Chronic diseases associated with meat consumption: epidemiology and mechanisms

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Summary

Meat is an integral part of the diet of many people. The consumption of meat has tremendously contributed to human evolution, and its huge variability within and between populations reflects economic development. It is a valuable source of energy and essential nutrients. Nevertheless, over the last decades a considerable number of epidemiological studies have reported positive associations between high red meat and especially processed meat consumption and all-cause mortality and the risk to develop colorectal cancer, cardiovascular disease and diabetes, whereas these associations are not present with white meat (poultry) consumption. The largest body of evidence is available for colorectal cancer. It should be mentioned that the increases in relative risk of chronic diseases with high red meat and/or processed meat consumption are rather low, and that more mechanistic studies are needed to prove causality. Compounds and processes that may be involved in the negative effects of meat consumption on human health can be divided in compounds intrinsic to meat (e.g. heme-Fe) and compounds formed during processing or preparation of meat prior to consumption (e.g. heterocyclic amines, polycyclic aromatic hydrocarbons), or in the gastrointestinal tract during digestion (e.g. trimethylamine-N-oxide), or both prior to or during gastrointestinal digestion (e.g. *N*-nitroso-compounds, oxidation products). The nature, formation and potential role of the compounds considered at present most involved are discussed in this chapter, as well as possible mitigation strategies. Very likely, there is no single causal factor responsible for each of the associations due to the interaction of meat with other foods and with the microbiome in the gastrointestinal tract. It is therefore advocated that dietary patterns rather than foods should be investigated when considering nutritional prevention of chronic diseases. Meats consumed as part of balanced diets with preference for unprocessed and minimally processed meats and in line with nutritional guidelines do not pose a health risk.

Keywords: chronic diseases, heme iron, N-nitroso compounds, oxidation products, heterocyclic amines and polycyclic aromatic hydrocarbons

1. Introduction

Meat is a valuable source of energy, high-quality protein and essential micronutrients in the human diet (Givens, 2005; Williamson *et al.*, 2005), and meat consumption has played a very significant role in human evolution (Leroy and Praet, 2015). However, meat consumption

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is highly variable among and within populations, with a 10-fold variation between high-consuming and low-consuming populations, hence the impact thereof on human health is also diverse (FAO, 2009). It is forecasted that the demand for meat will continue to grow strongly in developing countries in the coming decades, whereas in high income countries meat consumption may stagnate or even decline in future (FAO, 2009). The current high levels of consumption of meat in many countries have been criticized for contributing to the burden of chronic diseases (WCRF/AICR, 2007), to competition between feed and food resources and to climate change and other environmental problems (Foley *et al.*, 2011). These concerns apply more to red and processed meat than to white meat, and lowering the consumption of meat in general, but particularly red and processed meat is now encouraged in high-consuming countries for these reasons. It is clear that meat consumption is under transition and the future role of meat in society will be influenced by economic, environmental, ethical and health issues. However, notwithstanding large variability in the types of meat and levels of consumption, meat is an integral part of the diet of many people and has always played and still plays a biocultural role in almost all societies (Leroy and Praet, 2015). It therefore elicits more than any other food strong emotional responses. This probably also explains why the current debate on the benefits versus the health risks of meat consumption is often polarized and irrational.

The present chapter will focus on the latest epidemiological data linking the high consumption of meat to all-cause mortality and several chronic diseases. The increased risk for developing several chronic diseases with high consumption of red meat and processed meat is discussed and put in perspective. The distinction between red and white meat relies on the higher myoglobin and heme-Fe content in red meat – directly related to the colour of meat, but this difference is not always clear and can be debated (Demeyer *et al.*, 2016; Keeton and Dikeman, 2017). In most studies, red meat refers to unprocessed mammalian muscle meat, e.g. beef, pork, lamb, etc., including minced or frozen meat. It is usually consumed cooked. Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats contain pork or beef, but may also contain other red meats, poultry, offal (e.g. liver), or meat by-products such as blood. The current poor definition and classification of fresh and processed meats hampers a more detailed evaluation of their health effects beyond the broad distinction between red and white and between unprocessed and processed meat.

In addition to the body of observational epidemiological studies that have emerged over the years, many other types of studies, e.g. food analytical, animal toxicological, human intervention studies, etc., have been conducted to better understand the underlying mechanisms of both the positive and the potential negative health effects of meat consumption. Whereas there are still many unresolved questions in this regard, it has now become clear that compounds that may be involved do not only originate from the meat itself or its processing or preparation prior to consumption, but the digestive process and the interaction of meat with other foods and the microbiome in the gastrointestinal tract may play a crucial role that needs further study. The most widely supported hypotheses so far are briefly discussed in this chapter, as well as possible mitigation strategies.

Reducing the consumption of meat for environmental or health reasons may pose nutritional challenges for some key nutrients in specific population groups, e.g. inadequate intake of vitamin B12, protein intake below requirements for the elderly, low Zn intake in relation to child growth (Millward and Garnett, 2010). Nutrient deficiency risks resulting from low meat consumption or vegetarian/vegan diets are not considered in this chapter.

2. Human health risks associated with high meat consumption

During the last decades, a considerable number of observational epidemiological studies have reported a positive association between high red meat and processed meat consumption and the risk to develop several chronic diseases, in apparent contradiction to the valuable nutritional composition of meat. High versus low red and/or processed meat consumption has been linked in meta-analyses to an increased risk of all-cause mortality (Rohrmann and Linseisen, 2016), colorectal cancer (Aune *et al.*, 2013; Bouvard *et al.*, 2015; Chan *et al.*, 2011), coronary heart disease (Micha *et al.*, 2010; updated by Micha *et al.*, 2012) and type 2 diabetes (Micha *et al.*, 2012; Pan *et al.*, 2011) (Table 1). The increase in relative risk (RR) per unit change in consumption is comparable for the mentioned chronic diseases and for all-cause mortality, except for no effect of red meat consumption on cardiovascular disease in contrast to processed meat. The strength of the evidence from these observational epidemiological studies is always higher for processed meat than for red meat (note the difference in unit in Table 1). Among the several diseases, the body of information for a potential health-compromising effect of red or processed meat consumption is greatest for colorectal cancer, mainly because of a larger number of studies. In contrast, no negative associations between white meat consumption, mainly derived from poultry, and chronic diseases have ever been reported in the scientific literature, and some studies rather claim a protective effect (Marangoni *et al.*, 2015).

In prospective cohort or case-control observational studies, associations are investigated by comparing the frequency of a disease in a group of individuals with high versus a group with low meat consumption (typically the highest versus the lowest quartile). Because chronic diseases are multifactorial, a correct assessment of the effect of a single factor, in

Table 1. Significant increases in relative risks (RR) from meta-analyses for developing chronic diseases with consumption of red meat and processed meat.

