

PhysiciansCommittee

for Responsible Medicine

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Re: Nominations to the National Toxicology Program (NTP) for the Report on Carcinogens, “Meat-Related Exposures”

Dear Drs. Lunn and Rooney:

Thank you for the opportunity to submit scientific evidence to the office of the Report on Carcinogens and the Office of Health Assessment and Translation regarding including consumption of red meat, processed meat, and meat cooked at high temperatures in future editions of the Report on Carcinogens.

The Physicians Committee for Responsible Medicine is a nonprofit public health organization representing 170,000 medical professionals, scientists, and laypersons. The Physicians Committee conducts clinical research on nutrition and health and provides a variety of nutrition education services.

More than half of the meat products Americans consume is red meat, while nearly a quarter consumed is processed.¹

Red and processed meat can increase risk for various cancers, including pancreatic,² stomach,³ bladder,⁴ colon, and most significantly, colorectal cancer.⁵ The risk is higher for processed meat consumption, though it is still significantly increased with unprocessed red meat consumption.

The World Cancer Research Fund (WCRF), in conjunction with the American Institute for Cancer Research (AICR), found, in a comprehensive and ongoing analysis of research, that red

and processed meat are, together and individually, “convincing” as risk factors for colorectal cancer. The combination of evidence indicates a 30 to 50 percent increased risk for colorectal cancer when consumption is highest.^{5,6} Regarding processed meat consumption, investigators in the European Prospective Investigation into Cancer and Nutrition study discovered an 11 percent increased risk of dying from cancer with the consumption of 50 grams per day.⁷

Researchers also established the dose-response nature of red and processed meat consumption and colorectal cancer risk. A 2011 meta-analysis found that risk increased by 17 percent for every 100 grams of red meat consumed per day and by 18 percent for every 50 grams of processed meat consumed per day.⁸ Similarly, a 2016 review found that 50 grams of processed meat per day increased the risk for colorectal cancer, pancreatic cancer, death from heart disease, and diabetes by 18, 19, 24, and 32 percent, respectively.⁹

A substantial body of scientific evidence attributes the consumption of processed meat to significantly increased cancer risk. Critically, a 2015 review by the World Health Organization provided further evidence that processed meat consumption is “carcinogenic to humans.”¹⁰

There are several explanations for the causal association between red and processed meat and cancer, including DNA-damaging n-nitroso compounds, heme iron, heterocyclic amines, and npolycyclic aromatic hydrocarbons, among others.^{2,11} Just as tobacco causes cancer by more than one presumed mechanism, the same is likely true for red and processed meat. Therefore, the Report on Carcinogens should list as known carcinogens red meat, processed meat, and meat cooked at high temperatures—each one a collective substance with multiple potential cancer mechanisms—as the Report did for “Tobacco Smoke, Environmental,” “Tobacco Smoking,” and “Tobacco, Smokeless.”

SCIENTIFIC EVIDENCE ESTABLISHES CANCER RISKS OF MEAT

The prevailing consensus among government agencies and public health organizations is that consumers should be warned of the dangers of consuming processed meat. Processed meat, including ham, bacon, pastrami, salami, bologna, liverwurst, bratwurst, sausages, frankfurters, hot dogs, luncheon meats, and, depending on the processing, hamburgers and minced meats,^{12,13} represents a broad category of meat products that are often prepared and/or preserved by curing, smoking, salting, or adding chemical preservatives, such as nitrites and nitrates.

The following summaries state the findings or stances from various public health authorities:

World Cancer Research Fund/American Institute for Cancer Research (2007)

To establish consensus on the state of evidence supporting links between specific types of food and cancer risk, the World Cancer Research Fund and the American Institute for Cancer Research created a panel that, over a five-year period, studied evidence regarding the extent to which cancer can be prevented through healthy patterns of eating and physical activity and created a comprehensive report based on its findings.¹² Previously, the groups had worked together to create and publish *Food, Nutrition and the Prevention of Cancer: a Global*

Perspective (1997), which quickly became the standard in the field and helped raise awareness about the importance of research on this issue.

