

Received via email on October 11, 2016
From: Shalene McNeill, The Beef Checkoff

Comments: Dear Dr. Lunn:

The Beef Checkoff appreciates the opportunity to submit scientific evidence to the Office of the Report on Carcinogens (RoC) in response to its September 9, 2016, Federal Register (80 FR 62513-14) request for information regarding the possible evaluation of consumption of red meat, processed meat, and meat cooked at high temperatures for future editions of the Report on Cancer (RoC).

In response to the request for recently published, ongoing, or planned studies related to evaluating cancer outcomes, we submit the following non-exhaustive list of relevant scientific literature published within the past 5 years, and ongoing and planned studies:

*Ongoing and planned studies funded by the Beef Checkoff
Title: Development and validation of gas chromatography mass spectrometry methodologies for the assessment of polycyclic aromatic hydrocarbons and heterocyclic amines in beef. As described by the researchers (Legako, J. and co-workers), the objective of this project is to validate methodologies for measurement of polycyclic aromatic hydrocarbons (PAH) and heterocyclic amines (HCA) in beef. The researchers propose the use of gas chromatography mass spectrometry (GC-MS) due to its relatively cheaper operation costs and greater availability to other researchers.

Title: Beef as a Component of a Healthy Dietary Pattern in Cancer Survivors. As hypothesized by the researchers (Clinton, S. and co-workers), overweight and nutritionally stressed cancer survivors who actively participate in a 6-month intensive intervention comparing a DGA /AICR approach or a DGA / AICR based diet plus beef will both show improved body composition and successfully maintain a healthy dietary pattern and physical activity effort over time and that regular consumption of lean beef may favorably impact specific nutritional outcomes.

Title: Heme and mechanisms of carcinogenicity. The researchers (Kruger, C. et al.) will conduct a weight of evidence, systematic review studies investigating proposed mechanisms of dietary heme ingestion on initiating or promoting colorectal cancer. Mechanisms to be reviewed will include genotoxicity,

catalytic formation of N-nitroso compounds and cytotoxicity due to lipid peroxidation end-products, as outlined by the investigators.

Title: Evaluation of the relative risks due to consumption of red meat compared to other common food items. The investigators (Zagmutt, F. and Costard, S.) aim to determine preliminary, baseline estimates of relative exposure to hypothesized carcinogenics through consumption of selected food items (including red meat); 2) Identify other important potential health risks caused by red meat substitutes; 3) Identify data sources and knowledge gaps. This will also include a broad overview of data and corresponding gaps that would be necessary to perform a traditional dose-response assessment of HCAs & PAHs.

Title: Association between Red Meat Consumption and Colon Cancer: A Systematic Review of Experimental Results Turner, N and Lloyd, S. are completing a systematic review of the available evidence to determine the availability of plausible mechanistic data linking red and processed meat consumption to CRC risk. Turner and Lloyd have found fifty-nine studies using animal models or cell cultures that met specified inclusion criteria, most of which were designed to examine the role of heme iron or heterocyclic amines (HCAs) in relation to colon carcinogenesis. Turner and Lloyd note that most studies used greatly elevated levels of meat or meat components as compared to those found in human diets. Turner and Lloyd note that, although many of the experiments used semi-purified diets designed to mimic the nutrient loads in current westernized diets, most did not include potential biologically active protective compounds present in whole foods. Turner and Lloyd note that, because of these limitations in the existing literature, there is currently insufficient evidence to confirm a mechanistic link between the intake of red meat as part of a healthy dietary pattern and CRC risk.

*Recent Publications Related to Exposure Assessment Complications for Red Meat, Processed Meat and Meat Cooked at High Temperatures:

Alaejos, M. S., Afonso, A. M. (2011). Factors that affect the content of heterocyclic aromatic amines in foods. *Comprehensive Reviews in Food Science and Food Safety*. 10(2):52-108.

