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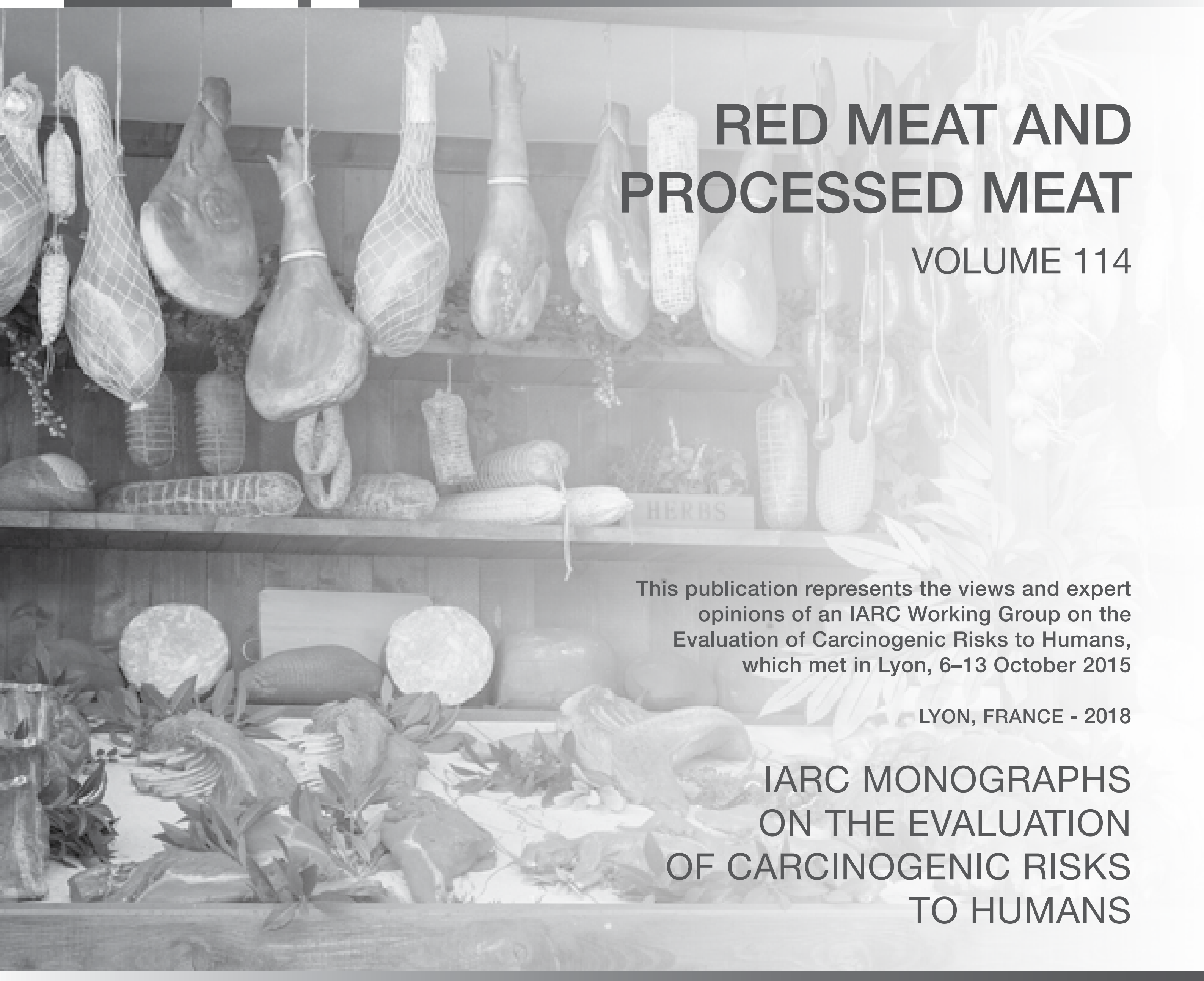

RED MEAT AND PROCESSED MEAT

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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

This *Monograph* focuses on the consumption of red meat and processed meat. Red meat refers to fresh unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb, mutton, horse, or goat meat), which may be minced or frozen, and is usually consumed cooked. Offal (e.g. liver, kidney, heart, thymus, or brain) when consumed as such is considered to be a specific food category in food consumption surveys; however, in some epidemiological studies, offal has been reported together with red meat. Processed meat refers to any meat that has been transformed through one or several of the following processes: salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats are made from pork or beef, but may also include other meats such as poultry and/or offal, or meat by-products such as blood.