The panel's report reviewed all relevant research using the most scientifically valid methodology, provided a comprehensive assessment of the state of evidence linking foods to cancer risk, and provided a set of recommendations on food, nutrition, and physical activity to reduce the risk of cancer. The panel consisted of world-renowned scientists, including world leaders in research of the epidemiology and biology of cancer, nutrition, and public health.

To maximize objectivity and transparency, the project was separated into three distinct processes: collection, analysis, and recommendations. First, a task force developed a methodology for reviewing the voluminous amounts of scientific literature. Second, research teams collected and reviewed the material based on the developed methodology. Finally, the expert panel assessed and judged the evidence and agreed on recommendations.

Based on its review of 14 cohort studies and 44 case-control studies investigating processed meat, the report concluded that consuming processed meat is strongly associated with the specific increased risk of colorectal cancer. This form of cancer is the third most common cancer in men and women separately and the second most common cause of cancer death in men and women combined.¹⁴ According to the report, colorectal cancer risk increases on average by 21 percent for every 50 grams of processed meat—approximately the size of a typical hot dog—consumed daily and by 29 percent for every 100 grams of red meat consumed daily. The report cited evidence that consuming processed meat may also contribute to cancers of the esophagus, lung, stomach, and prostate.¹²

National Institutes of Health (2009) / National Cancer Institute (2010)

Two years later, scientists from the National Institutes of Health (NIH) published a 10-year study of more than a half-million people that investigated the relationship between meat intake and mortality.¹⁵ The study concluded that higher consumption of processed meat leads to an overall increased risk of mortality, cancer mortality, and cardiovascular disease mortality. The NIH study attributed the cancer risk from processed meat to heterocyclic amines, polycyclic aromatic hydrocarbons, iron, and saturated fat. However, the NIH study went one step further than the WCRF/AICR report by specifying that higher intake of meat, including processed meat, contributes not only to cancer but to cancer mortality.

According to a 2010 National Cancer Institute report, “Red meat and processed meat are associated with an increased risk of colorectal cancer, and there is also suggested evidence for some other cancers, such as prostate cancer.”¹⁶

President's Cancer Panel (2010)

The President's Cancer Panel's 2008-2009 annual report on environmental toxins noted that meats, when cured, form dangerous and carcinogenic nitrosamines and N-nitroso compounds.¹⁷ The panel recommended a preventive approach, as opposed to a reactionary approach, to such cancer-causing contaminants. In its executive summary, the panel acknowledged the convincing evidence showing a link between processed meat and cancer.

Centers for Disease Control and Prevention (2010)

The Centers for Disease Control and Prevention acknowledged in a 2010 *Morbidity and Mortality Weekly Report* that a diet high in processed and red meat increases the risk for colorectal cancer.¹⁸

Harvard School of Public Health (2011)

Since 2011, the Harvard School of Public Health has recommended replacing red and processed meat with more healthful foods, such as nuts and beans.¹⁹

American Cancer Society (2012)

The American Cancer Society recommended in its guidelines on nutrition to limit consumption of processed meat, including bacon, sausage, lunch meats, and hot dogs, as well as red meat.²⁰

World Health Organization (2015)

The World Health Organization released a report based on an examination of more than 800 studies.¹⁰ The authors highlighted the 2011 meta-analysis that found that colorectal cancer risk increased by 17 percent for every 100 grams of red meat consumed per day and by 18 percent for every 50 grams of processed meat consumed per day. The report classified consumption of red meat as “probably carcinogenic to humans” and consumption of processed meat as “carcinogenic to humans.” The researchers also observed associations between red and processed meat consumption and stomach, pancreatic, and prostate cancers. In addition the authors noted that processing and other cooking methods for meat, including curing, pan-frying, and smoking, produce various carcinogenic chemicals.