Alomiraha, H., Al-Zenkia, S., Al-Hootia, S., Zaghloula, S.,

Sawayaa, W., Ahmedb, N., Kannan, K. (2011). Concentrations and dietary exposure to polycyclic aromatic hydrocarbons (PAHs) from grilled and smoked foods. *Food Control*. 22:2028-2035.

Archer E, et al. Validity of U.S. Nutritional Surveillance: National Health and Nutrition Examination Survey Caloric Energy Intake Data, 1971-2010. *PLoS ONE* 2013;8(10):e76632.

Archer E, et al. The Inadmissibility of What We Eat in America and NHANES Dietary Data in Nutrition and Obesity Research and the Scientific Formulation of National Dietary Guidelines. *Mayo Clinic Proceedings* 2015;90(7):911-26.

Daniel CR, et al. Trends in meat consumption in the USA. *Public Health Nutr* 2011;14(4):575-83

Dietary Guidelines Advisory Committee (DGAC). 2015. Scientific report of the 2015 Dietary Guidelines Advisory Committee. Washington DC: Department of Health and Human Services and USDA.

Fehrenbach KS, et al. A critical examination of the available data sources for estimating meat and protein consumption in the USA. *Public Health Nutr* 2016;19(8):1358-67.

Forsberg, N.D., Stone, D., Harding, A., et al. (2012). Effect of Native American fish smoking methods on dietary exposure to polycyclic aromatic hydrocarbons and possible risks to human health. *J Agric Food Chem*, 60:6899-6906.

Gibis, M. (2016). Heterocyclic aromatic amines in cooked meat products: causes, formation, occurrence, and risk assessment. *Comprehensive Reviews in Food Science and Safety*. 15:269-302.

Hallström E, Björsson P. Meat-consumption statistics: reliability and discrepancy. *Sustainability: Science, Practice, & Policy* 2013;9(2):37-47.

Jørgensen, R. B., Strandberg, B., Sjaastad, A. K., Johansen, A., Svendsen, K. (2013). Simulated restaurant cook exposure to emissions of PAHs, mutagenic aldehydes, and particles from frying bacon. *Journal of Occupational and Environmental Hygiene*. 10:122-131.

Kitts, D. D., Chen, X. M., Broda, P. (2012). Polyaromatic hydrocarbons of smoked cured muscle foods prepared by Canadian and Lheidli T'enneh first nation

communities. *Journal of Toxicology and Environmental Health*. 75:1249-1252.

Klurfeld DM. Research gaps in evaluating the relationship of meat and health. *Meat Sci* 2015;109:86-95.

Lee JG, Kim SY, Moon JS, Kim SH, Kang DH, Yoon HJ. Effects of grilling procedures on levels of polycyclic aromatic hydrocarbons in grilled meats. *Food Chem* 2016;199:632-638.

McNeill SH, et al. The evolution of lean beef: Identifying lean beef in today's US marketplace. *Meat science* 2012;90(1):1-8.

McNeill SH, Van Elswyk ME. 2016. "Meat: Role in the Diet" in *Encyclopedia of Food and Health*, 1st ed.

Mitka M. Do Flawed Data on Caloric Intake From NHANES Present Problems for Researchers and Policy Makers? *JAMA* 2013;310(20):2137-2138.

Meurillon M and Engel E (2016). Mitigation strategies to reduce the impact of heterocyclic aromatic amines in proteinaceous foods. *Trends in Food Science & Technology*. 50:70-84.

Mohammadi, A., Ghasemzadeh-Mohammadi, V., Haratian, P., Khaksar, R., Chaichi, M. (2013). Determination of polycyclic aromatic hydrocarbons in smoked fish samples by a new microextraction technique and method optimisation using response surface methodology. *Food Chemistry*. 141:2459-2465.

National Food Institute, Technical University of Denmark. (2016). The role of meat in the diet. ISBN:978-87-93109-74-2. Available at www.food.dtu.dk

Olatunji, O. S., Fatoki, O. S., Opeolu, B. O., Ximba, B. J. (2015). Benzo[a]pyrene and benzo[k]fluoranthene in some processed fish and fish products. *International Journal of Environmental Research and Public Health*. 12:940-951.

