On 9/11/18, 8:29 AM, "NTP Website" <ntpweb-noreply@ntp.niehs.nih.gov> wrote:

The following comments have been submitted to the Office of the Report on Carcinogens.

Our record of the submission is:

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Input Type: citations
Input: Dr. Ruth Lunn Director,
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Re: Nomination of Meat-Related Exposures to the National Toxicology Program for the Report on Carcinogens

Dear Dr. Lunn:

In a submission made on October 7, 2016, The Beef Checkoff provided evidence (reference number 13333) to the Office of the Report on Carcinogens (RoC) regarding the insufficiency of mechanistic evidence from experimental animals and humans for the carcinogenicity of red or processed meat.

Since our earlier comment, a new study (Kruger and Zhou 2018; see attached) has been published which reviews the mechanistic evidence for heme iron from red and processed meat and colorectal cancer (CRC) risk. We would like to take this opportunity to provide your Office with a brief review of this new study.

Kruger and Zhou (2018) completed a systematic review of the published literature from 1998 to the present. Evidence from all studies (i.e. in vitro, animal, clinical) that used heme, hemin, or red meat as treatments, and considered outcomes relevant to CRC was considered. In vitro studies largely examined the mechanisms by which hemoglobin could contribute to DNA damage either directly or via the generation of lipid peroxide radicals or potentiation of nitric oxide-mediated nitrosation.

In vivo studies primarily involved rats given hemin or hemoglobin at levels that corresponding to 11–360,724 times the current recommendations by the Dietary Guidelines for Americans for total intake of meat and evaluated the potential for increased lipid peroxidation and neoplastic promotion via analysis of the composition of fecal water. The authors note that such study designs do not evaluate exposure conditions that are representative of realistic human exposures to red or processed meat.

Finally, clinical studies examined the production and potential genotoxic consequence of apparent total nitroso compounds (ATNC) formed with and without the ingestion of red meat. Similar to the observations for in vivo studies with laboratory animals, the levels of red meat ingestion in many of the studies far exceeded U.S. dietary guidance for total meat intake. In addition the authors report, "…methodologic inconsistencies such as errors in dose calculations, errors in units reported for NOC and heme, lack of or unspecified wash-out periods, inconsistent reporting of dietary periods, no non-meat controls and lack of analytical method validation."

The authors determine that, "… the relevance of the findings from many of the studies for a human health risk assessment is unknown because there are no data that bridge the level and duration of exposure used in these studies to the conditions of exposure that would occur in an in vivo situation." The authors further note that although clinical studies report a strong link between dietary hem and NOC formation, "…most did not differentiate between the N-nitrosamines that are mainly linked to colorectal cancer and other compounds, such as S-nitrosothiols, iron nitrosyls, and dinitrosyl iron complexes which are not linked to cancer." Results from the few studies that did differentiate between nitrosamines indicate that ATNC found after ingestion of red meat are mainly of nitrosyl iron and nitrosothiols, compounds not linked to increased cancer risk in humans.

The authors conclude that the current evidence base is insufficient to indicate "…that heme would contribute to an increased risk of initiation or promotion of preneoplasia or colon cancer at usual dietary intakes of red meat in the context of a normal diet." These results are consistent with previous reports including those by Turner and Lloyd (2017) and Habermeyer et al., (2015).

REFERENCES:

Habermeyer M, et al. 2015. Nitrate and nitrite in the diet: how to assess their benefit and risk for human health. Mol Nutr Food Res. 59:106-128.

Kruger C and Zhou Y. 2018. Red meat and colon cancer: a review of mechanistic evidence for heme in the context of risk assessment methodology. Food Chem Tox. 118:131-153.

Turner ND and Lloyd SK. 2017. Association between red meat consumption and colon cancer: A systematic review of experimental results. Exp Biol Med (Maywood). 242:813-839.

The files sent as attachments were:

Kruger and Zhou, 2018.pdf
