breastfeeding was balanced with the health gain associated with each scenario. These scenarios were:

- Current situation: Reference scenario
- All infants are formula fed during six months
- All infants are breastfed during six months
- All infants are breastfed zero month longer than the current situation
- Infants breastfeeding less than three months are breastfeed up to three months
- Etc.

To compare these scenarios together and integrate different health effects, the incidence of each disease was converted into the same indicator DALY. The output of this model represents the

overall burden of disease. The best scenario in terms of health and cost saved was the third one, *i.e.* all infants are breastfed during six months. This scenario was associated with 28 DALYs saved/year per 1,000 newborns and 205 euros gained per newborn, representing 50 million euros saved on health care costs annually; this result integrates mother and infant health effects. This gain is mainly associated with the reduction of the incidence of infants' asthma and mothers' rheumatic arthritis.

All the results presented above were obtained by data gathering, statistical analysis and modelling. This approach enables to rank different management options by comparing health effects; it enables also to estimate the health gain expected per euro spent for each intervention. This comparison is made possible because risks and benefits were converted into the same public health measure, specifically DALY. This indicator is valuable for policy maker to compare different interventions, to support preventive measures and to set policy objectives. This is illustrated in the RIVM report (Büchner et al., 2007) with the successful implementation of the "Masterplan" in the Netherlands. This plan was implemented in 2002 to extend the duration of breastfeeding with the certification of hospitals that implement the "Ten steps to successful breastfeeding" established by WHO and UNICEF (1989), the training of medical staff and the development of a communication plan. Five years later, the duration of breastfeeding has notably increased and a gain of 0.002 DALY and 20 euros per newborn were estimated. The new objective of the second phase of the Masterplan was to reach 85% of mothers initiating breastfeeding with 60% continuing until one month, and 25% until six months. This would result in a gain of 0.006 DALY and 50 euros per newborn. This quantitative risk and benefit assessment also constitutes a key progress toward the comprehensive and multidisciplinary

assessment of infant milk consumption. RIVM performed the individual risk-benefit assessment of BM consumption, from the nutritional side, until the harmonisation of health impacts (step 5 in RBA presented before); it gives results, data and methodological considerations from the nutritional field for the assessment of the BM diet.

In light of these three main studies and the current advances published in the literature, a multidisciplinary assessment of both infant diets integrating adverse and beneficial health effects would be required: an integrated risk-benefit assessment. The use of a public health measure such as DALY would allow a comparison of different potential management options, targeted by scenario analysis, and thus give a decision tool for policy makers.

Current gaps in the risk-benefit assessment of infant formula and breast milk consumption

Despite the studies described above on PIF (FAO/WHO, 2004, 2006, 2011; Paoli and Hartnett, 2006) and breastfeeding nutritional values (Büchner et al., 2007; Van Rossum et al., 2005), there are still health effects which have not yet been quantitatively assessed. For example, in microbiology the effect of different potential contaminants, and route of contamination, remains unquantified. The intrinsic contamination of PIF by *Salmonella* spp. could be of interest because this microorganism was judged responsible with a clear evidence and causality for infant illness following formula milk consumption (FAO/WHO, 2004). Although the intrinsic contamination of IF is limited thanks to the regulation, the rate of compliance with regulatory levels depends also on sampling plans. Nevertheless there is at present no study assessing the impact of regulatory levels and sampling plan on infant illness due to formula contaminated consumption. Other sources of contamination than the milk itself have not been considered either. Indeed there