Oostindjer M, et al. The role of red and processed meat in colorectal cancer development: a perspective. *Meat Sci* 2014;97(4):583-96.

Puangsoombat, K., Gadgil, P., Houser, T. A., Hunt, M. C., and Smith, J. S. (2012). Occurrence of heterocyclic amines in cooked meat products. *Meat Science*. 90:739-746.

Singh, L., Varshney, J.G., and Agarwal, T. (2016). Polycyclic aromatic hydrocarbons' formation and occurrence in processed food. *Food Chemistry*, 199:768-781.

Tapsell, L.C., Neale, E., Satja, A., and Hu, F.B. (2016). Foods, nutrients, and dietary patterns: interconnections and implications for Dietary Guidelines. *Advances in Nutrition*, 7:445-54.

Viegas, O., Novo, P., Pinto, E., Pinho, O., Ferreira, I. M. P. L. V. O. (2012). Effect of charcoal types and grilling conditions on formation of heterocyclic 3 aromatic amines (HAs) and polycyclic aromatic hydrocarbons (PAHs) in grilled muscle foods. *Food and Chemical Toxicology*. <http://dx.doi.org/10.1016/j.fct.2012.03.051>.

Viegas, O., Moreira, P. S., and Ferreira, I. M. P. L. V. O. (2015). Influence of beer marinades on the reduction of carcinogenic heterocyclic aromatic amines in charcoal-grilled pork meat. *Food Additives and Contaminants: Part A*. 32(3):315-323.

Yao, Z., Li, J., Wu, B., Hao, X., Yin, Y., Jiang, X. (2015). Characteristics of PAHs from deep-frying and frying cooking fumes. *Environmental Science and Pollution Research International*. doi: 10.1007/s11356-015-4837-4. Epub.

*Critical Reviews Debating Proposed Mechanisms for Meat and Cancer Risk Andersen, V., Christensen, J., Overvad, K., Tjonneland, A., and Vogel, U. (2011). Heme oxygenase-1 polymorphism is not associated with risk of colorectal cancer: A Danish prospective study. *European Journal of Gastroenterology and Hepatology*, 23(3), 282-285.

DeMeyer, D., Mertens, B., De Smet, S., Ulens, M. (2016). Mechanisms linking colorectal cancer to the consumption of (processed) red meat: a review. *Critical Reviews in Food Science and Nutrition*. 56:2747-66.

EFSA NDA Panel. (2015). Scientific opinion on dietary reference values for iron. *EFSA Journal*, 13:4254-4369.

Lippi G, Mattiuzzi C, Cervellin G. Meat consumption and cancer risk: a critical review of published meta-analyses. *Crit Rev Oncol Hematol* 2016;97:1-14.

National Food Institute, Technical University of Denmark. (2016).

Mechanisms behind cancer risks associated with consumption of red and processed meat. ISBN 978-87-93109-82-7. Available at www.food.dtu.dk

Oostindjer M, Alexander J, Amdam GV, Andersen G, Bryan NS, Chen D, Corpet DE, De Smet S, Dragsted LO, Haug A, Karlsson AH, Kleter G, de Kok TM, Kulseng B, Milkowski AL, Martin RJ, Pajari AM, Paulsen JE, Pickova J, Rudi K, Sødring M, Weed DL, Egelandstal B. The role of red and processed meat in colorectal cancer development: a perspective. *Meat Sci* 2014;97(4):583-596.

Richi, E.B., Baumer, B., Conrad, B., et al. (2015). Health risks associated with meat consumption: a review of epidemiological studies. *Int J Vitam Nutr Res* 85:70-78.

Trudo. S.P. and Gallaher, D.D. (2015). Meat and colorectal cancer: associations and issues. *Current Nutrition Reports*. 4:33-39.

Yebra-Pimentel, I., et al. (2015). A critical review about the health risk assessment of PAHs and their metabolites in foods. *Critical Reviews in Food Science and Nutrition*. 55:1383-1405.

