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Subject: Comments on Draft Food Contact Chemicals of High Concern Criteria Documentation (dated February 8, 2021)

Dear Ms. Malinowski,

The Alkylphenols & Ethoxylates Research Council (APERC) provides the following comments on the Draft Food Contact Chemicals of High Concern Criteria Documentation (Feb. 8, 2021) issued by the Maine Department of Environmental Protection (DEP). [1] The Draft identifies food packaging substances proposed for listing as food contact chemicals of high concern under Maine's *Toxic Chemicals in Food Packaging* law, which requires DEP to publish a list of no more than ten food contact chemicals of high concern to gather information on whether they are currently used in food packaging in Maine and to evaluate the possibility of safer alternatives. Nonylphenol (NP) and 4-Octylphenol (4-OP) are among the ten chemicals being proposed. APERC membership includes United States manufacturers of NP and 4-OP and their derivatives.[2]

In APERC's view the Draft Food Contact Chemicals of High Concern Criteria Documentation does not provide sufficient justification that either NP or 4-OP would be present in food contact packaging at sufficient levels to support their listing as food contact chemicals of high concern. The comments below are provided to further inform the DEP's consideration of these two substances.

[1] Maine Department of Environmental Protection. (2021, February 8). Toxic Chemicals in Food Packaging: Food Contact Chemicals of High Concern Criteria Documentation – Draft Posted for Public Comment
[2] Member companies of the Alkylphenols & Ethoxylates Research Council are The Dow Chemical Company, Dover Chemical Corporation and SI Group.

1. APERC is not aware of any use of NP and/or 4-OP as intentional ingredients in the manufacture of food packaging.

The *Toxic Chemicals in Food Packaging* law distinguishes "intentionally added chemicals", "intentional introduction" of a chemical in the formation of a package or packaging component from "incidental presence" as an unintended or undesired ingredient in packaging.

The law defines "intentionally added chemical" as a chemical that was added during the manufacture of a product or product component to provide a specific characteristic, appearance or quality or to perform a specific function.[3] [4]

The law defines "intentional introduction" as the act of deliberately using a regulated metal or other regulated chemical in the formation of a package or packaging component when its continued presence is desired in the final package or packaging component to provide a specific characteristic, appearance or quality".[5] Furthermore, this section states "the use of a regulated metal or other regulated chemical as a processing agent or intermediate to impart certain chemical or physical changes during manufacturing, when the incidental retention of a residue of the metal or chemical in the final package or packaging component is neither desired nor deliberate, is not considered intentional introduction for the purposes of this chapter".

The law defines "incidental presence" as "the presence of a regulated metal or other regulated chemical as an unintended or undesired ingredient of a package or packaging component." [6]

Reporting of chemical use of a priority food contact chemical or food contact chemical of high concern is required for any amount greater than the *de minimis.* [7] The d*e minimis* level for a food contact chemical of high concern that is an intentionally added chemical in a food package is defined as the practical quantification limit. [8] For a food contact chemical of high concern that is a contaminant present in a food package, the *de minimis* is defined as a concentration of 100 parts per million. [9]

The Draft Food Contact Chemicals of High Concern Criteria Documentation listing for 4-OP states that this substance is "commonly used as an intermediate in manufacturing processes." [10] It is APERC's understanding, as manufacturers of 4-OP and its derivatives, that this substance is used exclusively as a chemical intermediate precursor in the synthesis of other substances and has no

[3] Maine Chapter 277 An Act to Protect the Environment and Public Health by Further Reducing Toxic Chemicals in Packaging §1741, 11
[4] Maine Chapter 26-B Toxic Chemicals in Food Packaging §1741, 11
[5] Maine Chapter 277 §1732, 2-B
[6] Maine Chapter 277 §1732, 2-A
[7] Maine Chapter 26-B §1744, 1
[8] Maine Chapter 26B §1741, 6A
[9] Maine Chapter 26B §1741, 6B
[10] Maine Department of Environmental Protection. (2021, February 8).

known use as a direct ingredient on its own or in any formulated product, including food packaging.