	Red meat (RR per 100 g/d)	Processed meat (RR per 50 g/d)	Reference
Colorectal cancer	+ 17%	+ 18%	Chan *et al.*, 2011
	+ 27%	+ 29%	Aune *et al.*, 2013
Coronary heart disease	NS[1]	+ 42%	Micha *et al.*, 2010; 2012
Diabetes mellitus type 2	+ 19%	+ 51%	Pan *et al.*, 2011
	+ 19%	+ 51%	Micha *et al.*, 2012

[1] NS = not significant.

this case meat consumption, is dependent on correction for possible confounding factors by using appropriate statistical models. It is well known that low-meat eaters have in general a healthier lifestyle, for instance by consuming less alcoholic beverages, being no smokers, or performing more exercise; factors that all contribute to a lower risk of certain chronic diseases (Klurfeld, 2015; Rohrmann and Linseisen, 2016). The outcome of independent studies is variable, with several studies showing no significant effect due to lack of statistical power or simply because there is no effect. Meta-analyses are therefore conducted in which all valid independent studies available up to a certain moment are grouped and analysed jointly, thereby increasing the power. The above-mentioned relationships in Table 1 are based on meta-analyses encompassing a large number of participants of different ethnicities and dietary patterns. E.g. for colorectal cancer, Chan *et al.* (2011) reported in their meta-analysis of ten cohort studies a statistically significant dose–response relationship, with a 17% increase (RR 1.17, 95% CI 1.05-1.31) per 100 g per day of red meat and an 18% increase (RR 1.18, 95% CI 1.10-1.28) per 50 g per day of processed meat (Figure 1). These RR values should be interpreted against a cumulative incidence risk of colorectal cancer until the age of 75 y of approximately 3.5% in Europe (across sexes) and a corresponding cumulative mortality risk of 1.4% (IARC, 2012) meaning that per 100 g per day increase in red meat consumption or per 50 g per day increase in processed meat consumption, the absolute incidence risk increases to approximately 4.1% and the mortality risk to approximately 1.65%, *ceteris paribus*. These units of consumption are large compared to the average consumption of red or processed meat, and should not erroneously be interpreted as threshold values or maximum recommended intake values. Hence, it is also clear that these small increases in RR values have little relevance at the individual level, considering the differences in genetic predisposition that exist and the many other dietary and lifestyle factors that are involved, whereas the public health impact at the population level deserves attention as discussed later.

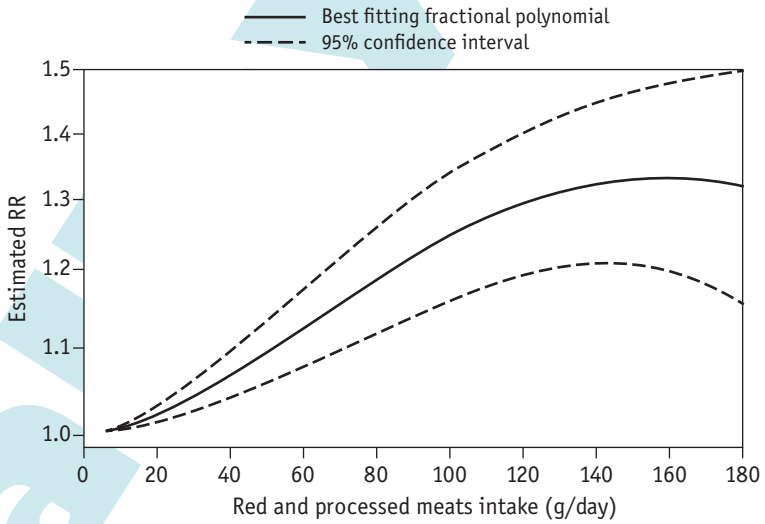

Figure 1. Non-linear dose-response meta-analysis of red and processed meats consumption and the relative risks (RR) of colorectal cancer (Chan et al.*, 2011).*

Because of the increasing number of reports appearing in the scientific literature, a Working Group of the International Agency for Research on Cancer (IARC) convened in October 2015 to conduct a profound hazard analysis of the carcinogenicity of red and processed meat consumption. According to the evaluation principles and procedures of IARC, processed meat consumption was classified as 'carcinogenic to humans' (Group 1) and red meat consumption as 'probably carcinogenic to humans' (Group 2A) with respect to colorectal cancer only, based on the strength of evidence (Bouvard *et al.*, 2015; IARC Monograph Volume 114). Minor associations were revealed for a few other cancer types. A positive association with the consumption of processed meat was found for stomach cancer. Consumption of red meat was also positively associated with pancreatic and with prostate cancer (Bouvard *et al.*, 2015). Putting processed meat consumption at the same level as plutonium or tobacco smoke, the outcome of this hazard identification has frequently been misinterpreted and has received polarized and scientific incorrect statements in the media (Leroy *et al.*, 2018). It has to be realized that this evaluation was not a full risk assessment, nor was it intended to make dietary recommendations (Bouvard *et al.*, 2015; De Smet and Vossen, 2016). The task of the working group consisted of a critical review of the pertinent scientific literature and evaluation of the weight of the evidence that red meat and processed meat consumption can alter the risk of cancer in humans. The strength of the scientific evidence was thus evaluated, irrespective of the level of the risk. An agent is considered a disease hazard if it is capable of causing the disease under some circumstances. Risk measures the probability that the disease will occur and should also consider dose and exposure, i.e. the frequency and amounts of consumption of red and processed meat in the present case.

The IARC working group on colorectal cancer reported that positive associations were seen with high versus low consumption of red meat data in 7 of 14 cohort studies and in 7 of 15 informative case-control studies. Positive associations of colorectal cancer with consumption of processed meat were reported in 12 of 18 relevant cohort studies, and in 6 of 9 informative case-control studies (Bouvard *et al.*, 2015). The IARC working group concluded from the epidemiological studies that there is sufficient evidence in human beings for the carcinogenicity of the consumption of processed meat. For red meat, the working group concluded that the evidence was limited since no clear association was seen in several of the high quality studies and residual confounding could not be excluded with the same degree of confidence (Bouvard *et al.*, 2015). In conclusion, there is a body of epidemiological evidence for an association between high consumption of red and/or processed meat and several chronic diseases, but the increases in risk are low to modest and should be cautiously interpreted vis-à-vis other confounding dietary and lifestyle factors. In addition, classifying the carcinogenicity of meat only on the strength of the evidence without proper consideration of the context and likelihood in which cancer may be caused in people has been questioned (Boobis *et al.*, 2016).

To support a causal role of meat consumption in the aetiology of chronic diseases, other types of studies, e.g. animal studies or human intervention studies, are required for unravelling mechanistic pathways responsible for the disease-inducing characteristics of meat. However, randomized controlled trials comparing different diets or foods are difficult if not impossible to conduct if the outcome is a hard endpoint such as cancer or diabetes, requiring long periods of follow-up. Using markers as intermediate endpoints, e.g. blood cholesterol levels or faecal

water DNA adducts, is also disputable because the link between a marker and the disease or mortality is often not unique (Rohrmann and Linseisen, 2016). Anyway, mechanistic studies do provide important information and insight into the associations, and do allow developing mitigation strategies in case specific associations appear to be robust and of global health concern.

