Via Electronic Mail to P65Public.Comments@oehha.ca.gov

May 8, 2014

Ms. Cynthia Oshita
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P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

RE: Notice of Intent to List: Nitrite in Combination with Amines or Amides

Dear Ms. Oshita,

This letter is in response to the Office of Environmental Health Hazard Assessment’s (OEHHA) February 7, 2014 Notice of Intent to List: Nitrite in combination with amines and amides as known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986. Our members located in Arizona and California provide half of the nation’s fresh produce and pride themselves in providing healthy choices for America. The Notice of Intent to List explicitly cites nitrite as a natural constituent of fresh produce, specifically celery and spinach. As fruits and vegetables are known to contain nitrite, we would like to address the validity of the reasoning to support the listing of nitrite in combination with amines and amides set forth by Proposition 65 authoritative bodies listing mechanism.

Additionally, the listing of “nitrite in combination with amines and amides” as a category of chemicals is inappropriate when performing a carcinogenicity assessment. The intent to list is based on the International Agency for Research on Cancer’s (IARC) conclusion that there is sufficient evidence that ingested nitrite in combination with amides and amines is carcinogenic in animals. However, there are already numerous nitrosamines listed in Proposition 65; the ability of OEHHA to regulate the formation of such nitrosamines exogenously and endogenously is a formidable and seemingly impossible task. Further, much of the research on which the IARC based its reasoning is more than 30 years old and outdated study designs raises questions about the results. Finally, in light of the current obesity health crisis now is not the time to cast public doubt on the health benefits of fresh produce consumption. Fresh produce provides a vast number of compounds that have consistently been shown to play a significant role in cancer prevention.
Nitrite with amines and amides as a broad category

The listing of amines as a broad category will make regulation impractical. Not all amines were found to be carcinogenic by study authors. For example, Lijinsky and Taylor (1977) exposed rats to 13 different secondary and tertiary amines in combination with nitrite, and only a few of the exposed experimental animal groups had increased tumor incidence. Two studies by Greenblatt et al. (1971 and 1973) concluded that piperazine, morpholine, or N-methaniline in combination with nitrite induced lung adenomas. However, in another study by the same author, a different set of amines failed to induce lung adenomas (Greenblatt and Lijinsky, 1972). Similar findings were found throughout the IARC’s report; some amines were found to increase the incidence of carcinogenicity, when others did not. Such differences will provide OEHHA with the difficult task of determining the specific compounds and the concentrations at which these compounds may be carcinogenic. Further, determining Safe Harbor Limits for particular compounds will be impossible to enforce as the type and concentrations of nitrite, amines, and amides varies within each food. Currently there are amines already listed by Proposition 65 (e.g., acetamide, acrylamide, amoxapine, N-nitrosodi-n-butylamine, etc.), in addition to nitrite already being regulated and limited in food products and drinking water. It is unclear why OEHHA chose to list amines as a broad category, instead of specifically listing amines known to interact with nitrite. Listing nitrite in combination with amines and amides as a broad category is confusing and uninformative at best, and at worst, misrepresents the scientific findings. Listing all amines and amides in combination with nitrite is not supported by studies cited by the IARC, the authoritative body on which OEHHA is basing their decision.

The validity of the IARC’s classification for sufficient evidence for carcinogenicity in animals

The IARC used several studies to support their conclusion that there is sufficient evidence in experimental animals for the carcinogenicity of specific secondary and tertiary amines (e.g., morpholine, butylurea, disulfiram, aminopyrine, diphenhydramine, chlorpheniramine maleate, heptamethyleneimine hydrochloride, N,N-dimethyldecylelamine- N-oxide or bis(2-hydroxypropyl)-amine) in combination with nitrites. Each of the cited amines has different uses. Morpholine is an additive to fossil fuel and is found in shellac fruit wax. Disulfiram is a prescription drug rarely used to treat alcoholism due to its severe health effects. Aminopyrine is an analgesic used in the early twentieth century that is rarely used today due to its fatal bone marrow toxicity. Diphenhydramine and chlorpheniramine maleate are antihistamines. Butylurea and heptamethyleneimine hydrochloride are industrial chemicals. N,N-dimethyldecylelamine- N-oxide is a surfactant. Bis(2-hydroxypropyl)-amine is used in research. Morpholine is the only amine or amide specifically cited by the IARC that may result in exposure to both an amine cited by IARC and nitrite due to consumption of fruits or vegetables.