Red meat contains proteins of high biological value and important micronutrients, including B vitamins, iron (both free iron and haem), and zinc. The fat content of red meat can vary across species and breeds. For example, the fat content of the longissimus dorsi muscle of cattle ranges from 0.6% to 16% weight per weight. The fat content can also vary depending on the animal's age, sex, breed, and diet, as well as the cut of the meat. Meat may contain residues of veterinary drugs or contaminating environmental pollutants. Meat processing, such as curing and smoking can result in the formation of carcinogenic chemicals, including *N*-nitroso compounds (NOCs) and polycyclic aromatic hydrocarbons (PAHs). The cooking of meat improves the digestibility, palatability, and organoleptic quality of meat; however, it can also produce carcinogens, including heterocyclic aromatic amines (HAAs) and PAHs. The amounts of these chemicals formed in cooked red meat can vary by more than a hundredfold, depending on the kind of meat and the method of cooking (temperature, time, and heating source). High-temperature cooking by frying, grilling, or barbecuing generally produces the highest amounts of these chemicals.

In most countries for which data are available, the consumption of red meat for consumers only is around 50–100 g/day, and high consumption is more than 200 g/day. For processed meat, the mean consumption in most countries for which data are available is also about 50–100 g/day, and high consumption is more than 200 g/day. The main source of variability between countries is the percentage of consumers, which ranges from less than 5% to 100% for red meat and from 2% to 65% for processed meat. The consumption of red meat and processed meat is lower in some countries (e.g. Japan and Thailand), despite a percentage of consumers of around 90%, due to frequent substitution of meat with fish and other seafood. In developing countries for which consumption data are available (e.g. Bangladesh, Burkina Faso, and Uganda), the percentage of consumers of red meat is less than 10%, but mean consumption is up to 90 g/day.

The tools used to assess usual dietary intake in epidemiological studies include food frequency questionnaires (FFQs), which can be calibrated and/or validated using more robust assessment methods, such as a diet history or multiple 24-hour recalls. FFQs are designed to assess dietary habits and consumption of foods, including meat and specific products containing meat; in some cases, additional information on meat cooking practices is included to provide inferences about exposure to HAAs, PAHs, or NOCs.

Biomarkers for some of these chemicals have been established, but are not exclusively attributed to the consumption of cooked meat, since PAHs, HAAs, and NOCs are also pollutants present in tobacco or tobacco smoke, and in the environment. Urinary metabolites, protein or DNA adducts, or residues of some chemicals in hair are biomarkers of exposure to HAAs, PAHs, or NOCs. Recent metabolomics approaches using plasma and urine have been implemented to assess meat consumption. The use of long-term stable biomarkers in epidemiological studies would strengthen data on exposure and health risks derived from inferences about dietary exposures obtained from FFQs.

5.2 Human carcinogenicity data

5.2.1 Cancer of the colorectum

The association between cancer of the colorectum and consumption of red and processed meat has been examined in numerous cohort and case–control studies conducted in countries in Europe, North America, South America, Asia, and Australia. There was heterogeneity across studies regarding the study design and instruments used to assess red and processed meat intake. In particular, different definitions of red meat and processed meat were used across studies, with an important source of variability being the inclusion or not of processed meat together with (unprocessed) red meat in the total red meat variables. A subset of studies (about 20) also presented data on cooking methods or preferences.

In evaluating the evidence from the epidemiological studies, the Working Group placed the most weight on the cohort studies in the general population with quantitative data on the consumption of red and processed meat derived through validated dietary questionnaires. In addition, information from the most informative case–control studies complemented the evaluation.