Wolk, A. (2016). Potential health hazards of eating red meat. *J Intern Med*, ahead of print.

Zanini, S., Marzotto, M., Giovinazzo, F., Bassi, C., and Bellavite, P. (2015). Effects of dietary components on cancer of the digestive system. *Critical Reviews in Food Science and Nutrition*, 55, 1870-1885.

*Epidemiologic Studies of Meat and Cancer Risk Kim, A.E., Lundgreen, A., Wolff, R.K., et al. (2016). Red meat, poultry, and fish intake and breast cancer risk among Hispanic and non-Hispanic white women: The Breast Cancer Health Disparities Study. *Cancer Causes Control*, 27:527-43.

Ward, H.A., Norat, T., Overvad, K., et al. (2016). Pre-diagnostic meat and fibre intakes in relation to colorectal cancer survival in the European Prospective Investigation into Cancer and Nutrition. *British Journal of Nutrition*, 116;316-25.

Wu, K., Spiegelman, D., Hou, T., et al. (2016). Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: a pooled analysis of 15 prospective cohort studies. *Int J Cancer*, 138:2368-82.

*Meta-Analyses of Epidemiologic Studies regarding Meat and Cancer Risk Ananthakrishnan, A.N., Du, M., Berndt, S. I., et al. (2015). Red meat intake, NAT2, and risk of colorectal cancer: a pooled analysis of 11 studies. *Cancer Epidemiol Biomarkers Prev* 24:198-205.

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

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.

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.

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;34(6):521-543.

Bylsma LC, Alexander DD. A review and meta-analysis of prospective studies on red and processed meat, meat cooking methods, heme iron, heterocyclic amines and prostate cancer. *Nutr J* 2015;14:125.

*Epidemiological Studies Estimating HCA/PAH Intake from Meat Using CHARRED and Reporting Cancer Risk Ho, V., Peacock, S., Massey, T. E., Ashbury, J. E., Vanner, S. J., and King, W. D. (2014). Meat-derived carcinogens, genetic susceptibility and colorectal adenoma risk. *Genes and Nutrition*. 9(6):430.

Le, N.T., Michels, F.A.S, Song, M. (2016). A prospective analysis of meat mutagens and colorectal cancer in the Nurses' Health Study and Health Professional Follow-up Study. *Environmental Health Perspectives*, 124:1529-1536.

Lee, H. J., Wu, K., Cox, D. G., Hunter, D., Hankinson, S. E., Willett, W. C., Sinha, R., and Cho, E. (2013). Polymorphisms in xenobiotic metabolizing genes, intakes of heterocyclic amines and red meat, and postmenopausal breast cancer. *Nutrition and Cancer*. 65(8):1122-1131.

Barbir, A., Linseisen, J., Hermann, S., Kaaks, R., Teucher, B.,

Eichholzer, M., and Rohrmann, S. (2012). Effects of phenotypes in heterocyclic aromatic amine (HCA) metabolism-related genes on the association of HCA intake with the risk of colorectal adenomas. *Cancer Causes Control*. 23:1429-1442.

Fu, Z., Shrubsole, M. J., Li, G., Smalley, W. E., Hein, D. W., Chen, Z., Shyr, Y., Cai, Q., Ness, R. M., and Zheng, W. (2012). Using gene-environment interaction analyses to clarify the role of well-done meat and heterocyclic amine exposure in the etiology of colorectal polyps. *American Journal of Clinical Nutrition*. 96:1119-1128.

Melkonian, S.C., Daniel, C.R., Ye, Y., et al. (2015). Gene-Environment Interaction of Genome-Wide Association Study-Identified Susceptibility Loci and Meat-Cooking Mutagens in the Etiology of Renal Cell Carcinoma. *Cancer*, 122:108-15.

Steck, S. E., Butler, L. M., Keku, T., Antwi, S., Galanko, J., Sandler, R. S., and Hu, J. J. (2014). Nucleotide excision repair gene polymorphisms, meat intake and colon cancer risk. *Mutat Res* 762, 24-31.