2015-2020 Dietary Guidelines for Americans (2015)

The *Dietary Guidelines for Americans*, a joint collaboration between the Department of Agriculture and the Department of Health and Human Services (HHS), state that (1) lower intake of processed meat is a characteristic of healthy eating patterns; (2) there is “strong evidence” that lower intake of processed meat is associated with reduced risk of cardiovascular disease; and (3) there is “moderate evidence” that lower intake of processed meat is associated with reduced risk of obesity, type 2 diabetes, and some types of cancer.²¹

* * *

Only a small percentage of cancer cases are inherited, leaving environmental factors, including food and nutrition, as the most important and modifiable.¹⁵ It has long been estimated that anywhere from 35 to 60 percent of cancer is attributable to diet.^{22,23} Because the intestinal tract is in constant contact with foods, food additives, and the products of digestion, individuals who consume processed meat are at a significantly increased risk of developing colorectal cancer, compared with those who avoid consuming processed meat. The risk increases with increased consumption, as noted above. Accordingly, the WCRF/AICR report recommended that processed meat be eliminated from the diet.¹²

A. Processed Meat and Meats Cooked at High Temperature

Processed meats contain a variety of potentially carcinogenic chemicals. These may include nitrates, nitrites, N-nitroso compounds (NOCs) such as N-nitrosodimethylamine (NDMA), heme iron, heterocyclic amines (HCAs), such as 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and 2-amino-3,8-dimethylimidazo[4,5]quinoxaline (MeIQx), and polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene (BAP).²⁴ The associated cancer risks from these chemical components through the consumption of processed meat have been described for decades. N-nitrosamines and NOCs were identified as carcinogenic substances more than 50 years ago.²⁵

Nitrites used in meats as a preservative, as well as coloring and flavoring agents, can combine with amino acid degradation products during the curing process or during digestion to produce N-nitroso compounds (nitrosamines or nitrosamides). Nitrates, used as preservatives, are converted to nitrites. In addition, processed meat cooked at high temperatures may contain chemical carcinogens, including HCAs and PAHs. Moreover, heme iron, plentiful in red and processed meat, promotes the production of N-nitroso compounds, and its iron content leads to free radical production.

B. Chemicals in Processed Meat and Meats Cooked at High Temperature that Increase the Risk of Cancer

NOCs: A body of scientific literature concludes that NOCs exhibit mutagenic and carcinogenic activity and are associated with an increased risk of cancer of the esophagus, oral cavity, pharynx, larynx, lung, and colorectum.²⁶ NOCs are formed as a result of the nitrosation of amines, amides, and amino acids by nitrites and nitrates, which are commonly used as food preservatives in processed meat.²⁷ Consumption of processed meat, especially processed red meat, has a dose response consistent with the endogenous formation of NOCs, resulting in increased amounts of these compounds in the gastrointestinal tract.²⁸ Thus, consumers of these products have an increased risk for gastrointestinal cancers, such as colorectal cancer.²⁹⁻³¹

NOC metabolites (metabolically activated NOCs) may contribute to an increased risk of leukemia as well as colon, stomach, esophagus, and brain cancer by inducing the formation of DNA-adducts and miscoding of noncomplementary bases during polyribonucleotide and polydeoxyribonucleotide synthesis.^{25,29,32} No safe threshold dose, at which tumor formation would not be expected to occur, has been determined for NOCs. Moreover, NOCs that are carcinogenic in animals are commonly considered human carcinogens for regulatory purposes when establishing safety levels.³³⁻³⁵

One of the most studied NOCs, NDMA, a nitrosamine present in processed meat, was listed as a human carcinogen by the State of California in 1987.³⁶ Similarly, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization, identified NDMA as a probable human carcinogen decades ago.³⁷ HHS identified NDMA as a substance reasonably anticipated to cause cancer.³⁸