For both types of epidemiological studies, the Working Group judged that the most informative studies were those with a wider range of variation of meat intake, clear definition of meat variables, sufficient number of cases to investigate cancer by location within the colorectum, and adequate control for potential confounders in the statistical analysis, specifically by adjusting for age, sex, total caloric intake, and other potential confounders, such as body mass index (BMI), alcohol drinking, tobacco smoking, and several lifestyle and dietary variables. For cohort studies, those considered to be highly informative had virtually complete case ascertainment and a low number of participants lost to follow-up. For case–control studies, more weight was given to the studies that used population-based approaches for case identification and control selection.

Close to 20 large, high-quality cohort studies were considered in the evaluation, with the results of some studies reported in several publications. The follow-ups of these studies extended from as early as the 1990s until the 2010s. A large number of case–control studies (approximately 150), conducted across the world were reviewed for this evaluation. These studies captured regions of the world with a wide range of intake of red meat and processed meat.

The Working Group considered separately the data on red meat, processed meat, as well as red and processed meat combined into a single group. Fourteen cohort studies investigated the association between consumption of red meat and risk of cancer of the colorectum. Positive associations between high consumption of red meat and cancer of the colorectum were observed in seven studies, including most of the larger studies: the European Prospective Investigation into Cancer and Nutrition (EPIC) study in 10 European countries, the Swedish Mammography Cohort (SMC), and the Melbourne Collaborative Cohort Study (MCCS).

The Working Group judged that only about 10% of all reviewed case–control studies were informative for the evaluation of the consumption of red meat. Seven studies (about half of those judged informative) showed positive associations between cancer of the colorectum and consumption of one of the red meat items investigated. In several other case–control studies, although no association with consumption of red meat was observed, significant associations emerged with cooking practices (e.g. pan-fried red meat) or doneness preferences (e.g. well-done red meat). For example, in two large case–control studies including more than 4000 cases, positive associations were found with pan-fried red meat.

Eighteen cohort studies investigated the association between processed meat and incidence of cancer of the colorectum. Positive associations between consumption of processed meat and incidence of cancer of the colorectum were observed in 12 studies, including some of the larger studies: a Japanese cohort, the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), the EPIC study, the Cancer Prevention Study II (CPS-II), and the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study.

The Working Group considered that approximately 10% of all case–control studies reviewed were informative for the assessment of the consumption of processed meat in relation to incidence of cancer of the colorectum. Six of the nine studies considered showed positive associations with cancer of the colorectum.

Several cohort and case–control studies investigated the association between consumption of red meat and processed meat combined and incidence of cancer of the colorectum. Positive associations between incidence of cancer of the colorectum and consumption of red and processed meat were observed in the majority of these studies.

A meta-analysis including data from 10 cohort studies reported a statistically significant dose–response association between consumption of red meat and/or processed meat and cancer of the colorectum. The relative risks of cancer of the colorectum were 1.17 (95% CI, 1.05–1.31) for an increase in consumption of red meat of 100 g/day and 1.18 (95% CI, 1.10–1.28) for an increase in consumption of processed meat of 50 g/day.

Based on the balance of evidence, and taking into account study design, size, quality, control of potential confounding, exposure assessment, and magnitude of risk, an increased risk of cancer of the colorectum was seen in relation to consumption of red meat and of processed meat. The large amount of data, strength of association, and consistency across cohort studies in different populations, including most of the larger cohort studies, makes chance, bias, and confounding unlikely as explanations for the association of consumption of processed meat with cancer of the colorectum . However, chance, bias, or confounding could not be ruled out for consumption of red meat, as no association was observed in several of the larger studies. The available evidence from a subset of studies suggested that some cooking methods used in the preparation of red meat may contribute to the observed associations.

5.2.2 Cancer of the stomach

The association between consumption of red meat and cancer of the stomach was evaluated in several cohort studies from Europe, the USA, and China. A positive association was observed in two studies (EPIC Cohort and nested case–control study from the Shanghai Cohort). Evidence was also available from two well-designed, population-based case–control studies from the USA and Canada, but the findings were somewhat inconsistent.

Among seven cohort studies, four studies showed positive associations between processed meat consumption and stomach cancer incidence. Two of these studies (the EPIC cohort study and the Swedish Cohort) reported statistically significant results. Another large study and two smaller ones did not find an association.

