WESTERN
WOOD PRESERVERS
INSTITUTE

October 12, 2015

Dr. Lauren Zeise
Acting Director
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, CA 95814

Dear Dr. Zeise:

Western Wood Preservers Institute (WWPI) is a non-profit trade association founded in 1953 based in Vancouver, Wash. WWPI serves the interests of the wood preserving industry in western North America so that renewable resources, exposed to the elements, can maintain favorable use in aquatic, building, commercial and utility industries.

WWPI represents companies that both manufacture pentachlorophenol (penta) and utilize it to treat utility poles. Naturally, WWPI has a keen interest in the Office of Environmental Health Hazard Assessment's (OEHHA) examination of penta. A listing under the Proposition 65 process would create onerous labeling requirements with the potential to invite unwarranted litigation and create other challenges.

OEHHA determined in its August 2015 "prioritization" document that the quality and quantity of epidemiological studies on penta were satisfactory, and warranted proceeding with review by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) under Proposition 65. However, WWPI asserts this conclusion is erroneous and unsupported by the scientific literature.

Expert review of the penta epidemiology studies concludes that penta should not proceed in the listing process because the fundamental epidemiologic data screen requirements are not met. The selected studies do not include two or more analytical epidemiologic studies of adequate quality, with proper control of confounding factors, bias and effect modifiers, as required by the OEHHA process (OEHHA 1993, 2004) and generally accepted principles of epidemiological research. None of the identified studies are of adequate quality nor provide sufficient evidence to demonstrate that penta is the cause of adverse human developmental or reproductive effects.

Based upon the attached technical comments by Integral Consulting Inc. (Integral), pentachlorophenol should be dropped from further review by the OEHHA, the DARTIC, and the Proposition 65 process to list reproductive and developmental toxicants. In response to your August 28, 2015 request for public comments, we submit the attached technical assessment for DARTIC review and consideration. You will find the assessment fully supports our position that penta should not proceed in the Proposition 65 listing process.

Please contact us should you wish to discuss Integral's technical review.

Sincerely,

Dallin Brooks
Executive Director

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COMMENTS ON *PRIORITIZATION: CHEMICALS IDENTIFIED FOR CONSULTATION WITH THE CALIFORNIA DEVELOPMENTAL AND REPRODUCTIVE TOXICANT IDENTIFICATION COMMITTEE, AUGUST 2015*

Per the Office of Environmental Health Hazard Assessment (OEHHA) document *Prioritization: Chemicals Identified for Consultation with the Developmental and Reproductive Toxicant Identification Committee, August 2015* (OEHHA 2015), OEHHA is seeking public comment regarding its proposal for pentachlorophenol (PCP) to proceed to the next stage of the listing process for developmental and reproductive toxicants under Proposition 65.[1] In support of this proposal, OEHHA has requested the Developmental and Reproductive Toxicant Identification Committee (DARTIC) advisory board review, evaluate, and provide input on four epidemiological studies published since OEHHA's most recent review of PCP in 2007. This document presents Integral Consulting Inc.'s technical review and comments on these four epidemiological studies, on behalf of the Western Wood Preservers Institute.

OEHHA established criteria for the DARTIC advisory board's listing of a chemical as a reproductive toxicant for the State of California (OEHHA 1993). According to this guidance, the "sufficiency of the data" utilizing a "weight-of-evidence" approach shall be used to evaluate the available information. Standard evaluation of epidemiologic data involves consideration of numerous factors, including type of study, size of the study population, exposure situation, biological relevance of the endpoint, dose-response analysis, and possible roles of bias and confounding factors, in addition to overall study quality. According to generally accepted principles of epidemiology, assessment of whether PCP exposure causes reproductive or developmental effects in humans requires the following:

- A thorough review of the epidemiology literature, and within this context, giving appropriate weight to the overall quality of the study and robustness of study designs that are applied to identify causal relationships
- A robust statistical analysis that properly addresses potential confounding, bias, and effect modifiers
- Consideration of study population size and representativeness to the population at large.

