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April 20, 2015

Veronique Bouvard, Responsible Officer  
Kurt Straif, Head of the IARC Monographs programme  
IARC  
Lyon, France

**Re:** Volume 114: Red Meat and Processed Meat – Call for Data

Dear Drs. Bouvard and Straif:

As a trained cancer epidemiologist working in the field of nutrition and chronic disease outcomes for more than a decade, I appreciate the opportunity to provide a collective summary of the work to date in the area of red and processed meat consumption and cancer risk.

As the members of the Working Group may already know or will soon discover, determining if the scientific evidence supports an association between intake of red and/or processed meat and risk of cancer is a complex and methodologically challenging undertaking for several reasons.

- First, the interdependency of food consumption with other dietary and lifestyle factors, socioeconomic characteristics, clinical variables, and genetic traits makes it difficult to isolate the independent effects of a specific food or food group, such as meat intake, on disease risk.
- Second, interpretation of findings from nutritional epidemiology studies are further complicated by the fact that this research area is particularly prone to reporting bias because of the numerous types of foods, food combinations, nutrients, and cooking methods ascertained on a typical food frequency questionnaire.
- Third, results of many studies fail to distinguish fresh red meat from processed meat, to parse out individual red meat types (pork, beef, lamb, etc.), or to report results for red meat apart from a broad grouping of meat products, thus limiting the certainty with which specific conclusions can be made regarding cancer associations for red and processed meat.
- Finally, for many cancer sites (e.g., prostate, breast), there is an abundance of data from prospective cohort studies that specifically evaluate fresh red meat and processed meat for which conclusions can be drawn. In fact, my team and I are currently updating previously published meta-analyses and conducting meta-analysis of additional cancer sites. We expect our results to be available and in peer-review over the next few months.

Well-conducted meta-analyses of high quality and methodologic rigor can provide strong evidence when making informed decisions on a body of literature. As such, I'd like to alert the Working Group to the existence of a series of meta-analyses of red and processed meat intake (alone or in combination) as well as animal fat and protein for several cancer sites, based on publications through 2015. In addition, I've included a pre-publication version my recently updated meta-analyses regarding the association between red meat and colorectal cancer, currently in press in the *Journal of the American College of*

*Nutrition* (2015). I've included an annotated bibliography of these publications at the end of this letter and have also provided a zip file containing each publication. For the Working Group's convenience, I'm also providing additional zip files containing each individual publication that contributed to these meta-analyses. Generally speaking, our findings can be summarized as follows:

- Most summary associations between red meat and processed meat are weak in magnitude (i.e.,  $RR < 1.2$ ), and not statistically significant
- Many associations for red/processed meat and cancer from individual studies are null or inverse
- The majority of associations from individual studies are not statistically significant
- Patterns of association often vary by sub-group characteristics, such as gender and study country
- Red and processed meat definitions are heterogeneous across studies
- Dietary ascertainment and analytical metrics vary across studies
- Confounding and residual confounding, such as that for physical activity, body mass index, smoking, alcohol intake or adherence to screening recommendations, impact associations
- Reporting bias is a prevailing issue when interpreting the collective body of evidence

While meta-analyses are not immune to the shortcomings and challenges associated with individual studies, given a large volume of literature, a meta-analysis can be used to create informative sub-group stratifications, to evaluate potential dose-response relationships, to examine potential sources of heterogeneity and to evaluate the consistency of results by partially controlling for some of the study-specific characteristics. In addition, a meta-analysis improves the precision of summary estimates of effect, which is especially important when attempting to demonstrate patterns of associations across subgroups.

Again, I appreciate the opportunity to provide this comprehensive overview of the epidemiology surrounding red meat and processed meat and cancer risk. I would like to offer myself as a resource to the Working Group as they further deliberate this complex and challenging undertaking.

Sincerely,

Dominik D. Alexander, PhD, MSPH  
Principal Epidemiologist  
EpidStat Institute

Attachments:

Alexander, DD et al. Meta-analyses.zip  
Appendix to Alexander 1.zip  
Appendix to Alexander 2.zip  
Appendix to Alexander 3.zip  
Appendix to Alexander 4.zip  
Appendix to Alexander 5.zip  
Appendix to Alexander 6.zip

## Annotated Bibliography

**Alexander DD, Cushing CA. Quantitative assessment of red meat or processed meat consumption and kidney cancer. *Cancer Detect Prev.* 2009;32(5-6):340-351.**

Although many of the summary results were positive, all were weak in magnitude, most were not statistically significant, and associations were attenuated among studies that adjusted for key potential confounding factors. In summary, the findings of this meta-analysis are not supportive of an independent relation between red or processed meat intake and kidney cancer.