The majority of well-designed, population-based case–control studies, from Canada, the USA, and Mexico that reported on the association with consumption of processed meat, showed increased risks for gastric cancer, which were also statistically significant in three of the studies. A published meta-analysis reported positive associations for case–control studies, and for cohort studies. Positive associations between processed meat consumption and stomach cancer were observed in several case–control and cohort studies in diverse populations. However, the modest number of studies and lack of association in the other cohort studies suggested that chance, bias, and confounding could not be ruled out.

5.2.3 Cancer of the pancreas

Among 9 cohort studies with relevant data, 3 studies showed positive associations between consumption of red meat and cancer of the pancreas: the Multiethnic Cohort Study, a Swedish cohort of women, and the Japan Collaborative Cohort Study (JACC Study) (about 200 to > 2000 cases each). Two of these studies reported statistically significant results. The other cohort studies, including two large ones, showed no association. Data were also available from case–control studies in the USA, Canada, Italy and China. One of the two large population-based case–control studies reported a positive, statistically significant association between consumption of red meat and cancer of the pancreas, while the other reported a null result. Positive associations between consumption of red meat and cancer of the pancreas were observed in several cohort and case–control studies in diverse populations, but the modest number of studies and lack of association found in two large cohort studies suggested that chance, bias, and confounding could not be ruled out.

Among eight cohort studies, three studies showed positive associations between consumption of processed meat and cancer of the pancreas (Multiethnic Cohort Study, the Nurses' Health Study and JACC Study), which were statistically significant only in the Multiethnic Cohort Study. The other five studies showed null results. Positive associations or trends were observed in two well-designed case–control studies from North America.

5.2.4 Cancer of the prostate

More than twenty cohort studies were evaluated for consumption of red or processed meat and cancer of the prostate. The most informative studies were those with large sample sizes and accurate exposure assessments based on many food items, FFQs, information on cooking methods, and estimates of doneness.

A pooled analysis of a consortium of 15 cohort studies was based on more than 50 000 incident cases of cancer of the prostate, and reported positive associations between consumption of red meat and cancer of the prostate (mainly at advanced stages and in studies in North America), with an increased risk of 19% in the highest intake category (P_{trend} = 0.07). Weaker associations were found for consumption of processed meat in the same pooled analysis.

Approximately a third of the cohort studies, included or not in the pooled analysis, found statistically significant associations, usually between degree of doneness (well-done meat) and advanced cancer of the prostate (The Netherland Cohort Study, The Prostate, Lung, Colorectal, and Ovarian Study, the CLUE II Study, the Agricultural Health Study and the NIH-AARP Diet and Health Study). The association between consumption of red meat as such or processed meat as such, irrespective of cooking method, and cancer of the prostate was null or weak, and not statistically significant except for cured meat in one study.

Three population-based case–control studies from the USA and New Zealand were considered informative. These studies found associations mainly or exclusively with the degree of doneness of red meat and with cancers at advanced clinical stages. One study examined a population of subjects with high levels of prostate-specific antigen who underwent biopsy, and found an association between consumption of red meat (that included ham and sausages) and increased risk of cancer of the prostate. Inconsistent results for processed meat were reported from case–control studies.

Overall, associations were described almost exclusively between the degree of doneness and advanced stages of cancer. Subgroup analysis (multiple comparisons) and reporting bias could not be ruled out. Specific methodological problems with cancer of the prostate included the heterogeneity of the definition of clinical aggressiveness and the potential confounding introduced by prostate-specific antigen levels, which could be associated with dietary habits.

5.2.5 Cancer of the breast

The most informative data on the association between consumption of red meat or processed meat and cancer of the breast were available from cohort studies with large sample sizes, accurate exposure assessments, and adequate adjustment for confounding. About 10 cohort studies (with a total of about 20 000 cases of cancer of the breast), and a consortium of eight prospective cohort studies (> 7000 cases of cancer of the breast), assessed risk of cancer of the breast in relation to consumption of red meat (which may or may not have included processed meat) in North America and Europe. Four of these cohort studies found a statistically significant positive association between risk of cancer of the breast and consumption of red meat or red and processed meat combined. Multiple case–control studies conducted in the USA, South America, Europe, and Asia provided inconsistent evidence.

