Received via email on October 7, 2016
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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 data on dietary intake estimates of red meat, processed meat, or meat cooked at high temperatures, we submit the following:

Current Dietary Intake Estimates Limit the Ability to Clearly Define the Exposure or Isolate a Single Substance Indicative of Exposure, as discussed in the following evidence-based reviews and studies Gibis 2016; Alaejos and Afonso, 2011; Singh et al., 2016; Le Marchand et al., 2016; Trudo and Gallaher, 2015; DGAC, 2015; Oostindjer et al., 2014.

Several scientific issues confound the ability to accurately assess the consumption of red meat, processed meat, and meat cooked at high temperatures as potentially carcinogenic exposures as discussed in the these evidence-based reviews and studies DGAC, 2015; Oostindjer et al., 2014; Gibis 2016; Alaejos and Afonso, 2011; Le Marchand et al., 2016. These include, but are not limited to:

*limited availability of reliable national data regarding the intake of meat cooked via high or low temperature cooking methods (Le Marchand et al., 2016; DeMeyer et al., 2016); *limited ability to separate red and processed meat both from national survey data as well as in research studies (DGAC 2015; Trudo and Gallaher, 2015; Oostindjer et al., 2014); *a myriad of reactions and compounds generated during the cooking of meat (regardless of temperature) that need to be considered in isolation rather than grouped together as a single exposure (Gibis, 2016); *the fact that meat is consumed as part of a total diet which allows for the contribution and interaction of nutrients and compounds from other foods that may inhibit or enhance the potential

carcinogenicity of meat-related substances and (Oostindjer et al., 2014); *few, if any, nutrients, compounds, substances associated with the consumption of meat are uniquely related to meat (DeMeyer et al., 2015)

Most importantly, at least two of these issues have already been recognized by the National Toxicology Program(NTP).

Meat cooked at high temperatures can result in the formation of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). In the 13th edition of the RoC, NTP evaluated four HCAs, specifically MeIQ; MeIQx; PhiP; and IQ, and all were found to be "reasonably anticipated to be a human carcinogen" (NTP, 2014). However, regarding a common source of these compounds, i.e. meat, the NTP concluded "Epidemiological evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans. However, the presence of an individual HCA in cooked meat is highly correlated with the presence of other HCAs and with many other constituents, including protein, animal fat, nitrosamines, and substances other than HCAs formed during cooking, such as polycyclic aromatic hydrocarbons. Furthermore, the carcinogenic effects of these HCAs may be inhibited or enhanced by many factors, including interactions of HCA mixtures."

Consistent with NTP's conclusions above, the following studies and evidence-based reviews provide similar conclusions:

*The complexity of cooked meat precludes a reliable and targeted exposure assessment of compounds formed during cooking (Gibis 2016; Alaejos and Afonso, 2011) **"In complex matrices such as meat and fish products, heterocyclic aromatic amines (HAAs) are only present in pbb concentrations and the efficiency of sample preparation is affected by the matrices. The sensitive and precise quantification of these compounds is complicated." (Gibis, 2016) [Note: HCAs and HAAs are the same chemical compounds] **In their comprehensive review, Alaejos and Afonso (2011) recognize research gaps and recommend the following to improve exposure assessments of compounds formed during cooking, "… (1) to establish databases on HAAs content in cooked foods that are representative for the eating habits of the population being studied, and taking into account each ingredient of the recipe; (2) to record the inside and outside food appearance in the food frequency questionnaires, instead of simply recording the "doneness level;" (3) to consider the possible role of HAAs in the cancer development in conjunction with PAHs and other

toxic compounds; and (4) to use biomarkers in order to determine the HAAs exposure."

**In the Report on Carcinogens Background Document (2012), commissioned by NTP, the authors note: "Dietary exposure to PhIP, MeIQ, MeIQX has been difficult to quantify because many studies fail to include descriptions of the cooking methods. These studies, which are concerned primarily with method development, typically report results for samples that are cooked to maximize HCA production; they are not representative of general domestic cooking methods."

The complexity of a complete diet causes difficulty in the evaluation of the carcinogenicity of individual substances associated with consumption of various food components(NRC, 1996) .

*More specifically, Oostindjer and co-workers (2014) conclude, "A major question, however, in relation to meat in the diet that remains is how the formation of carcinogenic compounds during the digestion of meat is modulated by nutrients and compounds from other food items in a meal".

*DeMeyer and coworkers (2016) conclude, "Indeed, comparable levels of PAHs are found in cereal products and in grilled poultry and fish, foods not found to be associated with an increased risk for CRC."

*"Assessment of exposure is a major challenge in epidemiological studies of diet and cancer. Exposure to PhIP and other HAAs is usually assessed in these studies with food frequency questionnaires (FFQs), which are problematic when exposure to the compound of interest spreads over a range of food items at varying levels of concentrations." (Le Marchand et al., 2016)

*"Two highly impactful discrepancies in epidemiologic studies of meat and colorectal cancer are how red and processed meat are defined (i.e., no uniform classification/categorization) and the frequent grouping of the two together despite the great variability in the composition of red meat and processed meat." (Trudo and Gallaher, 2015).

*Lippi et al. (2015) conclude, "…development and application of universally agreed definitions of meat subtypes and products are unavoidable steps in future clinical studies aimed to investigate the association between meat consumption and cancer".

In response to the request for scientific issues important for

prioritizing and assessing adverse health outcomes related to consumption of red meat, processed meat, or meat cooked at high temperatures, we submit the following:

2. NTP provides three criteria that qualify a substance to be considered as “reasonably anticipated to be a human carcinogen”:

NTP Criteria 1 - There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not be adequately excluded.