The IARC examined four studies on rats using morpholine in combination with nitrite. Each study was flawed in a number of ways. The Newberne and Shank (1973) study exposed groups of rats to a combination of nitrite and morpholine through diet. However, the study failed to create a treated control group exposed to morpholine alone. In the absence of such a control group, it is impossible to determine whether or not the increased incidence in tumors was the result of exposure to morpholine. Shank and Newberne (1976) conducted another study using nitrite and morpholine in rats and hamsters, and found a significant increase of tumor incidence only in the highest exposed rats but not
in hamsters. The studies by Mirvish et al. (1976) and Mirvish et al. (1983) also lacked treated control groups. Without a group exposed to morpholine or sodium nitrite alone, it is impossible to know if any increase in tumor incidence is a result of a combination of morpholine and nitrite and not simply due to an error in study design. Once more, these studies only focused on small groups of male rats. Additionally, the statistics used in the 1976 study were extremely unclear (as the IARC noted) and failed to report statistical significance between groups. However, both studies found that ascorbate inhibited in-vivo formation of N-nitroso compounds believed to be responsible for carcinogenicity. These findings provide evidence that fresh produce is the main source of many compounds that are known to protective against carcinogens (e.g., antioxidants such as ascorbate) and that it is ineffectual to evaluate these compounds in isolation from a complete normal human diet.

Further, of the sixteen rat studies used as evidence for carcinogenicity by the IARC, only one was completed within the last twenty years. In 1998 the EPA released guidelines for carcinogenicity research in animals and (EPA, 1998) and these studies do not meet the criteria. The studies consistently lacked a sufficient number of animals in each treatment or control group, as well as failed to report key statistical tests used for analysis.

Finally, doses of nitrite used in most of these studies far exceeded any potential exposure from a serving of spinach (1000 mg/kg versus 2.0 x 10^-6 mg/kg (Griesenbeck et al., 2009)) and an increase in tumor incidence was not seen in groups exposed to lower doses. A decision to list compounds as carcinogens carries strong economic and public health repercussions and the research used to support it must be scientifically sound.

The potential labeling of fresh produce as cancer causing goes against science and public policy

The listing of nitrite in combination with amines and amides as known to cause cancer will potentially require the labeling of particular fresh produce commodities as carcinogenic. Such labeling will be misleading and is contradictory to significant public health initiatives that are promoting the health benefits of eating diets rich in fruits and vegetables. Currently the Center for Disease Control and Prevention is taking part in a national campaign to increase fruit and vegetable consumption citing health benefits such as decreased risk of cancer, diabetes, and stroke (CDC, 2011). As part of their “ChooseMyPlate” initiative, the U.S. Department of Agriculture currently recommends that individuals fill half of their plate with fruits and vegetables (USDA, 2011). The State of California has embarked on several initiatives to encourage better nutrition. For example, the number one target area set forth by the California Obesity Prevention Program is increasing fruit and vegetable consumption (California Department of Public Health, 2014a). Another initiative focuses on increasing consumption of fresh produce in California school children (California Department of Education, 2013). The Network for a Healthy California targets lower income Californians to increase physical activity and fruit and vegetable consumption (California Department of Public Health, 2014b). Listing of nitrates in combination with amines and amides such that it requires the labeling of particular fruits and vegetables as known to cause cancer challenges the public health goals of these state-established programs and could potentially reduce any gains in the state’s efforts to improve the eating habits of its citizens.
OEHHA must assess the difference between exposure to nitrite in combination with amines and amides from fresh produce and exposure to these compounds that occurs when consuming processed and preserved meats. When consuming vegetables and fruit, the conditions that result in nitrosation are inhibited and therefore Proposition 65 listing should not include the risk of nitrite carcinogenicity when consuming fresh fruits and vegetables. Studies have shown that though vegetables contain naturally occurring nitrates and nitrites, carcinogenic nitrosamines are not present (Griesenbeck et al., 2009). Naturally occurring vitamin C, a common component of fresh produce, endogenously inhibits the formation of potentially carcinogenic N-nitroso compounds (Licht et al., 1988; Tannenbaum et al., 1991, OEHHA, N.D.). The IARC uses studies that do not include the consumption of various molecules, vitamins and minerals that are present in fresh produce that have been shown to counteract or prevent the potential formation of carcinogenic compounds. Individuals who consume increased levels of leafy green vegetables and other fresh produce have been shown to benefit by having lower rates of cancer, cardiovascular disease, and diabetes. In contrast, diets lacking in fruits and vegetables are associated with 14% of gastrointestinal cancer deaths, 11% ischemic heart disease, and 9% of stroke deaths globally (WHO, 2004). Even further, the World Health Organization (WHO) concluded that 2.7 lives would be saved per year with additional fruit and vegetable consumption (WHO, 2003).

Vegetables and fruits are the foundation of a healthy diet and the potential requirement for particular fresh produce items to be labeled as carcinogenic could lead to public confusion, mistrust, and avoidance and directly contradicts scientific evidence to the contrary.

In summary, the health benefits of consumption of fruits and vegetables are indisputable. Potentially requiring the labeling of particular fresh produce items as carcinogenic directly contradicts both state and national efforts to encourage increased fruit and vegetable consumption. Moreover, listing nitrites in combination with amines and amides as a category of chemicals known to cause cancer is inappropriate when performing a carcinogenicity assessment, and the evidence used by the IARC is insufficient, dated, and unsubstantiated, and should be rejected as justification for the Proposition 65 listing via the authoritative bodies mechanism.

Respectfully Submitted,

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References