About 10 cohort studies (with a total of more than 16 000 cases of cancer of the breast) assessed risk of cancer of the breast in relation to consumption of processed meat in North America and Europe. Two of these cohort studies found a statistically significant association between intake of processed meat and risk of cancer of the breast. A cohort consortium evaluated individual processed meat items and found no association with any processed meat items. As for consumption of red meat, case–control studies provided inconsistent evidence.

The available evidence did not permit the Working Group to determine whether the association between consumption of red meat or processed meat and cancer of the breast differs by menopausal status, as large amounts of data were from postmenopausal women. Similarly, insufficient data existed to determine whether this association differs by hormone receptor status. The Working Group was not able to determine the effect on risk of cancer of the breast of cooking method and doneness of red meat, and on effect modification by genetic polymorphisms.

5.2.6 Cancer of the lung

Six cohort studies contributed to the assessment of the association between consumption of red meat or processed meat and cancer of the lung. Two of the studies had large sample sizes and highly informative designs (adjusting for tobacco smoking and energy intake, and with inclusion of incident cases): the EPIC study (Europe) and the NIH-AARP study (USA).

A positive association between increasing intake of red meat and cancer of the lung was found in most prospective studies, which was statistically significant in the NIH-AARP study. Residual confounding from tobacco smoking cannot be ruled out given the strong association between smoking and cancer of the lung. Similarly positive association between consumption of processed meat and cancer of the lung detected in some cohort studies was only significant in the NIH-AARP study in men.

Several case–control studies provided relevant data for the evaluation, particularly those that stratified by smoking habits. Associations between red meat or processed meat consumption and cancer of the lung were occasionally detected. Few case–control studies and one cohort study described an association between meat intake and cancer of the lung in never-smokers alone, finding generally positive but statistically non-significant associations.

A meta-analysis reported an overall increased risk of cancer of the lung with increasing levels of intake of red meat, but not with processed meat (adjustment for relevant confounders, particularly tobacco smoking, was heterogeneous in the contributing studies). The interpretation of the findings for cancer of the lung must also consider exposure to cooking fumes among individuals who consume high levels of meat as a potential confounding variable.

5.2.7 Cancer of the oesophagus

Only three cohort studies, two with a limited number of cases, investigated the association between consumption of red meat or processed meat and different subtypes of oesophageal cancer. The results of these studies were inconsistent. Data on the consumption of red meat or processed meat were also available from multiple case–control studies; for population-based, well-designed case–control studies, the results were inconsistent.

5.2.8 Other cancers

Associations between consumption of red meat or processed meat and cancers at several other sites, including non-Hodgkin lymphoma and leukaemia, as well as cancer of the liver, gallbladder and biliary tract, thyroid, testis, kidney, bladder, ovary, endometrium, and brain (in children and in adults), were investigated in a few studies, cohorts and mostly case–control studies. However, the number and/or quality of the available studies did not permit conclusions to be drawn.

5.3 Animal carcinogenicity data

The carcinogenicity of red meat was assessed in two feeding studies in *Apc*$^{Min/+}$ mice, a strain that spontaneously develops tumours of the small intestine. In the first study in male mice, a diet containing red meat did not affect the total number of tumours in the small intestine; however, there was a significant increase in the number of tumours in the distal small intestine. In the second study in male and female mice, a diet containing red meat did not affect the number of tumours of the small intestine in either sex.

In another study, male rats fed diets containing red meat and other substances found in typical human diets had higher incidences of tumours of the pituitary gland (pars distalis), and light-cell adenoma and carcinoma (combined) of the thyroid gland than rats fed the control diets.

In an initiation–promotion study, in which tumours of the colon in male mice were initiated with dimethylhydrazine and promoted with red meat, there was no increase in the incidence of tumours of the colon in mice fed a diet containing red meat.

Eight studies in male rats were conducted in which tumours of the colon were initiated with dimethylhydrazine and promoted with diets containing red meat. In one of the eight studies, rats fed diets containing red meat and other substances found in typical human diets had a higher incidence of adenocarcinoma of the colon than rats fed the control diets. In the other seven studies, the incidence of tumours of the colon was not increased by diets containing red meat.