Heme: Heme, a red organic pigment, is the iron porphyrin component of hemoproteins, such as hemoglobin and myoglobin.³⁹ Dietary heme forms a highly cytotoxic metabolite that damages the colonic mucosa, resulting in the increased risk of gastric and colon cancer.^{28,39} Due to the contribution of heme to NOC formation, the consumption of nitrate and nitrite-rich processed meat leads to an increased risk for gastrointestinal cancers, such as colorectal cancer. Heme iron, as opposed to inorganic iron, is considered to be a principal determinant of endogenous gastrointestinal N-nitrosation by acting as a nitrosating agent, and, for reasons similar to those applied to NOCs, cannot have a determined safe threshold level.^{13,26,30}

HCAs: HCAs are major contributors to mutagenicity of cooked meat. Therefore, consuming these products poses a public health risk. Through metabolic pathways including cytochrome-mediated (e.g., CYP1 and CYP2) N-hydroxylation and O-esterification by phase II enzymes, HCA compounds create genotoxic metabolites that are known mutagens and carcinogens.⁴⁰ HCAs form inside and on the surface of meats from creatine or creatinine, amino acids, and sugars as a result of exposure to high temperatures through cooking processes, including barbecuing, frying, roasting, and grilling.⁴¹

In cooked processed meats, HCAs suspected of increasing cancer risk include 2-amino-3-methylimidazo[4,5-f]quinoline.⁴² The HCAs 2-amino-3,4,8-trimethylimidazo[4,5]quinoxaline, MeIQx, and PhIP are specifically linked to an increased risk for colorectal cancer.⁴³ The State of California has identified PhIP and MeIQx as known human carcinogens since 1994,³⁶ and IARC labeled them as possible human carcinogens in 1993.³⁷ Because there are no known safe levels of exposure, PhIP, MeIQx, and any other likely genotoxic compounds should be avoided as much as possible.^{44,45}

PAHs: Studied for decades, PAHs contribute to mutagenic and carcinogenic activity. Processed meat contains precursors to PAHs, creating PAHs when animal fat drips onto a heated surface and burns.⁴⁶ Processed meat is of concern due to the routine use of high temperature cooking methods to prepare such foods.⁴⁷ Through a process of metabolic activation by cytochrome P450 enzymes and/or peroxidases, PAHs become reactive intermediates with carcinogenic potential.⁴⁸ PAH exposure results in genotoxic markers such as DNA adducts, chromosome aberrations, sister chromatid exchanges, *ras* oncogene overexpression, and impacts on cellular pathways.⁴⁹ PAHs generally exist in complex mixtures, making it difficult to pinpoint the relative contribution of any individual PAH to carcinogenic effects.

BAP is one of the most prevalent and readily identifiable carcinogenic PAHs.⁵⁰ Since the 1930s, BAP has been studied for its carcinogenic effect.⁵¹ BAP was listed as a known carcinogen by the State of California in 1987 and was upgraded to this status by IARC in 2007.^{36,37} HHS has identified BAP and PAHs as substances reasonably anticipated to cause cancer.³⁸ Because there is no known safe level of exposure for BAP or other genotoxic PAHs, they should be avoided as much as possible.

CONCLUSION

In the face of incontrovertible evidence that Americans are at risk of cancer as a result of continuing exposure to red meat, processed meat, and meat cooked at high temperature, the Report on Carcinogens should list these substances as known carcinogens. The carcinogenicity of meat is an increasingly urgent issue, as the U.S. rate of meat consumption is among the highest in the world.⁵² This February, the National Cancer Institute reported that colorectal cancer rates are on the rise for young people. Researchers tracked cancer incidence rates for 490,305 participants from the Surveillance, Epidemiology, and End Results Program areas and found that for those within the 20 to 39 year age range, cancer rates have increased as much as 2.4 percent each year since the 1980s and through the 1990s.⁵³

The Physicians Committee is happy to provide additional support, if requested, in pursuit of this critical public health goal.

Respectfully submitted,



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