are no assessments of potential cross-contaminations during milk preparation while there are rehydrated formula contaminated with different bacteria such as *Bacillus cereus* (Buchanan and Oni, 2012; Haughton et al., 2010; Kim et al., 2011; Shaheen et al., 2006), and even BM with *Staphylococcus aureus* for example. In addition, the water used to rehydrate the powder formula is also a potential source of contamination not yet assessed. All these contaminations might evolve according to different scenarios of preparation. Regarding the chemical component, the current major concerns are referred to the endocrine disrupting effects following a perinatal exposure. In line with the Developmental Origin of Health and Disease (DOHaD) and early programming concepts, this challenge is imposing new integrated approaches and new metrics for investigating and assessing the "real" overall and long term impact consecutive to the early consumption of milk (BM or IF) during the first months of life. Finally, in nutrition the main health effects were quantified but not compared with microbiological and chemical contaminants whereas nutritional factors mainly led to beneficial health effects or a decrease of risks and the others to an increase of risks. An overall RBA approach is necessary to quantify the health effect of BM and IF consumption integrating microbiological, nutritional and chemical factors.

Beside these scientific gaps, it would also be interesting to investigate furthermore the consequence of current diets and potential alternatives in infant milk feeding by scenario analysis, as encouraged in risk-benefit assessment, (see RBA methodology, steps 1 to 6, above). This comprehensive approach, from hazard identification to DALY calculation, would be valuable when assessing infant milk consumption risk and benefit. This will enable further progress on the evaluation of potential management options such as recommendations by the policy makers on the "ideal" duration of exclusive breastfeeding and the food intake for lactating

mothers (depending on diet, country, etc.), a guidance on practices of milk preparation and packaging choice (bottle, nipple, etc.) or regulation of final manufactory controls of PIF production (sampling plan, frequency, method, criteria, etc.).

CONCLUSION

Infant food intake during the first months of life, whether it be breast milk or infant formula, affects their health status during the short and long term. Different beneficial and adverse health effects have been linked to both diets in the fields of nutrition, chemistry and microbiology. The main risks and benefits have been assessed individually and even partially compared. However, an integrative and quantitative approach would be required to compare all risks and benefits and to assess different scenarios of consumption and milk preparation. In addition, other complex issues remain unassessed, like guidance on practices of milk preparation and packaging choice or regulation of final manufactory controls of PIF production for chemical and microbiological hazards. The use of a public health measure such as DALY or other quantitative metrics to compare different outcomes related to different scientific fields appears to be valuable to compare results from the three fields and also, to enable policy makers to compare different potential interventions or, to underpin preventive actions.

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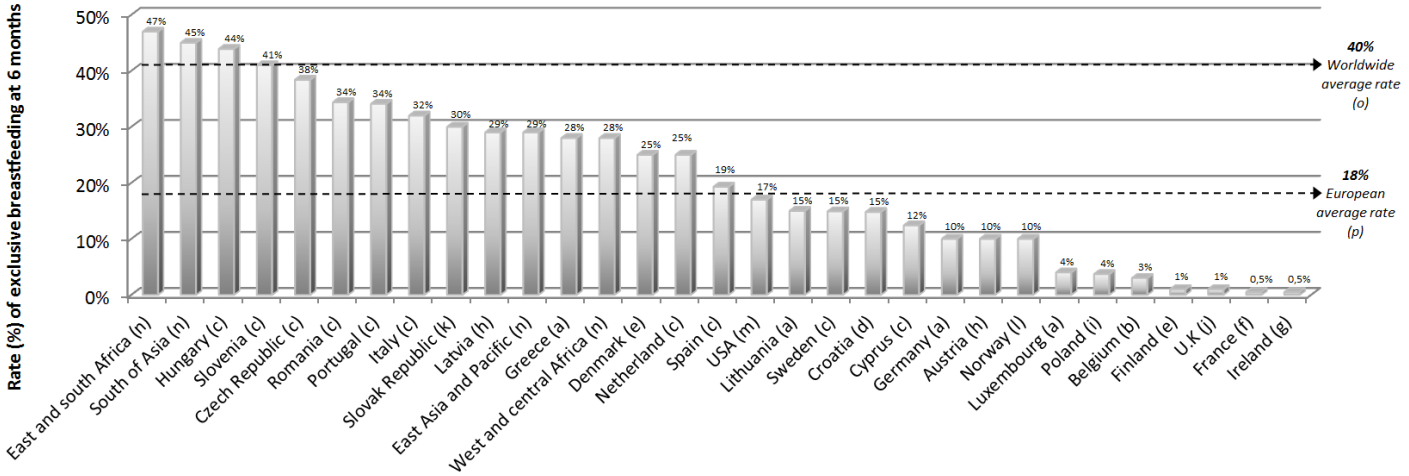