In one study without a chemical initiator, a diet containing processed meat did not induce the formation of aberrant crypt foci (ACF).

Seven studies were conducted in which male or female rats were treated with dimethylhydrazine or azoxymethane, and promoted with diets containing red meat. In three of the seven studies, red meat had no effect on the occurrence of ACF or mucin-depleted foci (MDF) in the colon. In four of the seven studies, there was an increase in the occurrence of ACF and/or MDF in rats fed diets containing red meat and with a low calcium content. In one of these four studies, the comparison was made to whey protein, which may have chemopreventive activity.

Six studies were conducted in which female rats were treated with dimethylhydrazine or azoxymethane, and promoted with diets containing processed meat. In two of the six studies, processed meat had no effect on the occurrence of ACF or MDF in the colon. In four of the six studies, there was an increase in the occurrence of ACF and/or MCF in rats fed diets containing processed meat and with a low calcium content.

Haem iron, HAAs, PAHs, and *N*-nitrosamines have been identified in red meat and processed meat.

The carcinogenicity of haem iron was assessed in two feeding studies. In one study, *Apc*$^{\mathrm{Min/+}}$mice fed haemoglobin had an increased number of tumours in the jejunum. In an initiation–promotion study in which tumours of the colon in female rats were initiated with *N*-methyl-*N*-nitrosourea and promoted with haemoglobin, there was an increased incidence of adenoma and adenocarcinoma (combined) of the colon in rats fed diets containing haemoglobin.

The carcinogenicity in experimental animals of HAAs, PAHs, and *N*-nitrosamines found in red meat and processed meat has been evaluated by the Working Groups of previous *IARC Monographs*.

5.4 Mechanistic and other relevant data

Meat is mostly composed of highly digestible protein and fat, and provides many essential nutrients. Digestion of protein and fat, which are also provided by other food types, yields toxic compounds (secondary bile acids, ammonia, phenols, and hydrogen sulfide) in the gut. These compounds are not considered further, as they are not specific to red or processed meat.

There is *moderate* evidence that the consumption of red or processed meat is genotoxic. In humans, two intervention studies found increased levels of DNA adducts putatively related to *N*-nitroso-compound (NOCs) in colonic crypts or exfoliated colonocytes of volunteers consuming high levels of red meat (300 g/day or 420 g/day). These studies and other available data provided evidence to suggest that there may be an association between consumption of red meat, and possibly processed meat, and the formation of DNA adducts in human tissue (colon and breast). Observational data in humans showed associations between consumption of red or processed meat and gene mutations relevant to carcinogenesis in tumours of the colon. Multiple studies indicated that consuming cooked meat increased the mutagenicity of human urine in assays in bacteria. In several studies in rodents in vivo, cooked red meat induced DNA damage (DNA adducts and DNA strand breaks) in colonocytes. No genotoxic effect was reported for processed meat in one small study of four mice. Extracts from cooked red or processed meat were mutagenic in bacteria after metabolic activation.

There is *moderate* evidence that consumption of processed meat induces oxidative stress, few data are available for red meat. In three intervention studies (with blood sausage or cured pork) in humans, consumption of processed meat increased levels of an oxidative stress marker in the urine, faeces, or plasma. One observational study in humans found an association between consumption of red meat and levels of oxidative stress markers in blood. In three studies in rats, consumption of red meat increased levels of faecal and urinary lipid oxidation products, an effect reduced by calcium but not by antioxidants. In humans and experimental animals, effects on oxidative stress markers were attributed to haem iron since they could be suppressed by blocking haem iron with calcium.

There is *weak* evidence that red meat consumption alters cell proliferation, while few data are available for processed meat. In two intervention studies and one observational study in humans, consumption of red meat increased cell proliferation in the colon. No correlation was reported in a third study of red meat. In several studies in rats, consumption of red meat increased toxicity or apoptosis in colonocytes.

