May 8, 2014

Ms. Cynthia Oshita
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

RE: Comments on: "Notice of Intent to List: Nitrite in Combination with Amines or Amides" February 7, 2014.

Dear Ms. Oshita:

On behalf of the members of the North American Meat Association (NAMA), we respectfully submit the following comments in response to the "Notice of Intent to List: Nitrite in Combination with Amines or Amides" issued by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) on February 7, 2014.

Organized in 1942, NAMA represents the interests of meat packers and processors throughout the United States, Canada, and Mexico. With nearly 400 meat processing members, many of whom produce processed meat items using nitrites and market products in California, NAMA has a profound interest in the outcomes related to this specific Notice of Intent to List. Since its inception, NAMA has been a leader in supporting effective measures and good manufacturing practices designed to protect public health.

NAMA Strongly Opposes the Listing of "Nitrite in Combination with Amines or Amides" as known to the State of California to Cause Cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

The opposition to list "nitrite in combination with amines or amides" as known cancer causing agents is based primarily on two significant facts. First, current scientific evidence refutes the International Agency for Research on Cancer's (IARC) Monograph Number 94's conclusions. Second, a technical report published by the U.S. National Toxicology Program (NTP) in 2001, also has findings which contradict the IARC's conclusions.

The OEHHA incorrectly relies on IARC's Monograph Number 94 on ingested nitrites and nitrates as the basis for the proposed Proposition 65 listing. IARC's overall evaluation was "Ingested nitrate or nitrite under the conditions that result in endogenous nitrosation is probably carcinogenic to humans (Group 2A)." This conclusion was based primarily on their findings of "limited evidence in humans for the carcinogenicity of nitrite in food" and "sufficient evidence in experimental animals for the carcinogenicity of nitrite in combination with amines or amides."

IARC conducted its monograph review meeting in June 2006 and published the final monograph in July 2010. Since 2006, scientific evidence has been published that, if now fully considered by IARC, would change their determination to "not classifiable as to its carcinogenicity to humans-Group 3."

This assertion is supported by the fact that a group of experts in nitrite physiology, toxicology, meat-curing chemistry, and epidemiology published, in 2012, a review of the new and growing scientific body of evidence regarding nitrites, nitrates and cancer.[1] These scientists concluded that if the following information had been considered by IARC, the Group 2A classification would not have been scientifically supportable:

- The human nitrogen oxide metabolism was not addressed, specifically the importance of *S*-nitrosation;
- New epidemiological evidence shows no association between dietary intake of nitrite and stomach cancer, which was the only organ determined by the IARC Working Group to demonstrate an increased incidence of cancer; and
- Quality of animal toxicology studies considered by IARC did not have the scientific rigor that other authoritative groups used for their determinations.

This scientific evidence was submitted to IARC in 2012.[2] To date, IARC has not refuted the experts' assessment of the scientific evidence submitted. The experts requested IARC reconsider its 2006 conclusion as they believed:

"*…there is inadequate evidence for carcinogenicity in humans and also inadequate evidence in experimental animals for the carcinogenicity of nitrite* per se*. Therefore, according to IARC carcinogenicity criteria, the overall classification for ingested nitrite and nitrate would then be determined to be Group 3*-**The agent is not classifiable as to its carcinogenicity to humans.**"[3]

Over two decades ago, the Food and Drug Administration (FDA) nominated sodium nitrite for further carcinogenicity and genotoxicity evaluation to NTP to better assess whether nitrite *per se*

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1 Bryan, N., Alexander, D., Coughlin, J., Milkowski, A. and Boffetta, P. (2012a). Ingested nitrate and nitrite and stomach cancer risk: an updated review. *Food Chem Tox.* 50:3646-3665.

2 Bryan, N., Alexander, D., Coughlin, J., Milkowski, A. and Boffetta, P. (2012b). Personal Correspondence to Dr. Christopher Wild, Director, International Agency for Research on Cancer

3.*Id.*

was a carcinogen. The two-year cancer bioassay study in rats and mice was commissioned based on nitrite's use in cured meat and poultry products, and at that time, concerns regarding the formation of carcinogenic *N*-nitrosamines. The *NTP Technical Report No. 495* (2001) for sodium nitrite was the most definitive, chronic carcinogenic bioassay study ever conducted and the resulting conclusion went through extensive public peer review. The only adverse finding of this study was "equivocal evidence" in the forestomach in female mice. Since humans do not have a forestomach, it is not considered to be an appropriate organ for human cancer hazard assessment.