With respect to cardiovascular disease, the effects of saturated fat have for a long time been regarded as the main driver for explaining a possible role of (ruminant) meat consumption. Indeed, animal fats and in particular ruminant fats are generally more saturated than most vegetable oils and fats, although their fatty acid composition is diverse and modifiable (De Smet and Vossen, 2016). However, the modest contribution of lean meat to the total intake of saturated fatty acids is not compatible with a potential detrimental effect. Mente *et al.* (2009) used the Bradford Hill guidelines to derive a causation score based on 4 criteria (strength, consistency, temporality, and coherence) for dietary exposures in relation to coronary heart disease. After a systematic literature search, these authors concluded that there are valid associations (4 criteria fulfilled) from cohort studies for several protective factors (e.g. intake of vegetables, a Mediterranean dietary pattern) and harmful factors (e.g. trans-fatty acids), but insufficient evidence (⩽2 criteria fulfilled) is available for saturated and polyunsaturated fatty acids, total fat, meat and several other factors. In randomized trials, only a Mediterranean dietary pattern was related to coronary heart disease. This shows the relevance of using different types of studies for complex diseases, and that it now has become clear that the long held and widespread belief of the detrimental effect of saturated fat and by extension animal fats is no longer justified. Some alternative mechanisms to explain the epidemiological association between processed meat consumption and cardiovascular disease are given later on.

With respect to colorectal cancer, there is more convincing mechanistic insight, but many questions remain at the same time unresolved. Several theories have been advanced, including the catalytic role of heme-Fe on the formation of N-nitroso-compounds (NOCs) and lipid peroxidation products in the gastro-intestinal tract, and the presence of heterocyclic amines and polycyclic aromatic hydrocarbons due to improper cooking methods (Bastide *et al.*, 2016; Bouvard *et al.*, 2015; Demeyer *et al.*, 2016; Hammerling *et al.*, 2015). These will be discussed in the next sections. It is unlikely that a single causal factor or compound can be identified due to the interaction of meat with other foods and with the microbiome in the gastro-intestinal tract. As an example, it was recently shown that the association between heme-Fe and colorectal adenoma risk depends on the total dietary antioxidant capacity, emphasising the need for assessing dietary patterns rather than foods or single nutrients when considering nutritional prevention of chronic diseases (Bastide *et al.*, 2016).

A major challenge is to translate observational and interventional epidemiological data into dietary recommendations. An important question in this respect is then what the potential is for primary prevention of a chronic disease through limiting the intake of red meat and processed meat in high-meat consumers. At a population level in different countries, preventability estimates for red and processed meat intake and colorectal cancer were estimated between 5 and 25% (Chan *et al.*, 2011; Whiteman and Wilson, 2016). Also, 8.2% of cardiometabolic deaths in the USA were related to high processed meat consumption, with in

comparison 9.5% to high sodium intake, and 7.4% to high consumption of sugar-sweetened beverages (Micha *et al.*, 2017). Hence, although the RR values may not be meaningful at the individual level, they have implications at the population level and may be relevant from a public health perspective. The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) had already indicated in 2007 and confirmed in 2011 that red meat and processed meat are to be considered as convincing factors for an increased risk of colorectal cancer. It was subsequently recommended not to exceed the consumption of 500 g of red meat per week at the level of the individual, in order to achieve a public health goal for a population average consumption of less than 300 g per week. For processed meat, the recommendation was even to avoid its consumption. These recommendations have received widespread attention and have induced changes in dietary guidelines formulated by health and nutrition bodies in several European countries (Leroy *et al.*, 2018). It should be mentioned that the threshold of 500 g per week of red meat is well above the level of consumption of many meat eaters around the world. It remains to be seen if these recommendations will induce dietary shifts, particularly in the high-meat consumers target group, and if this will reduce the incidence of chronic diseases. An important question in this respect is the nutritional quality of meat replacers and the resultant overall diet. It is obvious that simply omitting or largely reducing meat from the habitual diet may result in nutritional disorders in vulnerable population groups and will likely not be adopted because of the culinary role of meat and the unsatisfactory sensory properties of many meatless meals. On the other hand, in addition to health benefits, concerns on the environmental sustainability of mass livestock production urge for a transition toward less meat and more plant-based diets (Springmann *et al.*, 2016).

3. Chemical hazards in fresh and processed meats in relation to chronic diseases

As discussed in the previous section, high consumption of red meat and/or processed meat is associated with an increased risk to develop several chronic diseases, as found from several in large-scale epidemiological studies. Various underlying mechanisms have been proposed to explain these associations, but are still a matter of debate. There is probably no single causal factor responsible for each of the associations, but several factors may be interfering and interacting simultaneously (Demeyer *et al.*, 2016). Compounds and processes that may be involved in the negative effects of meat consumption on human health can be divided in: (1) compounds intrinsic to meat (e.g. heme-Fe, *N*-glycolylneuraminic acid); (2) compounds formed during processing or preparation prior to consumption (e.g. heterocyclic amines, polycyclic aromatic hydrocarbons); (3) compounds formed in the gastrointestinal tract during digestion (e.g. trimethylamine-*N*-oxide); or (4) compounds that can be formed either prior to or during gastrointestinal digestion (e.g. NOCs, oxidation products).

Several hypotheses that were formulated in the past for these associations have now been abandoned, because the compounds formed are not specific to meat and may occur with consumption of other foods also. E.g. the high protein and saturated fat intake that may result from high meat consumption have been extensively forwarded as causes of negative human health effects, however the evidence for these hypotheses is very weak because they are not unique to red or processed meat. These mechanisms will therefore not be

discussed here. Other food toxicants that have caused incidents as a result of meat scandals consumption in the past and have been linked to human health, e.g. prions as the cause of transmissible spongiform encephalopathies (TSEs), dioxins/PCB's, residues of exogenous hormones or growth promoters, will also not be discussed here. Mostly, these chemical toxicants originating from the environment or veterinary and phytosanitary practices, are found at only trace levels in meat and meat products (Andrée *et al.*, 2010; Domingo, 2017; Engel *et al.*, 2015), and cannot solely explain the risk of chronic diseases associated with the consumption of meat.

3.1 Heme iron

Heme is a complex of an iron atom in the centre of a porphyrin ring (Figure 2). The iron directly attaches to a histidine residue of myoglobin, the pigment responsible for the typical red colour of meat. Meat shows a large variability in heme-Fe concentration, depending on the animal species and muscle type. Muscles from, e.g. chicken and rabbit are considered as white meat, with rather low concentrations of heme-Fe (range 0.12-0.29 mg/100 g). Pork and beef are both considered as red meat, although large differences in heme-Fe concentrations are found between pork (0.20-0.32 mg/100 g) and beef (1.68-2.11 mg/kg). In chicken, the breast muscle has lower amounts of heme-Fe (0.12 mg/100 g) compared to the lower part of the leg (0.29 mg/100 g) (Lombardi-Boccia *et al.*, 2002), hence average levels are not much lower than in pork.