There is *strong* evidence from numerous studies in humans and eight studies in rodents that red meat and processed meat consumption increase the formation of preneoplastic lesions. A recent meta-analysis of consumption of red meat and processed meat in relation to adenoma of the colorectum reported a modest but statistically significant association that was consistent across studies. Red meat promoted the growth of preneoplastic lesions of the colon in carcinogen-initiated rats in three studies from two research groups. Ham, hot dog, cured pork, or blood sausage promoted the growth of preneoplastic lesions in the colon of carcinogen-initiated rats in four studies from a single laboratory. These effects in rats could be modified by calcium and antioxidants.

A large number of studies have evaluated the associations between genetic polymorphisms and cancer susceptibility associated with consumption of red meat. These studies have focused mainly on genes involved in the metabolism of carcinogens present in cooked red meat. The results of these candidate gene studies have mostly been *inconsistent*. Many were underpowered and had multiple testing and publication biases.

There is *strong* evidence that haem iron contributes to the carcinogenic mechanisms associated with red and processed meat. Haem iron mediates the formation of NOCs and lipid oxidation products in the gut of humans and rodents. Haem iron may cause cytotoxicity in the gut, based on the results of studies in humans and rodents. As previously noted, the effects of haem can be suppressed by blocking haem iron with calcium.

Consumption of red or processed meat increases the formation of lipid oxidation products in the gut in humans and in experimental animals. In rats, lipid oxidation products from consumption of red meat, but not processed meat, promote the growth of chemically initiated preneoplastic lesions of the colon, providing *moderate* mechanistic evidence for carcinogenic mechanisms associated with the consumption of red meat.

Meat heated at a high temperature contains HAAs. There is *strong* evidence that HAAs, by causing DNA damage, contribute to carcinogenic mechanisms associated with the consumption of red meat. After exposure to HAAs, HAA–DNA adducts have been reported in the colon in studies in humans and in rodents. The extent of activation of HAAs to genotoxic metabolites is greater in humans than in rodents, and levels of specific HAA adducts are higher in human tissue than in rodent tissue after similar exposure. However, no studies of HAA genotoxicity after consumption of red meat in humans were available.

Meat smoked or cooked over a heated surface or naked flame contains PAHs. The mechanistic evidence is *moderate* that PAHs contribute to the carcinogenic mechanisms associated with the consumption of red meat and of processed meat. PAHs cause DNA damage, but little direct evidence is available following the consumption of meat. A few epidemiological studies provided some mechanistic evidence for certain cancers.

Consumption of red meat and of processed meat in humans induces the formation of NOCs in the gut based on multiple intervention studies. Direct evidence that consumption of red meat by humans leads to NOC-derived mutagenic DNA adducts in the human colon is provided by two intervention studies. There is *strong* evidence that the formation of NOCs contributes to the carcinogenic mechanisms associated with the consumption of red meat. Evidence for processed meat is less clear due to the lack of direct studies (i.e. after consumption of processed meat).

The Working Group noted that the carcinogenic mechanisms associated with the consumption of red meat and processed meat cannot be attributed to a particular meat component, and also that meat consumption is not the only context of exposure to some of these components. However, other important considerations adding considerably to the weight of the overall evidence in support of a carcinogenic mechanism for red meat and processed meat include the following: (i) strong mechanistic evidence exists for multiple interacting meat components (haem iron, NOCs, HAAs, lipid peroxidation); (ii) at least one of the effects of these components can be experimentally suppressed (i.e. haem iron by calcium); and (iii) the extent of conversion of HAAs to genotoxic metabolites is greater in humans than in rodents.

Overall, the mechanistic evidence for carcinogenicity is *strong* for red meat, based primarily on studies of colonic preneoplastic lesions in humans and rodents, and the considerable evidence concerning haem iron, HAAs, and NOCs in humans and rodents. Fewer data in humans, especially from intervention studies, are available for processed meat than for red meat. The mechanistic evidence for carcinogenicity is *moderate* for processed meat, based primarily on studies of colonic preneoplastic lesions in humans and rodents, human and other experimental evidence for NOCs, and studies of haem iron in rodents.

The carcinogenic mechanisms discussed in this section primarily apply to the digestive tract; there is little mechanistic evidence regarding other anatomical sites. The carcinogenic mechanisms discussed are likely to operate in humans.