Voutsinas, J., Wilkens, L. R., Franke, A., Vogt, T. M., Yokochi, L. A., Decker, R., and Le Marchand, L. (2013). Heterocyclic amine intake, smoking, cytochrome P450 1A2 and N-acetylation phenotypes, and risk of colorectal adenoma in a multiethnic population. *Gastroenterology*. 62(3):416-422.

*Epidemiological Studies Estimating HCA/PAH Intake from Meat through various methods and Reporting Cancer Risk Budhathoki, S., Iwasaki, M., Yamaji, T., Sasazuki, S., Takachi, R., Sakamoto, H., Yoshida, T., and Tsugane, S. (2015). Dietary heterocyclic amine intake, NAT2 genetic polymorphism, and colorectal adenoma risk: the colorectal adenoma study in Tokyo. *Cancer Epidemiology, Biomarkers and Prevention*. 24(3):613-620.

Burnett-Hartman, A. N., Newcomb, P. A., Mandelson, M. T., Adams, S. V., Wernli, K. J., Shadman, M., Wurscher, M. A., and Makar, K. W. (2011). Colorectal polyp type and the association with charred meat consumption, smoking, and microsomal epoxide hydrolase polymorphisms. *Nutr Cancer* 63, 583-92.

Gilsing, A. M. J., Berndt, S. I., Ruder, E. H., Graubard, B. I., Ferrucci, L. M., Burdett, L., Weissfeld, J. L., Cross, A. J., and Sinha, R. (2012). Meat-related mutagen exposure, xenobiotic metabolizing gene polymorphisms and the risk of advanced

colorectal adenoma and cancer. *Carcinogenesis*. 33(7):1332-1339.

Joshi, A. D., Corral, R., Catsburg, C., Lewinger, J. P., Koo, J., John, E. M., Ingles, S. A., and Stern, M. C. (2012). Red meat and poultry, cooking practices, genetic susceptibility and risk of prostate cancer: results from a multiethnic case-control study. *Carcinogenesis*. 33(11):2108-2118.

Van Hemelrijck, M., Rohrmann, S., Steinbrecher, A., Delbrueck, M., Kaaks, R., Teucher, B., and Linseisen, J. (2012). Heterocyclic aromatic amines [HCA] intake and prostate cancer risk: effect modification by genetic variants. *Nutrition and Cancer*. 64(5):704-713.

*Epidemiological Studies of Heme Iron Intake and Cancer Risk
Andersen, V., Christensen, J., Overvad, K., Tjonneland, A., and Vogel, U. (2011). Heme oxygenase-1 polymorphism is not associated with risk of colorectal cancer: A Danish prospective study. *European Journal of Gastroenterology and Hepatology*, 23(3), 282-285.

Andersen, V., Holst, R., and Vogel, U. (2013). Systematic review: diet-gene interactions and the risk of colorectal cancer. *Alimentary Pharmacology and Therapeutics*, 37, 383-391.

Andersen, V., Kopp, T.V., Tjonneland, A. and Vogel, U., (2015). No Association between HMOX1 and Risk of Colorectal Cancer and No Interaction with Diet and Lifestyle Factors in a Perspective Danish Case-Cohort Study. *International Journal of Molecular Sciences*, 16, 1375-1384.

Ashmore, J.H., Rogers, C.J., Kelleher, S.L., et al. (2016). Dietary iron and colorectal cancer risk: a review of human population studies. *Critical Reviews in Food Science and Nutrition*, 56:1012-1020.

Gilsing, A. M. J., Fransen, F., de Kok, T. M., Goldbohm, A. R., Schouten, L. J., de Bruine, A. P., van Engeland, M., van den Brandt, P. A., de Goeij, A. F. P. M., and Weijenberg, M. P. (2013). Dietary heme iron and the risk of colorectal cancer with specific mutations in KRAS and APC. *Carcinogenesis*, 34(12), 2757-2766.