Heme-Fe in meat is suggested to be the main factor explaining the epidemiological link between red meat and various chronic diseases, since its dietary intake was associated with an increased risk to develop colorectal cancer (Bastide *et al.*, 2011), cardiovascular disease (Fang *et al.*, 2015) and diabetes type 2 (Zhao *et al.*, 2012). Despite this epidemiological evidence, the exact mechanisms by which heme-Fe intake contributes to the onset and/or development of these diseases remain to be elucidated. Nevertheless, different hypotheses

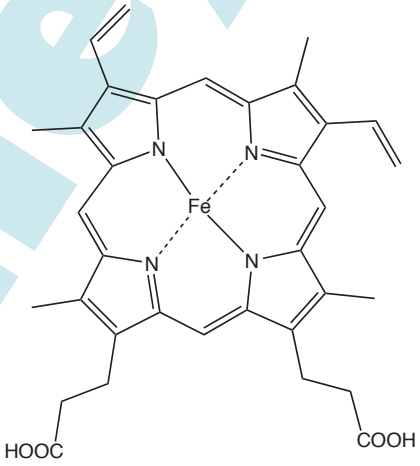

Figure 2. Chemical structure of heme-Fe (Bastide et al.*, 2011).*

have been proposed. Heme-Fe induces cytotoxicity in the faecal water of rats, whereas its constituents, porphyrin and ferric iron, do not (Sesink *et al.*, 1999). Bastide *et al.* (2011) suggested that the toxic effects of heme-Fe can be explained by its catalysing effect on the formation of toxic lipid oxidation products (LOPs) and NOCs. The formation and activity of these compounds will be discussed more in detail in the following sections. Another hypothesis states that the effects of heme-Fe may be mediated by changes in the colonic microbial composition and metabolic activity. Heme-Fe in the diet of mice induced a shift in the colonic microbial community, among which increased abundances of bacteria belonging to the phylum of the *Bacteroidetes* and of the *Proteobacteria,* whereas the phylum of the *Firmicutes* was decreased (Constante *et al.*, 2017; Ijssennagger *et al.*, 2012). Ijssennagger *et al.* (2015) showed that the heme-Fe induced hyperproliferation of the colonic mucosa of rats was mediated by the gut microbiota, since the effect disappeared when the heme diet was supplemented with antibiotics, despite remaining luminal cytotoxicity. The gut microbiota is now considered to be an important metabolic 'organ' due to its important impacts on health and disease (O'Hara and Shanahan, 2006). For example, it may be involved in the development of chronic diseases such as colorectal cancer (Louis *et al.*, 2014), cardiovascular disease (Tang and Hazen, 2014) and diabetes type 2 (Tilg and Moschen, 2014). Therefore, heme-Fe induced changes in the colonic microbial composition and metabolic activity may have important consequences on intestinal and systemic health including low-grade inflammation, and this microbiome interaction warrants further research.

3.2 *N*-nitroso-compounds

NOCs are a group of compounds referring to all substances with *N*-nitroso groups, including *N*-nitrosamines and *N*-nitrosamides (Figure 3). This group of compounds is easily formed by interaction of a secondary amino compound with a nitrosating agent. Interest in these compounds vastly increased following a case in the early 1960s in Norway, where a high mortality was observed in cattle, sheep and goats, following the consumption of rather high amounts of herring which originated from one factory (Koppang, 1964). This herring was supposedly treated with high doses of sodium nitrite, after which formed *N*-nitrosodimethylamine (NDMA) induced hepatic necrosis in acute cases, and hepatic fibrosis in more chronic cases. Since then, many studies demonstrated the carcinogenic potential of various *N*-nitrosamines. In 1978, the IARC recognised NDMA and *N*-nitrosodiethylamine (NDEA) as 'probably carcinogenic for humans', *N*-nitrosopiperidine (NPIP) and *N*-nitrosopyrrolidine (NPYR) as 'possibly carcinogenic for humans', whereas *N*-nitrosohydroxyproline (NHPRO) and *N*-nitrosoproline (NPRO) were 'not classifiable' (IARC, 1978).

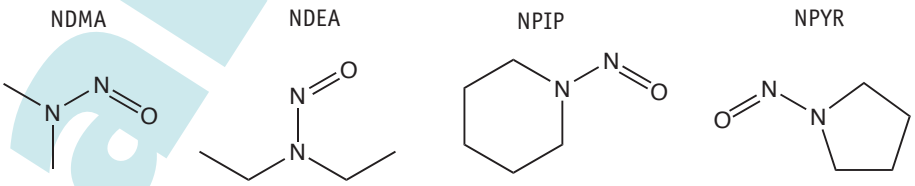

Figure 3. Chemical structure of various N-nitrosamines.

NDMA was detected in various foods and beverages including beers, smoked fish and nitrite-cured meats (Lijinsky, 1999). In meat processing, curing of meat with nitrite salt is a common procedure. Nitrite curing results in the typical desirable pink colour and nitrite odour and flavour of the meat product. Furthermore, it acts as an antioxidant and inhibits the outgrowth of *Clostridium botulinum* spores. On the other hand, the addition of nitrite may induce the formation of nitrosamines, therefore leading to strict regulations considering the use of nitrite in meat processing. In the EU, in general 150 mg nitrite/kg are allowed to be added for all meat products plus 150 mg nitrate/kg for non-heated meat products (Honikel, 2008). In cooked pork sausages, NPIP, NHPRO, NPRO, and other non-volatile nitrosamines were formed following the addition of nitrite (range 0-350 mg/kg), whereas concentrations of NDMA and NDEA remained low (Herrmann *et al.*, 2015). The same study showed that erythorbic acid inhibited this formation, whereas the formation of NPIP was stimulated when black pepper was added to the sausage. The content of nitrosamines was quantified in nearly 400 Estonian commercial fresh meats and meat products (Yurchenko and Mölder, 2007). Nitrosamines were not detected in fresh meat and varying amounts were detected in processed meats, with the highest levels in fried meat products, followed by grilled meat, smoked pork and ham.

Next to the exogenous exposure of humans to NOCs in foods, its formation can also occur endogenously during gastrointestinal digestion. The research group of the late Sheila Bingham (University of Cambridge, UK) conducted various human intervention studies attributing increased nitrosation reactions during digestion to dietary heme-Fe, resulting in the increased formation of NOCs. In human volunteers, a dose-responsive association was found between red meat (beef and pork) consumption (range 0-420 g/d) and faecal concentrations of 'apparent total *N*-nitroso-compounds' (ATNC), whereas this was not found when consuming white meat (chicken, turkey or cod) (Bingham *et al.*, 2002). These ATNC however do not specifically measure toxic NOCs but also include nitrosyl-heme-Fe, dinitrosyl iron complexes and nitrosothiols (Figure 4). A later study confirmed that it was indeed heme-Fe, not protein nor inorganic iron that was responsible for the endogenous intestinal *N*-nitrosation arising from red meat (Cross *et al.*, 2003).

Later, these faecal ATNC correlated well with the percentage of human colonic exfoliated cells staining positive for the NOC-derivative DNA adduct, O^6-carboxymethylguanine (O^6CMG) (Lewin *et al.*, 2006). The DNA adduct O^6-methyldeoxyguanosine (O^6MeG) was also increased in colonocytes of mice on a high red meat diets compared to mice on a casein diet (Winter *et al.*, 2011). The latter research group also demonstrated increased rectal O^6MeG adduct levels in a human intervention study following the consumption of 300 g cooked red meat per day for 4 weeks, compared to before the intervention period (Le Leu *et al.*, 2015).