[1] http://oehha.ca.gov/prop65/CRNR_notices/082815DARTprioritization.html

In consideration of the OEHHA prioritization process (OEHHA 2004), established criteria for an epidemiologic data screen (OEHHA 1993, 2015), and review of the four selected PCP epidemiological publications using accepted epidemiology principles, **PCP should not proceed to the next stage of the listing process because the fundamental epidemiologic data screen requirements are not met. The selected studies do not include two or more analytical epidemiologic studies of adequate quality, with proper control of confounding factors, bias, and effect modifiers, as required by the OEHHA process (OEHHA 1993, 2004) and generally accepted principles of epidemiological research.**

OEHHA determined that four epidemiology studies were analytical studies of adequate quality, and have proposed them for consideration by DARTIC. OEHHA also includes an additional five epidemiology studies as providing positive weight of evidence supporting the conclusion that PCP exposure results in reproductive or developmental effects in humans. However, none of the four primary epidemiologic studies are of adequate quality, and none properly control for confounding factors, bias, or effect modifiers; therefore, none of the studies are sufficient to determine a causal relationship between PCP and developmental or reproductive effects in people. Specifically:

- All of the studies have observational study designs, which are not appropriate for determining a "causal relationship between exposure to the chemical and the developmental or reproductive effect in question" (OEHHA 1993).
- Three of the four studies fail to demonstrate a clearly adverse reproductive or developmental endpoint associated with PCP exposure.
- None of the studies fully and adequately address potential confounding factors or effect modifiers, such as other co-contaminants, or the socioeconomic status and health condition of the participants; therefore, none of the four studies provide conclusive evidence that other chemicals or lifestyle factors did not contribute to the statistically significant findings in the studies.
- None of the additional supporting epidemiology studies provide sufficient weight to the conclusion that PCP exposure can cause developmental or reproductive effects in humans.

Specific review and critique of the four studies is provided by publication below.

Guvenius et al. (2003) does not report on reproductive endpoints, and only documents PCP exposures in a very small number of women in Sweden. Guvenius et al. (2003) measured and analyzed blood plasma, cord blood plasma, and breast milk from only 15 mothers for polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polychlorobiphenyls, and PCP to assess exposure. This study did not analyze for any reproductive/developmental biological markers, endpoints, or outcomes. This study does not show a relationship between PCP exposure and any reproductive/developmental endpoint.

Roze et al. (2009) is a self-described "explorative" cross-sectional study, with no longitudinal follow-up, from a small subsample of a cohort from a larger public health study in the Netherlands.[2] In epidemiological studies, "longitudinal follow-up" is typically conducted after an association between an etiological agent and a disease has been observed, and provides further support to the conclusion that exposure causes the noted adverse biological effect. In a longitudinal follow-up study, investigators follow the study population over time, collecting and analyzing additional data, to assess critical cause-effect relationships, evaluate biological relevancy of the endpoint, and help establish causality. Without the longitudinal follow-up, it is not possible to assess persistence of the effect and potential clinical relevance of the endpoints. In the absence of a longitudinal follow up study, the causal relationship between PCP exposure and measured endpoints cannot be determined from Roze et al. (2009).

In the Roze et al. (2009) study, PCP blood levels significantly correlated only with "worse coordination" and "worse attention" in children (N=62) after correcting the results for socioeconomic status and home environmental factors. PCP levels in blood were also statistically correlated with lower concentrations of the thyroid hormone, triiodothyronine (T3). However, whether the T3 levels were still within normal range was not discussed. Importantly, according to the study authors, noted changes in T3 levels were not associated with the type of neurobehavioral changes found to correlate to PCP exposure in this study (compare Tables 3 and 4), resulting in the question of biological relevance of reduced T3 levels, and an undefined mode of action for PCP-associated behavioral changes. Furthermore, the study did not statistically evaluate the relationship between concentrations of PCP and the magnitude of proposed PCP-related effects and, therefore, did not produce a dose-response relationship, which is necessary to support causal conclusions. Possible roles of confounding factors or effect modifiers were minimally controlled for in this study, and given the small sample size of only 62 children, extrapolation to the population at large without carefully controlling for these potential confounders is inappropriate. For example, in addition to PCP, this study detected numerous other chlorinated organohalogen compounds in the study group, such as PCBs and brominated flame retardants; however, statistical evaluation to control for potential confounding from multi-chemical exposures was not conducted. Finally, the authors also failed to assess co-exposures to other chemicals that have been reported to impact motor, cognitive, and behavioral indicators in children, such as lead and methylmercury. Roze et al. (2009) was designed as an initial explorative study that evaluated a small study population, did not identify a causal relationship between PCP exposure and a developmental effect, and did not adequately control for confounding contaminant co-exposures. Therefore, Roze et al. (2009) does not meet OEHHA requirements for evidence of developmental or reproductive effects caused by PCP exposure.

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[2] The Groningen infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) cohort, established between October 2001 and November 2002 in the northern provinces of The Netherlands, in Beatrix Children's Hospital.