NTP's bioassay study of sodium nitrite reported "None" for "neoplastic effects" in male and female rats and mice and "no evidence" of carcinogenic activity in male and female rats and male mice. In summary, NTP found no consequential toxicological hazard to humans through exposure to nitrite. Accordingly, NAMA believes OEHHA should fully and equally consider the findings of NTP in its deliberations for the proposed Proposition 65 listing. It must be noted that OEHHA considers NTP an authoritative body, and *NTP Technical Report No. 495* (2001) is considered a gold standard bioassay study by the scientific community.

Accordingly, there is a significant body of scientific evidence developed both before and after the IARC's Monograph Number 94 that contradict its conclusions. This body of evidence clearly demonstrates that the underlying foundation supporting the proposed Proposition 65 listing of nitrite in combination with amines or amides is clearly flawed and not scientifically supported. Therefore, the proposed Proposition 65 listing must be withdrawn.

Should OEHHA Proceed with the Proposed Listing of Nitrites in Combination with Amines or Amides, There Will be a Number of Significant Unintended Adverse Consequences.

A search of the National Institutes of Health ongoing projects reveals that more than 50 studies have been funded regarding the role of nitrite in human health. The goal of these studies is to better understand how nitrites impact cardiovascular disease and treatments for foodborne illnesses, and pulmonary and other diseases.[4] For example:

"*…the nutritional implications of nitrate and nitrite biology are among the most intriguing in this area of research. The amounts of these anions needed for the effects on the cardiovascular system, described in this review, are readily achieved via our everyday diet, most easily via a rich intake of fruits and vegetables. If the cardiovascular benefits of this healthy diet turn out to be related to their high amount of nitrate, we have to reconsider our current thinking and realize that inorganic nitrate may not necessarily be a threat to human health. Instead, in some years, we might even consider this anion as an essential nutrient."* [5]

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4 National Institutes of Health's Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. Accessed March 31, 2014.

5 Lundberg, J., Carström, M., Larsen, F., and Weitzberg, E. (2011). Roles of dietary inorganic nitrate in cardiovascular health and disease. *Cardiovascular Research*. 89:525-532.

This hypothesis is further supported by Bryan *et al.* (2014).6 Given this growing body of evidence, the proposed listing could stifle innovation and advances in the human medical arena and have an adverse impact on human health. OEHHA should not underestimate the impact of the proposed Proposition 65 listing on current research and potential future research and research funding in its final decision.

Saliva accounts for more than 90 percent of the total daily ingested nitrite exposure to humans. Nitrate absorbed from food such as green leafy vegetables, is excreted in saliva and bacteria in the human mouth convert the nitrate to nitrite. That being the case, human exposure to nitrites, amines, and amides is high because these substances are ubiquitous in nature. This physiological fact and considering almost all foods contain amines or amides, the proposed Proposition 65 listing would require all foods to display the required warning. Requiring such a warning label on all foods is counterproductive and unreasonable.

Summary and Conclusion

NAMA has been and will remain a leader in supporting science as the foundation to developing sound regulatory requirements, effective enforcement measures and good manufacturing practices, all of which are designed to protect public health. We strongly oppose the Proposition 65 listing of nitrite in combination with amines or amides because the underlying scientific justification is critically flawed. IARC, the authoritative body that OEHHA relied upon, did not fully consider the body of scientific evidence available at the time of their determination nor incorporate the extensive scientific evidence that became available after 2006. This clearly demonstrates that IARC's deliberative process and final determinations are not scientifically supportable. Further, the potential for adverse unintended consequences of the proposed Proposition 65 listing on current and future human medical research and the overreaching impact on all food labels must not be underestimated. For these reasons, NAMA strongly recommends that OEHHA withdraws the February 7, 2014, *Notice of Intent to List: Nitrite in Combination with Amines or Amides*.

Sincerely,

Barry L. Carpenter

Barry L. Carpenter
Chief Executive Officer

6 Bryan, N. (2014). Defining nitrite and nitrate as dietary nutrients. Under Review.