These NOCs were also measured as ATNC by the group of Corpet and Pierre (INRA, Toulouse, France) in a series of rat feeding trials. They demonstrated that rats on a diet of 'oxidized, cooked nitrite-cured red meat' had more faecal ATNC compared to rats fed a diet of 'anaerobic stored, cooked, nitrite-cured red meat', or 'oxidized, cooked, red meat without nitrite', or 'anaerobic stored raw red meat without nitrite' (Santarelli *et al.*, 2008). This study also reported that this increased faecal ATNC concentration was accompanied with an increase of pre-neoplastic lesions in the colon, more specifically mucin depleted foci (MDF). Another study of the same group showed that nitrite and nitrate in drinking water (0.17 g/l nitrite and

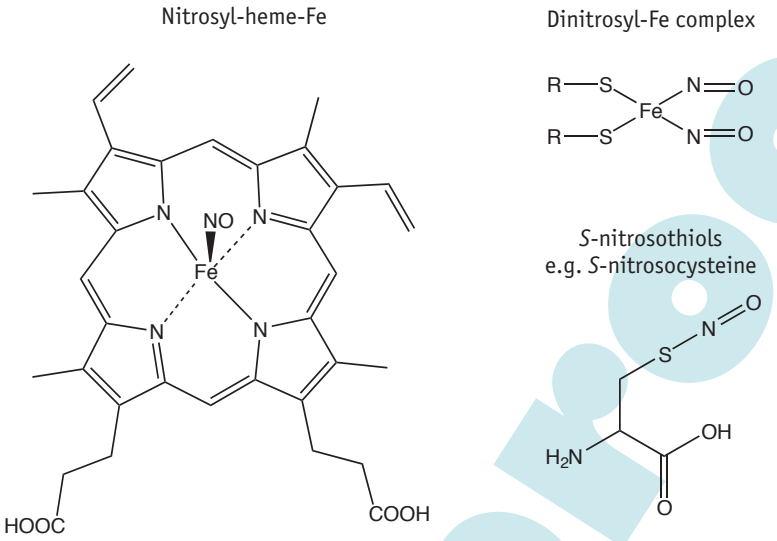

Figure 4. Chemical structure of nitrosyl-heme-Fe, dinitrosyl-Fe complexes and S-nitrosothiols (Hogg, 2007).

0.23 g/l nitrate) increased ATNC formation in rats on a diet containing 1% haemoglobin, but the authors argued that their concentration and nature (mainly nitrosyl-heme-iron) would probably not be associated with an increased risk to develop colorectal cancer (Chenni *et al.*, 2013).

3.3 Oxidation products

Meat is a complex medium containing fat, protein, and free and bound iron, all of which participate in oxidation processes. During the self-maintaining Fenton reaction, hydrogen peroxide (H_2O_2) catalyses the oxidation of Fe^{2+} to Fe^{3+} (Equation 1) and its reduction back to Fe^{2+} (Equation 2), producing a hydroxyl radical (HO•) and a hydroperoxyl radical (HOO•), respectively:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO\bullet + OH^- \quad (1)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO\bullet + H^+ \quad (2)$$

These reactive oxygen species (ROS) are very unstable and, in the absence of suitable antioxidants, initiate a chain reaction with polyunsaturated fatty acids (PUFAs) to generate LOPs (Figure 5), or with protein to generate protein oxidation products (POPs) (Figure 6). The most described LOP in meat is malondialdehyde (MDA), which can be derived from both n-3 and n-6 PUFAs in meat, whereas 4-hydroxy-nonenal (4-HNE) and hexanal are generated during the oxidation of n-6 PUFAs, and 4-hydroxy-hexenal (4-HHE) is generated during the oxidation of n-3 PUFAs. These ROS and various LOPs may contribute to the oxidation

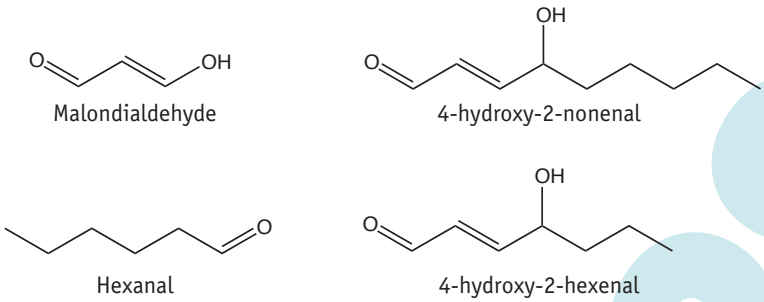

Figure 5. Chemical structure of some lipid oxidation products.

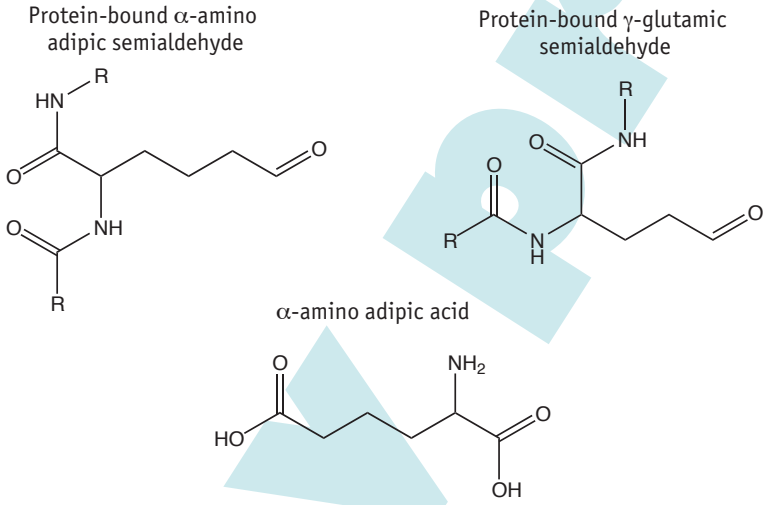

Figure 6. Chemical structure of the most important meat protein oxidation products.

of proteins, leading to the formation of protein carbonyl compounds. The specific protein carbonyls α-amino adipic semialdehyde (AAS) and γ-glutamic semialdehyde are oxidation products of lysine, and of arginine and proline, respectively. Subsequently, AAS can oxidize further into α-amino adipic acid (AAA), which is a more stable end-product (Estévez, 2011).