Figure 1 Worldwide exclusive breastfeeding rates at 6 months

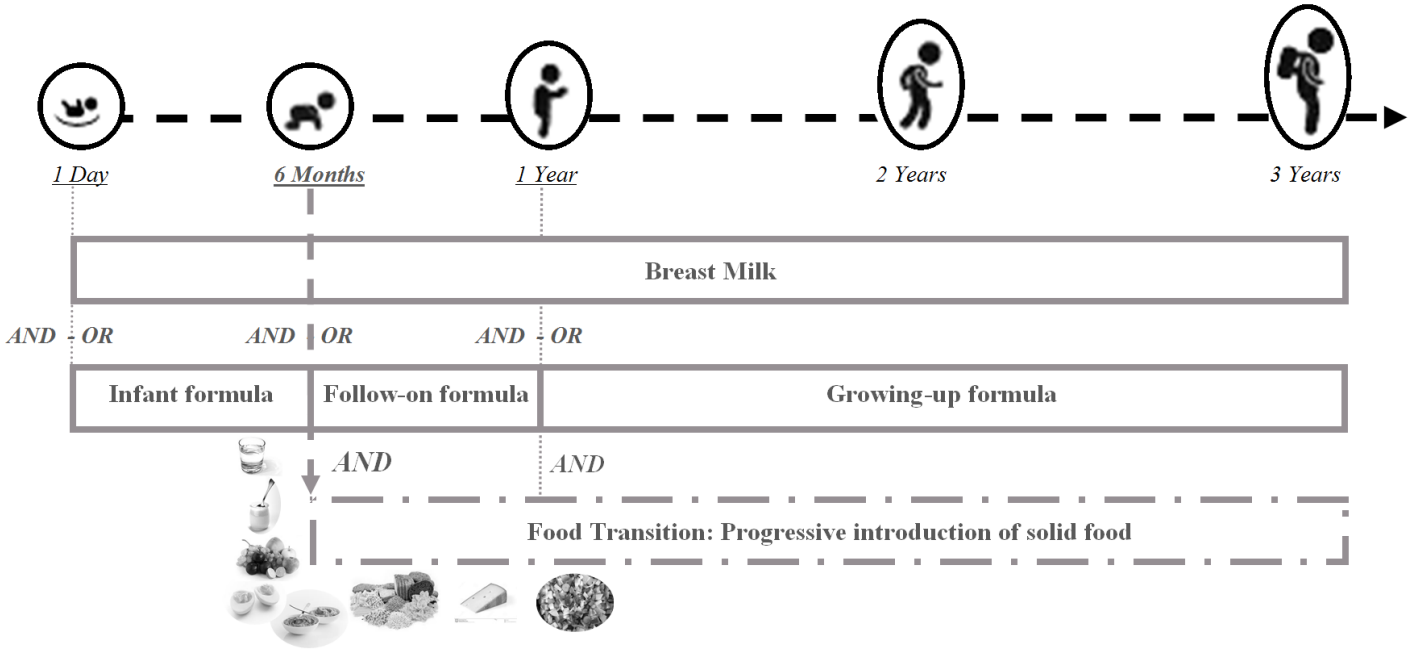

Figure 2 Infant food diet from 0 to 3 years (Based on French nutritional recommendations (Inpes, 2004))