The Draft Food Contact Chemicals of High Concern Criteria Documentation listing for NP states "among its many manufacturing uses, nonylphenol (NP) is commonly used as a stabilizer and intermediary in plastics production". [11] NP is not used on its own as a stabilizer. NP is used as a chemical intermediate in the manufacture of some plastic stabilizers.

2. The U.S. Centers for Disease Control and Prevention (CDC) conducted human biomonitoring on 4-OP in human urine between 2005 and 2010 and discontinued monitoring for this substance in 2015 on the basis that it was "largely undetectable in previous survey periods".

CDC's Division of Laboratory Sciences (DLS) operates the National Biomonitoring Program (NBP). CDC states that biomonitoring is the worldwide standard procedure for assessing people's exposure to chemicals that may be toxic, and responding to environmental public health issues.[12] CDC reports results for chemicals in human blood and urine samples based on samples collected from participants in CDC's National Health and Nutrition Examination Survey (NHANES), which obtains and releases health-related data from a nationally representative sample in two-year cycles.

4-OP was measured in the CDC NHANES program in human urine for the US population between 2005 and 2010.[13] [14] Urinary levels of 4-OP were detectable only at the 90th to 95th percentiles in the U.S. population in the NHANES data. Also, CDC determined that 4-OP would not be measured after survey years 2009-2010 "because concentrations have been largely undetectable in previous survey periods". [15] [16]

While recognizing that biomonitoring is a good measure of exposure, CDC notes that finding measurable amounts of 4-OP in urine does not imply that the levels found cause adverse health effects.

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[11] Maine Department of Environmental Protection. (2021, February 8).
[12] US Centers for Disease Control and Prevention/(2019.Jan). National Report on Human Exposure to Environmental Chemicals, Volumes 1 and 2 National Report on Human Exposure to Environmental Chemicals | CDC
[13] US Centers for Disease Control and Prevention (CDC). (Jan. 2019) Fourth National Report on Human Exposure to Environmental Chemicals Updated Tables, Jan. 2019, Volume One. CDC (2019, Jan) Fourth National Report on Human Exposure to Environmental Chemicals Update (cdc.gov)
[14] A footnote to the table summarizing the data for 4-tert-Octylphenol in the 2019 NHANES report states that the 2003-2004 data were removed due to potential for contamination that may have occurred during sampling.
[15] US Centers for Disease Control and Prevention (CDC) (2015, Feb). Fourth National Report on Human Exposure to Chemicals. Updated 2015
[16] US CDC (2015, Feb).

Considering that the premier national biomonitoring program in the U.S. has determined that further biomonitoring for 4-OP is not warranted because it is largely undetectable, it seems that an important criterion for listing 4-OP as a food contact chemical of high concern is not met.

3. Numerous chronic and multi-generational mammalian toxicity studies are available for NP, which do not suggest concern for reproductive or developmental effects.

The Draft Food Contact Chemicals of High Concern Criteria Documentation for NP lists its classification as a Category 2 Reproductive Hazard under the European Union Classification and Labelling regulation due to its suspected damage to fertility as a reason to list it as a food contact chemical of concern.[17] [18]

Traditional toxicological studies in rats that measure chronic effects (due to long-term exposure) and/or monitor effects in parents and offspring over multiple generations often include an evaluation of reproductive and developmental effects that can be indicative of an endocrine mode of action. Numerous studies - some conducted over two or three generations - have evaluated whether the alleged weak estrogenic activity of NP affected reproductive or developmental end points in rats.[19,20,21,22, 23,24] These studies uniformly concluded that there are no effects on reproductive function or performance from NP at any of the doses tested. These findings are consistent with and support the results of a five-generation rat study conducted by the US National Institute of Environmental Health Sciences, which concluded that "NP was not a selective reproductive or developmental toxicant."[25] Another study by Tyl et al (2006) determined that there were no adverse effects on sperm following three generations of exposure in rats.[26]