These oxidative reactions in meat already occur during refrigerated storage and cooking (Min and Ahn, 2005), and continue during gastrointestinal digestion (Van Hecke *et al.*, 2017a). For example, it was shown that saliva can play a dual role in oxidation, and can exert pro-oxidant, antioxidant, or no effect on oxidation of heated turkey muscle, depending on salivary concentrations of peroxidase, nitrite and thiocyanate (Gorelik *et al.*, 2007). Also, the stomach is described to be an excellent environment for enhanced lipid oxidation of meat due to its low pH and dissolved oxygen content (Kanner and Lapidot, 2001). Following the consumption of turkey meat, postprandial plasma MDA concentrations show temporarily increased levels in rats and humans (Gorelik *et al.*, 2008a,b). Also urinary metabolites of

4-HNE can be measured in humans following the consumption of blood sausage (Pierre *et al.*, 2006). These studies indicate absorption of LOPs into the bloodstream, after which they may exert various (patho-)physiological effects. For example, MDA and 4-HNE are known to oxidize low density lipoproteins (LDL), and increased ox-LDL levels were observed in humans following consumption of a turkey meal (Gorelik *et al.*, 2013). These ox-LDLs promote the onset and/or progression of atherosclerosis, since they induce the formation of macrophage-derived foam cells, leading to endothelial dysfunction and inflammation (Mitra *et al.*, 2011).

Additional pathways may contribute to the (patho-)physiological effects of LOPs. For example, some LOPs are known to form adducts with DNA, and hence may exert genotoxic effects. Following reaction with DNA, MDA can form the specific DNA adduct pyrimido[1,2-α]purine-10(3H)-one-2′-deoxyribose (M1dG), whereas 4-HNE can form various DNA adducts among which 1,N^6-etheno-2′-deoxyadenosine. More details regarding the chemistry and formation of these DNA adducts can be found in comprehensive reviews by Nair *et al.* (2007) and Hemeryck and Vanhaecke (2016). Furthermore, LOPs may evoke an inflammatory reaction, as was observed in mice following the consumption of a diet high in oxidized PUFAs compared to non-oxidized PUFAs (Awada *et al.*, 2012). However, studies on the effect of meat consumption on inflammation are inconsistent. Epidemiological data show that high consumption of red meat is associated with increased plasma concentrations of C-reactive protein, suggesting low-grade inflammation (Azadbakht and Esmaillzadeh, 2009; Ley *et al.*, 2014; Montonen *et al.*, 2013). In contrast, controlled intervention studies show stimulating (Arya *et al.*, 2010), inhibiting, or no effects (Nuora *et al.*, 2015) on inflammation following the consumption of various meats. Also, 4-HNE was observed to form adducts with insulin, resulting in decreased hypoglycaemic activities of insulin in mice (Pillon *et al.*, 2011).

Most research on oxidation so far has focused on oxidized lipids, and less attention has been given to oxidized protein. However, POPs may also exert important biological effects (Estévez and Luna, 2016). Protein oxidation in meat depends among others on the muscle type and various meat processing techniques (Estévez, 2011; Soladoye *et al.*, 2015), and was described to increase during simulated gastrointestinal digestion (Van Hecke *et al.*, 2014). Dietary AAA was previously described to accumulate in the pancreas and fat of mice, which was associated with higher fasting plasma insulin concentrations, and found to be a suitable biomarker for the risk to develop diabetes mellitus type 2 (Wang *et al.*, 2013). Studies by Li *et al.* (2014, 2017) reported induced hepatic and renal fibrosis, renal dysfunctioning and inflammation in rats following a diet high in oxidized vs non-oxidized casein, or high in oxidized tyrosine vs non-oxidized tyrosine. However, no studies are yet available reporting on (patho-)physiological effects of oxidized meat protein specifically.

Finally, it should be highlighted that lipid and protein oxidation does not only occur during red meat digestion. Recent reports showed that also fish, which is generally considered to be a healthy food, also generates various LOPs during its digestion. For example, digestion of salmon and herring generated considerable amounts of MDA and 4-HHE, whereas 4-HNE remained low (Larsson *et al.*, 2016). Steppeler *et al.* (2016) even reported higher MDA amounts in salmon digests compared to digests from chicken, pork and beef. Therefore, lipid oxidation alone cannot exclusively explain the adverse effects of high red meat consumption on health, but may contribute in other pathways. For example, oxidative reactions can activate

nitrosamines in processed meat, resulting into the formation of α-hydroxy nitrosamines, which spontaneously forms an alkyl diazonium ion and a free alkyl carbocation, able to alkylate DNA (Grisham *et al.*, 2000). More research is however required to elucidate the relationship between dietary oxidation products and health.

3.4 Heterocyclic amines and polycyclic aromatic hydrocarbons

Meat subjected to intense heating procedures may generate genotoxic heterocyclic amines (HCAs) (Figure 7) and polycyclic aromatic hydrocarbons (PAHs) (Figure 8). HCAs are formed at high temperatures during the Maillard reaction between creatine, creatinine, amino acids and sugars. PAHs are environmental contaminants and are formed during incomplete combustion of organic materials. When fat drips into an open fire during meat grilling, the flames contain various PAHs which adhere to the surface of the meat (Cross and Sinha, 2004). Within the group of HCAs, many compounds are classified as 'probably carcinogenic' (e.g. IQ or 2-amino-3-methylimidazo[4,5-f]quinolone), or 'possibly carcinogenic' (e.g. PhIP or 2-amino-1-methyl-6-phenylimidazo[4,5-β]pyridine; MeIQx or 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline) (IARC, 1993). Also within the group of PAHs, many compounds are classified as 'carcinogenic to humans' (e.g. BaP or benzo[α]pyrene), or 'possibly carcinogenic' (e.g. benz[α] anthracene, benzo[β]fluoranthene) (IARC, 2010).

The amount of HCAs in meat depends on its culinary preparation. For example, concentrations of MeIQx increase in steak and hamburgers along with their doneness level. In steak, PhIP was the most abundant HCA, whereas PhIP was only present in very well done grilled, barbecued, or pan-fried hamburgers, and not in oven-broiled hamburgers (Sinha *et al.*, 1998b). Large differences were found in the concentrations of PhIP and MeIQx between different kinds of processed pork, depending on the type of product and its heating procedure. The amounts measured in processed pork were generally much lower compared to those found in beef

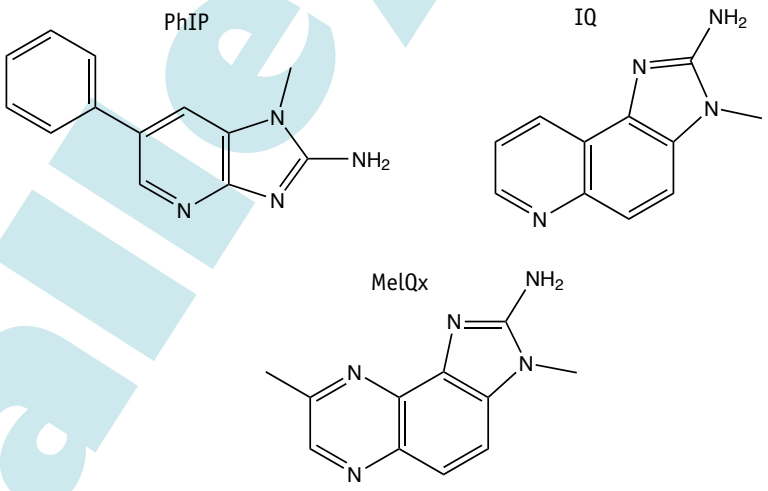

Figure 7. Chemical structure of some common heterocyclic amines (Sugimura et al.*, 2004).*