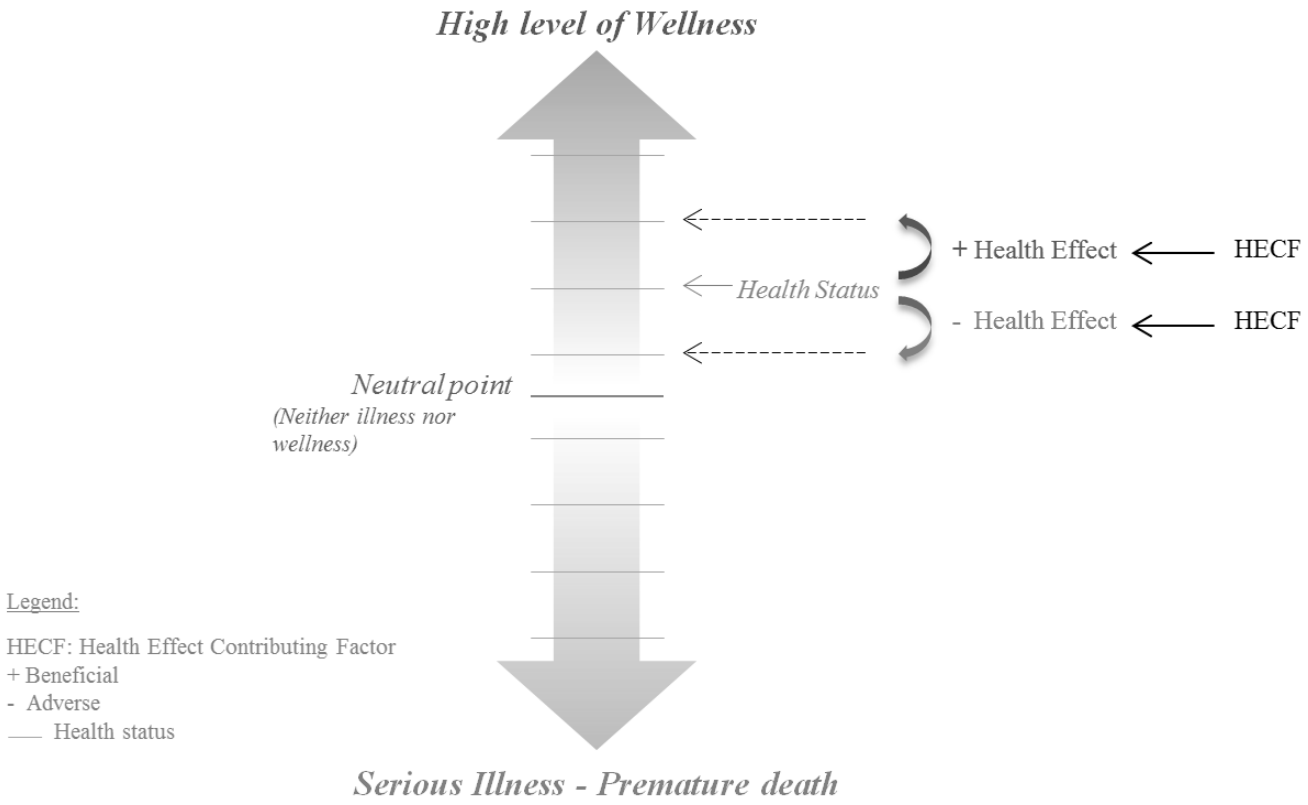

Figure 3 Schematic representation of the Illness-Wellness scale, with health status and HECF, adapted from Travis et al. (1988)*Rates were extracted from different sources: a (IPA, 2003), b (Robert et al., 2014), c (OECD, 2014), d (IBFAN, 2014), e (Elmadfa, 2009), f (Salanave et al., 2014), g (Black, 2012), h (WHO, 2014b), i (Magdalena, 2013), j (HSCIC, 2012), k (Cattaneo et al., 2005), l (VKM, 2013), m (National Research Council, 2004), n (Cai et al., 2012), o (WHO, 2014a) and p (WCRF, 2009).*