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[17] Maine DEP (2021, February 8).
[18] European Commission DG Environment. (2000, Nov. 10). Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption. Final Report. Annex 10.
[19] Latendresse, J.R., *et al.* (2004). A Five Generation Reproductive Toxicity Assessment of *p*-Nonylphenol (NP) In CD Sprague-Dawley Rats. Toxicologist, 1066, 219.
[20] Nagao, T., *et al*. (2001). Reproductive Effects of Nonylphenol in Rats after Gavage Administration: A Two-Generation Study. Reproductive Toxicology, 15, 293-315.
[21] Odum, J. and Ashby, J. (2000). Neonatal Exposure of Male Rats to Nonylphenol Has No Effect on the Reproductive Tract. Toxicological Sciences, 56, 400-404.
[22]Odum, J., *et al*. (1999). Effects of p-nonylphenol (NP) and diethylstilboestrol (DES) on the Alderley Park (Alpk) Rat: Comparison of mammary gland and uterus sensitivity following oral gavage or implanted mini-pumps. Journal of Applied Toxicology 19, 367-378
[23] Cunny, H.C., et al. (1997). Subchronic Toxicity (90-Day) Study with *para*-Nonylphenol in Rats. Regulatory Toxicology and Pharmacology, 26, 172-178.
[24] Tyl R. *et al* .(2006) Three-Generation Evaluation of Dietary para-Nonylphenol in CD® (SD) Rats in *Toxicol. Sci.*92: 295-310
[25] Chapin, R.E., et al. (1999). The Effects of 4-Nonylphenol in Rats: A Multigeneration Reproduction Study. Toxicological Sciences, 52, 80-91.
[26] Tyl. (2006).

Research has also confirmed that ingested NP is rapidly broken down into compounds that are not estrogenic and are eliminated within 24 hours. [27] This study, conducted on rats, also confirmed that no significant accumulation of NP occurs in any body organ or tissues following dosing at levels exceeding real-world exposure estimates.

DEP should consider the weight of evidence regarding the reproductive and fertility effects of NP, including on robust multigeneration rat studies that looked at these endpoints, which do not indicate adverse effects.

4. Human (adult and children) Margins of Exposure (MOEs) based on the use of a No-Observed-Adverse-Effect-Level (NOAEL) for sensitive toxicological endpoints of interest, that is, systemic and reproductive toxicity from continuous-feeding studies of more than 3.5 generations (13 mg/kg/day) range from 2863 to 8.4×10^7, clearly indicate reasonable certainty of no harm for source-specific and aggregate (based on exposure from all sources and measured through biomonitoring) exposures to NP.

Osimitz, T. et al (2015) presents a risk assessment for human exposure to nonylphenol (NP) based on specific sources including food, water, air and dust to calculate source-specific MOEs. However, the nature of the populations studied prevented the calculation of aggregate exposure calculations from these data. Therefore, more reliable estimates of aggregate exposure to NP were those derived from biomonitoring studies in exposed individuals. Using the daily absorbed dose estimates for NP, MOEs were calculated for these populations. The MOEs were based on the use of a No-Observed-Adverse-Effect-Level (NOAEL) for sensitive toxicological endpoints of interest, that is, systemic and reproductive toxicity from continuous-feeding more than 3.5 generations (13 mg/kg/day). The MOEs were all greater than 1000 (ranging from 2863 to 8.4×10^7), clearly indicating reasonable certainty of no harm for both source-specific and aggregate (based on biomonitoring) exposures to NP. A variety of food sources, including packaged foods also indicate reasonable certainty of no harm. The MOE for bottled water, which represents a specific food package application, was 3.25×10^6.

Based on the high MOEs for NP to humans (both adult and children) for food and food packaging specific sources as well as from aggregate exposure from all sources (as measured by biomonitoring) focus on NP as a food contact chemical of high concern does not appear warranted.

Thank you for the opportunity to comment. Please contact me at blosey@regnet.com if you would like additional information.

[27] Green, T. *et al.* (2003) Absorption, bioavailability, and metabolism of para-nonylphenol in the rat. Regulatory Toxicology and Pharmacology. 38: 43-51.

Respectfully,

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Executive Director