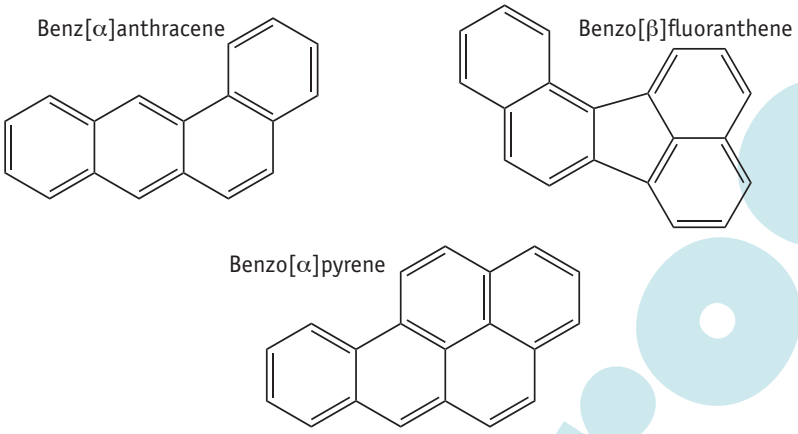

Figure 8. Chemical structure of some common polycyclic aromatic hydrocarbons (Phillips, 1999).

and chicken (Sinha *et al.*, 1998a). The highest levels of BaP in meat have been found in very well done grilled/barbecued steaks, hamburgers, or chicken with skin, whereas their concentrations were lower when the meat was only grilled/barbecued to well done, and low in all broiled or pan-fried meats, regardless of doneness level (Kazerouni *et al.*, 2001).

HCAs and PAHs can be absorbed and become systemically available. Urinary excretion of MeIQx and PhIP or their metabolites was reported in healthy humans following consumption of beef cooked on a griddle hot plate (Lynch *et al.*, 1992), char-broiled beef or pan-fried beef (Strickland *et al.*, 2002). Also urinary BaP metabolites were found in human volunteers following the consumption of charcoal-broiled hamburgers (Maanen *et al.*, 1994). Before they can react with DNA to generate DNA adducts (Kang *et al.*, 1995; Rothman *et al.*, 1990), HCAs and PAHs require activation to their carcinogenic form. This activation can occur either enzymatically (e.g. through cytochrome P450) (Shimada and Fujii-Kuriyama, 2004), or through oxidation (Dix and Marnett, 1983).

One of the weaknesses of this mechanism for explaining the association between red meat consumption and chronic diseases, is that a large proportion of the intake of BaP stems from the consumption of bread, cereals and grains (estimated at 29% of total intake), compared to an estimated intake of 21% through barbequed/grilled meat, and the consumption of vegetables and fruits also contributes to its intake (Kazerouni *et al.*, 2001). Also, as reviewed by Santarelli *et al.* (2008), chicken meat is a major contributor to HCA intake but its consumption is not associated with an increased risk to develop colorectal cancer. Furthermore, the doses of HCA that leads to colorectal cancer in rodents and monkeys is 1,000 to 100,000 times higher than the concentrations to which humans are exposed through the consumption of cooked meats.

3.5 Carnitine and trimethylamine-*N*-oxide

Carnitine is a quaternary ammonium compound that is especially present in high concentrations in red meat. Its concentration in beef amounts to 65-87.5 mg/100 g, whereas its concentration is lower in white meat such as chicken meat (circa 10 mg/100 g), followed by fish and seafood (range 0.7-5.8 mg/100 g), and concentrations are mostly very low in vegetables and fruits (Demarquoy *et al.*, 2004). In 2013, Koeth *et al.* published a widely cited research paper proposing a mechanism in which colonic microbiota are able to metabolize carnitine into trimethylamine (TMA), which is then, upon absorption, further metabolized by hepatic flavin monooxygenases (FMO) into trimethylamine-*N*-oxide (TMAO), to which the authors attributed atherosclerotic properties (Figure 9). The same study also showed that omnivorous humans produced more TMAO upon consumption of carnitine compared to vegetarians, and this difference was attributed to differences in the microbial communities. Recently, TMAO was found to be increased in patients with chronic kidney disease (Tang *et al.*, 2015) and diabetes mellitus type 2 (Shan *et al.*, 2017), and was associated with disease severity and survival of patients with heart disease (Trøseid *et al.*, 2015). In mice, a diet with 0.12% TMAO led to progressive renal tubulo-interstitial fibrosis and dysfunction (Tang *et al.*, 2015), whereas both promoting (Wang *et al.*, 2011) as well as inhibiting effects (Collins *et al.*, 2016) of TMAO on atherosclerosis have been reported.

The involvement of TMAO in the relationship between red meat consumption and chronic diseases is however not without criticism, and some important inconsistencies remain to be elucidated, issues which were reviewed by Cho and Caudill (2017). For example, TMAO has a biological role as an osmolyte in deep-sea fish in order to adapt to osmotic and hydrostatic stress. Compared to beef, consumption of fish (cod) resulted in 50-fold higher concentrations of TMAO and 10-fold higher TMA concentrations in plasma of healthy men, and similar changes were observed in the urine (Cho *et al.*, 2017). It remains unclear however if TMAO is a causal agent or just a biomarker for an underlying phenomenon, since circulating TMAO can be confounded by many factors, among which the kidney function and colon microbial composition (Cho and Caudill, 2017).

3.6 *N*-glycolylneuraminic acid

The association between high red meat consumption and the risk to develop various types of cancer was recently proposed to be explained by an unusual mechanism involving the non-human sialic acid *N*-glycolylneuraminic acid (Neu5Gc) (Samraj *et al.*, 2015). This hypothesis involves a mutation in the human gene encoding for an enzyme involved in the formation of

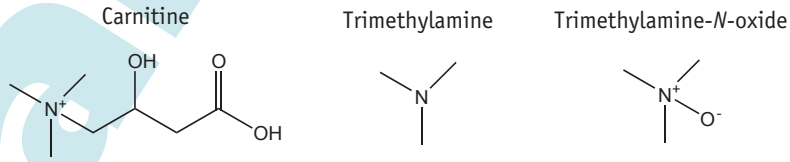

*Figure 9. Chemical structure of carnitine, trimethylamine and trimethylamine-*N*-oxide.*