NTP has already concluded that there is insufficient evidence for the carcinogenicity of the 4 most common HCAs when consumed from meats cooked at high temperatures (ROC, 2014).

*Specifically, NTP notes in the 13th addition of the RoC “Epidemiological evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans. However, the presence of an individual HCA in cooked meat is highly correlated with the presence of other HCAs and with many other constituents, including protein, animal fat, nitrosamines, and substances other than HCAs formed during cooking, such as polycyclic aromatic hydrocarbons. Furthermore, the carcinogenic effects of these HCAs may be inhibited or enhanced by many factors, including interactions of HCA mixtures. It is therefore difficult for human epidemiological studies to establish associations between cancer risk and specific HCAs. For each of these four selected HCAs, the data from epidemiological studies are insufficient to evaluate whether the increased cancer risk is due specifically to consumption of that particular HCA in food (NTP 2002).”

The following studies Bylsma and Alexander, 2015; Klurfeld, 2015; Alexander et al., 2015; Alexander et al., 2010; Alexander et al., 2010b; and Alexander et al., 2010c show that the available evidence-base from human epidemiologic studies is insufficient to support a causal relationship and thus does not contain sufficient evidence to meet the standard for a credible causal relationship.

*After systematic review of the epidemiological literature regarding meat and prostate cancer risk, Bylsma and Alexander (2015) conclude, “No significant summary relative risk estimates (SRREs) were observed for any of the meat cooking methods, HCA,

or heme iron analyses. Dose-response analyses did not reveal significant patterns of associations between red or processed meat and prostate cancer. In conclusion, the results from our analyses do not support an association between red meat or processed consumption and prostate cancer, although we observed a weak positive summary estimate for processed meats.

*Regarding if the evidence supporting the hypothesis that meat increases cancer risk satisfies Bradford Hill's criteria of causation, Klurfeld concludes, "The majority of the nine considerations Hill enumerated in 1963 for determining a causal relationship from observational studies have not been fulfilled for meat and any adverse health outcome; although there is no minimum number needed, when only a minority of factors are satisfied the confidence in the relationship being independently causal is necessarily low."

Additionally, in the last couple of decades, as reviewed by Lippi and co-workers (2015) epidemiological studies published on red meat and various cancers have reported mixed associations generally around a null association of 1.0 to a weakly positive association of 1.2. More specifically, in the data presented by Lippi and co-workers (2015) about one-third of the time the associations are null or even inverse and 2/3rds of the time only half of the weak positive associations reach statistical significance. As discussed by Oostindjer and co-workers (2014) and Trudo and Gallaher (2015), it is well accepted within the scientific community that weak positive associations are more representative of confounding by factors associated with overall diet and lifestyle patterns, i.e. smoking, obesity, limited fruit and vegetable consumption, and insufficient physical activity, rather than any single food's influence on cancer risk.

As discussed by Bouvard et al. (2015), while IARC has recently concluded that there is limited evidence of the carcinogenicity of red meat in humans, it must be remembered that to make this determination IARC relied, at least in part, on 29 epidemiological studies (14 prospective cohort studies; 15 case control studies) less than half of which reported any association between red meat and cancer. Furthermore, as discussed by DeMeyer et al. (2015) of all of the proposed biologically mechanisms (i.e. heme iron, HCAs, PAHs, N-nitroso compounds), none are unique to red meat and, in fact, considering all source of exposure to these compounds, red meat plays a minor role.

NTP Criteria 2 - there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset.

Studies in experimental animals provide inadequate evidence of carcinogenicity of red meat (Bouvard et al., 2015, on behalf of IARC).

IARC has recently concluded that “There is inadequate evidence in experimental animals for the carcinogenicity of consumption of red meat and of processed meat” (Bouvard et al., 2015, on behalf of IARC. Many animal studies of red meat and cancer risk employ flawed methodology including utilization of high levels of exposure (up to 3 orders of magnitude greater than USDA recommended human intake of meat) combined with methodologic perturbations known to exacerbate findings (such as low calcium or high fat diets) (Hayes et al., 2011; Trudo and Gallaher; 2015).

NTP Criteria 3 - there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous NTP Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

In addition to less than sufficient evidence of carcinogenicity in both humans and experimental animals, any of red meat, processed meat, and meat cooked at high temperatures, do not belong to a class of well-defined, structurally related substances previously reviewed in the RoC (see previously reviewed substances in ROCs to date), nor is there convincing relevant information that these foods act through mechanisms likely to cause cancer (Klurfeld, 2015). The RoC has never reviewed a whole food as a carcinogen as described by NTP Criteria 3. With regard to mechanisms likely to cause cancer, studies that have investigated mechanisms related to red meat and carcinogenicity include in vitro assays, animal models and clinical trials. It is important to note that many of the studies

contain methodologic flaws and are based on limited evidence in models that are not appropriate to utilize in risk assessment as reviewed by Hayes et al., 2011. These models explored mechanisms utilizing high levels of exposure (up to 3 orders of magnitude greater than USDA recommended human intake of meat) combined with methodologic perturbations known to exacerbate findings (such as low calcium or high fat diets) (Hayes et al., 2011; Oostindjer et al., 2014). A lack of appropriate studies documenting dose-response and thresholds for the mechanisms investigated precludes assignment of these mechanisms as relevant under conditions of more modest exposure as part of a usual diet (NRC, 1996; Bidlack et al., 2009).

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