**Alexander DD, Cushing CA, Lowe KA, Scurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009b;89(5):1402-1409.**

The available epidemiologic evidence does not appear to support an independent association between animal fat intake or animal protein intake and colorectal cancer.

**Alexander DD, Miller AJ, Cushing CA, Lowe KA. Processed meat and colorectal cancer: a quantitative review of prospective epidemiologic studies. *Eur J Cancer Prev.* 2010;19(5):328-341**

Overall, summary associations were weak in magnitude (i.e. most less than 1.20), processed meat definitions and analytical comparisons were highly variable across studies, and isolating the independent effects of processed meat intake is difficult, given the likely influence of confounding by other dietary and lifestyle factors.

**Alexander DD, Mink PJ, Cushing CA, Scurman B. A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer. *Nutr J.* 2010b;9(50):1475-2891.**

There was a weak association between red and processed meat intake and prostate cancer (SRRE = 1.05, 95% CI: 0.99-1.12), although heterogeneity was present, the association was attenuated in a sub-group analysis of studies that adjusted for multiple potential confounding factors, and publication bias likely affected the summary effect

**Alexander DD, Morimoto LM, Mink PJ, Cushing CA. A review and meta-analysis of red and processed meat consumption and breast cancer. *Nutr Res Rev.* 2010c;23(2):349-365.**

Heterogeneity was evident in most analyses, summary associations were sensitive to the choice of analytical model (fixed v. random effects), and publication bias appeared to have produced slightly elevated summary associations. On the basis of this quantitative assessment, red meat and processed meat intake does not appear to be independently associated with increasing the risk of breast cancer, although further investigations of potential effect modifiers, such as analyses by hormone receptor status, may provide valuable insight to potential patterns of associations.

**Alexander DD, Morimoto LM, Mink PJ, Lowe KA. Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. *Nutr Res Rev.* 2010d;23(1):169-179.**

The results of the present quantitative assessment are not supportive of a positive independent association between consumption of animal fat and breast cancer, although findings may be sensitive to the type of dietary instrument used in cohort studies.

**Alexander DD, Cushing CA. Red meat and colorectal cancer: a critical summary of prospective epidemiologic studies. *Obes Rev.* 2011;12(5).**

Collinearity between red meat intake and other dietary factors (e.g. Western lifestyle, high intake of refined sugars and alcohol, low intake of fruits, vegetables and fibre) and behavioural factors (e.g. low

physical activity, high smoking prevalence, high body mass index) limit the ability to analytically isolate the independent effects of red meat consumption.

**Alexander DD, Weed DL, Cushing CA, Lowe KA. Meta-analysis of prospective studies of red meat consumption and colorectal cancer. Eur J Cancer Prev. 2011b;20(4):293-307.**

The available epidemiologic data are not sufficient to support an independent and unequivocal positive association between red meat intake and CRC.

**Alexander DD. No association between meat intake and mortality in Asian countries. (Editorial) Am J Clin Nutr. 2013;98:856-6.**

Much of the data on meat intake and chronic disease originates from studies conducted in North American and European populations; less is known about consumption trends and the relationship between meat intake and chronic disease in Asian populations. The strengths and weaknesses of the pooled analysis by Lee and co-workers (AJCN 2103; 98:1032-41) of data from Asian prospective cohorts regarding meat intake and cancer incidence are discussed.

**Alexander D, Weed D, Miller P, M Mohamed. Red meat and colorectal cancer: a quantitative update on the state of the epidemiologic science. J Am Coll Nutr. 2015, *in press*.**

The current study updated and expanded our previous meta-analysis by integrating data from new prospective cohort studies and conducting a broader evaluation of the relative risk estimates by specific intake categories. Summary associations were attenuated (closer to the null and less heterogeneous) in models that isolated red meat (from processed meat), adjusted for more relevant factors, analyzed women only, and were conducted in countries outside of the United States. Furthermore, no clear patterns of dose-response were apparent.