Neu5GC. Therefore, modern humans lack the ability to express Neu5GC on the cell surface, in contrast to the great apes and other mammals (Varki, 2001). Especially beef contains high levels of Neu5GC (25-231 µg/g), lower amounts are measured in milk and milk products (0-43 µg/g) and it is not detected in white meat, fish and seafood (with the exception of caviar), or in vegetables and fruit (Samraj *et al.*, 2015). According to this theory, dietary Neu5GC is incorporated in human tissues, followed by inflammatory reactions due to interactions of this antigen with circulating anti-Neu5GC antibodies. When genetically modified mice deficient in Neu5GC were fed Neu5GC, followed by a challenge with anti-Neu5GC antibodies, systemic inflammation was observed, which increased the incidence (5-fold) of hepatocellular cancer on the long-term (Samraj *et al.*, 2015). In contrast, iso-energetic replacement of carbohydrates with lean red meat (circa 200 g/day) for 8 weeks in hypertensive human volunteers, decreased leukocyte counts and amyloid A protein as measurement of inflammation compared to before the intervention. In addition, C-reactive protein tended to be lower in these red meat eating subjects, compared to control subjects without dietary intervention (Hodgson *et al.*, 2007). Also rather contrasting to this theory is the fact that unprocessed red meat consumption does not increase the relative risk to develop coronary heart disease in large-scale epidemiologic studies (Micha *et al.*, 2010, 2012), despite inflammation is a risk factor for this disease (Danesh *et al.*, 2000). Finally, pork contains considerably lower Neu5Gc concentrations (range 7-40 µg/g) compared to beef (range 25-231 µg/g) (Samraj *et al.*, 2015), which is not compatible with the higher relative disease risks associated with predominantly pork-based processed meat compared to unprocessed red meat.

4. Mitigation strategies

Appropriate meat processing and culinary preparation techniques can reduce the formation and/or activity of some of the previously discussed toxic compounds. Also, by combining the consumption of meat with healthy food items such as present in a balanced meal, the formation and activity of some compounds can be mitigated. Therefore, both the meat processing industry and the consumer can contribute to a lower intake of some of these compounds.

To limit the formation of nitrosamines, the use of nitrite in meat processing is strictly regulated, allowing a maximum of 150 mg/kg ingoing sodium nitrite in general for most meat products (Honikel, 2008). Also, the simultaneous addition of ascorbate, which is now common practice, or erythorbic acid, limits but does not completely inhibit the formation of nitrosamines (Herrmann *et al.*, 2015). Next to the desirable nitrite flavours and odours and antibacterial effect, nitrite-curing results in improved oxidative stability of meat, which is also maintained during its gastrointestinal digestion (Van Hecke *et al.*, 2014). The current trend to lower ingoing and residual nitrite levels in meat products poses therefore a risk towards maintaining product quality, in particular oxidative stability during storage (Sebranek and Bacus, 2007). However, ingoing doses of 40-50 ppm nitrite are considered to be sufficient for obtaining acceptable cured meat colour and flavour. Whereas higher doses might be more effective for the antioxidant function, it must be said that the role of nitrite as antioxidant is not as unique as the colour and flavour effect and alternative antioxidants can be used in meat processing. Many meat researchers currently investigate the replacement

or reduction of nitrite in meat products by the addition of various antioxidants, natural plant extracts, herbs or spices. Addition of herbs and spices during meat processing resulted in a large reduction in lipid oxidation during the digestion of a high-fat beef product (Van Hecke *et al.*, 2017b). Addition of a spice mixture in beef hamburgers also reduced MDA in the meat, and in plasma and urine of human volunteers following its consumption (Li *et al.*, 2010). Turmeric, rosemary (Puangsombat *et al.*, 2011) and garlic (Jung *et al.*, 2010) inhibited PhIP formation in cooked beef. However, the addition of some spices may also have some undesirable opposite effects. For example, despite black pepper inhibited PhIP formation during frying of high-fat meatballs (Oz and Kaya, 2011), and moderately decreased lipid oxidation during gastrointestinal digestion of cooked high-fat beef (Van Hecke *et al.*, 2017b), it also stimulated the formation of NPIP in cooked cured sausages (Hermann *et al.*, 2015). Therefore, it should be realized that some spices may also provide precursors for nitrosamine formation, and inhibition of one type of toxic compound is not necessarily accompanied with reduction of another type of toxic compound.

The consumer itself can limit its intake of toxic compounds by applying appropriate culinary practices. For example, wrapping meat in aluminium foil during grilling completely prevented BaP formation (Farhadian *et al.*, 2011). The latter study also showed that pre-heating the meat by steam cooking or microwave, thereby decreasing the grilling time, also completely inhibited BaP formation. Pan-frying and deep-frying of dry-cured sausages generates more *N*-nitrosamines than boiling or micro-waving (Li *et al.*, 2012). Also, the addition of herbs and spices as a seasoning following the heating procedure of the meat reduced lipid oxidation during gastrointestinal digestion, however to a lower extent as compared to addition during meat processing (Van Hecke *et al.*, 2017b).

Research has shown that the formation and activity of various toxic compounds generated during red and/or processed meat digestion can be mitigated by other food items. For example, calcium and vitamin E were described to reduce faecal ATNC, lipid oxidation and the pre-neoplastic lesion mucin-depleted foci during the consumption of cured meats by rats and humans (Pierre *et al.*, 2013). Various fibres (Hur *et al.*, 2009), antioxidants (Van Hecke *et al.*, 2016), herbs and spices (Van Hecke *et al.*, 2017b), vegetables and fruits (Kanner *et al.*, 2017), red wine (Gorelik *et al.*, 2008a) and coffee polyphenols (Sirota *et al.*, 2013) reduced lipid oxidation during the digestion of various meat products. Red wine polyphenols also inhibited postprandial MDA-LDL modification, induced by turkey consumption in human volunteers (Gorelik *et al.*, 2013). Also, butyrylated high-amylose maize starch prevented an increase in the rectal DNA adduct O^6MeG, and attenuated the increase in epithelial proliferation following a high red meat diet in humans (Le Leu *et al.*, 2015).

5. Conclusions

5.1 What has been achieved?

Meat is an integral part of the diet of many people and contributes safely to fulfilling our dietary needs. However, high consumption of processed meat and to a lesser extent red meat has been linked to an increased risk for developing several chronic diseases. These

associations are never found with white meat. The observational epidemiology underlying these associations is well established, yet does not proof causality. Several chemical hazards that are present in meat prior to consumption or formed during gastrointestinal digestion, and that may be involved in the potential negative health impact of high red or processed meat consumption, have been defined. Their occurrence and routes of formation are rather well documented. At several points, the meat industry has taken action to reduce the level of harmful compounds.

5.2 What has been neglected?

The poor definition and classification of fresh and processed meats in many epidemiological studies has hampered accurate estimates of intake data for these foods. Consequently, it is at present not possible to identify which processed meats are more at risk than others among the large heterogeneity in this food category. In the mechanistic studies investigating potential causal factors, interactions of meat compounds with other foods in meals or diets and additivity of different causal factors has received little attention so far. In addition, some hypotheses have not yet been fully explored. More emphasis should also have been given to explaining the science to laymen to avoid confusion.

5.3 What needs to be done?

There is a need for epidemiological studies on dietary patterns containing fresh and processed meats in interaction with other foods. Concomitantly, the effect of the gut microbiome needs to be established. Mitigation strategies to reduce potential harmful compounds should be further developed at the level of meat processing and preparation in the kitchen, as well as at the level of meal and diet composition. Finally, when it comes to food-based dietary guidelines, a proper assessment of the benefits and risks of both meat and meat replacers should be made before formulating guidelines on nutritional prevention of chronic diseases.

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