Surya, R., Helies-Toussaint, C., Martin, O., et al. (2016). Red meat and colorectal cancer: Nrf2-dependent antioxidant response contributes to the resistance of preneoplastic colon cells to

fecal water of hemoglobin- and beef-fed rats. *Carcinogenesis*, 37:635-645.

Ruder, E. H., Berndt, S. I., Gilsing, A. M. J., Graubard, B. I., Burdett, L., Hayes, R. B., Weissfeld, J. L., Ferrucci, L. M., Sinha, R., and Cross, A. J. (2014). Dietary iron, iron homeostatic gene polymorphisms and the risk of advanced colorectal adenoma and cancer. *Carcinogenesis*, 35(6), 1276-1283.

*Human and/or Animal Studies of HCA/PAH from Meat and Markers of Cancer Risk Le Marchand L, Yonemori K, White KK, Franke AA, Wilkens LR, Turesky RJ. Dose validation of PhiP hair level as a biomarker of heterocyclic aromatic amines exposure: a feeding study. *Carcinogenesis* 2016;37(7):685-691.

Oberli, M., Lan, A., Khodorova, N., et al. (2016). Compared with raw bovine meat, boiling but not grilling, barbecuing, or roasting decreases protein digestibility without any major consequences for intestinal mucosa in rats although daily ingestion of bovine meat induces histologic modifications in the colon. *The Journal of Nutrition*, 146:1506-13.

*Human and/or Animal Studies of Heme Iron from Meat and Other Sources and Markers of Cancer Risk Bastide, N. M., Chenni, F., Audebert, M., Santarelli, R. L., Tache, S., Naud, N., Baradat, M., Jouanin, I., Surya, R., Hobbs, D. A., Kuhnle, G. G., Raymond-Letron, I., Gueraud, F., Corpet, D. E., and Pierre, F. H. F. (2015). A central role for heme iron in colon carcinogenesis associated with red meat intake. *Cancer Research*, 75(5), 870-879.

DeStefani, E., Boffetta, P., Ronco, A.L. (2016). Meat consumption, related nutrients, obesity and risk of prostate cancer: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 17:1937-1945.

Gueraud, F., Tache, S. Steghens, J. P., Milkovic, L., Borovic-Sunjic, S., Zarkovic, N., Gaultier, E., Naud, N., Helies-Toussaint, C., Pierre, F., and Priymenko, N. (2015). Dietary polyunsaturated fatty acids and heme iron induce oxidative stress biomarkers and a cancer promoting environment in the colon of rats. *Free Radical Biology and Medicine*, 83, 192-200.

Martin, O. C. B., Naud, N., Tache, S., Raymond-Letron, I., Corpet, D. E., and Pierre, F. H. (2015). Antibiotic suppression of intestinal microbiota reduces heme-induced lipoperoxidation

associated with colon carcinogenesis in rats. *Nutrition and Cancer*, 67(1), 119-125.

Sodring, M., Oostindjer, M., Egeland, B., and Paulsen, J. E. (2015). Effects of heme and nitrite on intestinal tumorigenesis in the A/J Min/+ mouse model. *PLoS One*, 10(4), 1-15.

*Human and/or Animal Studies of Meat as Part of a Whole Diet and Markers of Cancer Risk Shaughnessy, D. T., Gangarosa, L. M., Schliebe, B., Umbach, D. M., Xu, Z., MacIntosh, B., Knize, M. G., Matthews, P. P., Swank, A. E., Sandler, R. S., DeMarini, D. M., and Taylor, J. A. (2011). Inhibition of fried meat-induced colorectal DNA damage and altered systemic genotoxicity in humans by crucifera, chlorophyllin, and yogurt. *PLoS ONE*. 6(4):e18707. doi: 10.1371/journal.pone.0018707.

Parasramka, M. A., Dashwood, W. M., Wang, R., Abdelli, A., Bailey, G. S., Williams, D. E., Ho, E., and Dashwood, R. H. (2012). MicroRNA profiling of carcinogen-induced rat colon tumors and the influence of dietary spinach. *Molecular Nutrition and Food Research*. 56(8):1259-1269.
User Confirmation Number: 13340