Meijer et al. (2012) is a cross-sectional study using participants from the same cohort as Roze et al. (2009). As in that study, Meijer et al. (2012) did not conduct a longitudinal follow-up, and a causal relationship between PCP exposure and measured endpoints is not established. PCP levels in maternal serum were compared to various sex development-related hormones and physical measurements (testes volume and penile length at 3 and 18 months of age) in the study subjects' sons. PCP was statistically correlated with changes in two protein levels individually, reduced sex hormone binding globulin (SHBG) and inhibin B levels, and not with any biological reproductive or developmental endpoints. Furthermore, the authors did not discuss whether reduced levels of SHBG and inhibin B were still within the normal range for these hormones. The study authors also detected numerous elevated organohalogen compounds in the study population, but they only conducted general bivariate correlation statistical analysis for each of the compounds and each endpoint; multivariate statistical analysis would have allowed the authors to assess how these co-contaminants could confound positive PCP results, but was not done. Importantly, this study failed to adequately account for several additional critical confounding or effect modifiers, such as maternal age, nutritional status, gestational age of the children, and maternal exposures to other contaminants. Given the small sample size (N=55) and the fact that the most significant factor known to influence many infant growth and developmental parameters (maternal age) was not controlled by the authors, this study is inadequate to support a causal association between PCP exposure and adverse male sexual developmental outcomes. Therefore, Meijer et al. (2012) does not meet OEHHA screening requirements: it does not demonstrate a causal relationship between PCP and developmental or reproductive effects in people, and does not properly control for confounding factors, bias, or effect modifiers.

Chen et al. (2013a) is a limited case-control study and is not adequate to establish the causal relationship between PCP exposure and the measured endpoint (spontaneous abortion). Case-control studies are used to identify potential statistical association between exposure to an etiological agent and increased chance of the endpoint occurring in a human population. However, given the wide range of potential etiologic reasons for a miscarriage, a case-control study with this endpoint is only sufficient as a preliminary investigation. Analyses of the study population included PCP levels measured in both maternal and paternal urine (paired couples). Several other phenolic compounds were also measured in these subjects (bisphenol A, benzophenol-3, octyphenol, nonylphenol, and 2,3,4-trichlorophenol). Paternal higher PCP exposure was statistically correlated with an increased incidence of past spontaneous abortions. This study and Gerhard et al. (1998) (additional epidemiology study provided by OEHHA) both found no impact of maternal exposure to PCP and spontaneous abortion. Notably, in another study submitted by OEHHA as providing supporting evidence, Chen et al. (2013b) found no association with PCP exposure and male infertility. Therefore, there is no additional support for this specific endpoint. Furthermore, a postulated mode of action to support an association between paternal PCP exposure and increased spontaneous abortions has not been provided. Although smoking, drinking, and body mass index were controlled for by Chen et al.

(2013a), these authors did not control for additional confounding or effect modifiers, rendering the results uninterpretable. This is of critical importance, given the known presence of other contaminants both detected in study participants and also known to be present in people inhabiting this geographical area (e.g., dioxin-like compounds). Furthermore, the authors did not control for the role of socioeconomic status, family history, and other potential effect modifiers on the incidence of spontaneous abortion. In total, this study has numerous weaknesses (study-design, lack of controlling for confounding co-contaminants, lack of consideration of socioeconomic status and family history), is of poor quality, and does not demonstrate a causal relationship between PCP exposure and a reproductive effect. Therefore, Chen et al. (2013a) does not meet OEHHA screening requirements as it is not an adequate study, does not demonstrate a causal relationship between PCP exposure and developmental or reproductive endpoints, and does not properly control for confounding factors, bias, or effect modifiers.

In summary, none of the identified studies are of adequate quality or provide sufficient evidence to demonstrate that PCP is the cause of adverse developmental or reproductive effects in people. Given the specific weaknesses and issues with each of the four epidemiological studies proposed by OEHHA for DARTIC consideration, the OEHHA database will not include the required two or more analytical epidemiologic studies of adequate quality that demonstrate a causal relationship between PCP exposure and a developmental or reproductive effect. Guvenius et al. (2003) only evaluated potential exposure to PCP and did not evaluate a possible relationship between that exposure and reproductive/developmental effects. The other studies are observational, providing only bivariate statistical correlations, which do not fully explore potential causes and confounding factors using multivariate statistics and other analysis tools. These studies, therefore, do not establish a causal relationship between PCP exposure and reproductive and developmental endpoints. None of the studies fully or adequately addressed potential confounding factors or effect modifiers, such as co-contaminants or relevant participant health conditions; therefore, other chemicals or lifestyle factors may have contributed to the statistically significant findings in the studies. Finally, in addition to the individual weaknesses, the studies do not provide a consistent cumulative weight-of-evidence support for any specific reproductive or developmental endpoint and are not supported by the additional epidemiology studies identified by OEHHA.

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