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Environmental Working Group (EWG) comments supporting the priority review under California Proposition 65 of PFAS, parabens, glyphosate and other chemicals harmful to reproduction and development

Submitted via electronic docket at https://oehha.ca.gov/comments

The Environmental Working Group, a nonprofit research and policy organization with offices in San Francisco, Sacramento, Minneapolis and Washington, D.C., submits these comments to the California Office of Environmental Health Hazard Assessment (OEHHA) and the Developmental and Reproductive Toxicant Identification Committee for the upcoming meeting of the committee, scheduled for December 10, 2020.

EWG recommends the prioritization of four per- and polyfluorinated substances (PFAS), some of the most toxic parabens, glyphosate and other chemicals harmful to the reproductive system and fetal development, for review under Proposition 65. We urge the Developmental and Reproductive Toxicant Identification Committee and OEHHA to move forward with hazard identification materials and Proposition 65 listing of these chemicals. The comments below highlight information that supports listing specific chemicals or chemical groups.

PFAS

Two PFAS, perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), are already listed under Proposition 65 as causing developmental toxicity. The four PFAS that will be considered by the Developmental and Reproductive Toxicant Identification Committee at the December meeting, perfluorohexanesulfonic (PFHxS) acid, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnA), are structurally similar to PFOA and PFOS, show similar toxicological effects and should be prioritized for further review. Animal studies showed that PFOA and PFOS, as well as PFHxS, PFNA and PFDA, cause changes in thyroid hormone levels, TSH and thyroxine,[1] a toxic effect that would affect fetal development.

OEHHA should expand its priority review of PFAS beyond the long-chain PFAS compounds to include those still in widespread active use. Because of the documented association between PFAS exposures and low birth weight, changes in the endocrine system and endocrine function,

[1] National Toxicology Program. 2019. Toxicity Report 96. Toxicity studies of perfluoroalkyl sulfonates administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats. https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox096/index.html; Toxicity Report 97. Toxicity studies of perfluoroalkyl carboxylates administered by gavage to Hsd:Sprague Dawley SD rats. https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox097/index.html

harm to the male reproductive system, pregnancy-related hypertension, impacts on mammary gland development, and longer time to conception, EWG urges the committee and OEHHA to analyze the reproductive and developmental harms of PFAS as a class. As an example, recent studies of PFAS alternatives indicate that GenX and PFBS may harm the developing fetus.[2]

Parabens

Parabens, a chemical group used as antimicrobial preservatives, can act like the hormone estrogen in the body and disrupt the normal function of hormone systems affecting male and female reproductive system functioning, reproductive development, fertility and birth outcomes. Parabens can also interfere with the production of hormones. In 2017, the U.N. Environment Programme published a report summarizing worldwide initiatives to identify endocrine-disrupting chemicals. The report listed the group of parabens as potential endocrine-disrupting chemicals.[3]

In animal studies, exposure to propyl-, isopropyl-, butyl- and isobutylparabens disrupted hormone signals, and harmed female and male reproductive system development.[4,5,6] In human studies, researchers from the Harvard T.H. Chan School of Public Health reported that greater concentrations of propyl paraben may be associated with lower fertility indices in women seeking fertility treatment.[7] Another human study linked both butylparaben and total urinary paraben concentrations with shorter menstrual cycle length.[8] Higher concentrations of

[2] U.S. Environmental Protection Agency. 2018. Fact Sheet: Draft Toxicity Assessments for GenX Chemicals and PFBS. Available: https://www.epa.gov/sites/production/files/2018-11/documents/factsheet_pfbs-genx-toxicity_values_11.14.2018.pdf
[3] United Nations Environment Programme. International Panel on Chemical Pollution. 2017. Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs. https://wedocs.unep.org/bitstream/handle/20.500.11822/25633/EDC_report1.pdf?sequence=1&isAllowed=y
[4] Boberg J, Axelstad M, Svingen T, Mandrup K, Christiansen A, Vinggaard AM, Hass U. 2016. Multiple Endocrine Disrupting Effects in Rats Perinatally Exposed to Butylparaben. Toxicological Sciences 152(1) 244-256.
[5]Vo TT, Yoo YM, Choi KC, Jeung EB. 2010. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. Reprod Toxicol 29(3):306-316.
[6] Zhang L, Dong L, Ding S, Qiao P, Wang C, Zhang M, Zhang L, Du Q, Li Y, Tang N, and et al. 2014. Effects of n-butylparaben on steroidogenesis and spermatogenesis through changed E(2) levels in male rat offspring. Environ. Toxicol. Pharmacol 37:705-717.
[7] Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R. 2013. Urinary paraben concentrations and ovarian aging among women from a fertility center. Environ Health Perspect 121(11-12):1299-305.
[8] Nishihama Y, Yoshinaga J, Iida A, Konishi S, Imai H, Yoneyama M, Nakajima D, Shiraishi H. Association between paraben exposure and menstrual cycle in female university students in Japan. Reprod Toxicol. 2016 63:107-13.

butylparaben in the mother's urine and umbilical cord blood were associated with increased risk of pre-term birth and decreased birth weight.[9]

In sum, based on data from animal and human studies showing the effects of parabens on endocrine function, reproductive organs and birth outcomes, EWG recommends that these parabens be prioritized for further review under Proposition 65.

Glyphosate and its salts

Glyphosate has been the most commonly used herbicide in the U.S. and worldwide in the last two decades, resulting in the presence of glyphosate in food[10] and in people.[11] A study of pediatric cohorts in the U.S. published earlier this year reported that glyphosate was detected in one-third of newborns.[12]

Developmental harm relating to glyphosate exposure was identified in a recent population-based case-control study in California, which found a 60 percent increase in the risk of autism spectrum disorder and intellectual disability in children following prenatal exposure to pesticides sprayed within 2000 meters of their mother's residence during pregnancy.[13] Developmental neurotoxicity of prenatal exposure to glyphosate was also reported in studies of laboratory rats.[14] A study conducted by the Ramazzini Institute, in Italy, reported that prenatal and early life exposure to glyphosate affected multiple parameters related to the development of the reproductive system in rats, including changes in anogenital distance and time to first estrous, as well as altered concentrations of testosterone and thyroid-stimulating hormone.[15]

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[9] Geer LA, Pycke BFG, Waxenbaum J, Sherer DM, Abulafia O, Halden RU. 2017. Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in Brooklyn, New York. J Hazard Mater 323(Pt A):177-183.

[10] EWG's Tests of Hummus Find High Levels of Weedkiller. 2020. https://www.ewg.org/research/glyphosate-hummus/; Roundup for Breakfast, Part 2: In New Tests Weed Killer Found in All Kid's Cereals Sampled. 2018. https://www.ewg.org/release/roundup-breakfast-part-2-new-tests-weed-killer-found-all-kids-cereals-sampled

[11] Center for Environmental Health. Glyphosate in Adults and Children: A CEH Biomonitoring Study. 2019. Available: https://www.ceh.org/wp-content/uploads/2019/07/Glyphosate-Factsheet.pdf

[12] Trasande L, Aldana SI, Trachtman H, Kannan K, Morrison D, Christakis DA, Whitlock K, Messito MJ, Gross RS, Karthikraj R, Sathyanarayana S. Glyphosate exposures and kidney injury biomarkers in infants and young children. Environ Pollut. 2020; 256:113334

[13] von Ehrenstein OS, Ling C, Cui X, Cockburn M, Park AS, Yu F, Wu J, Ritz B. Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population-based case-control study. BMJ. 2019; 364:l962.

[14] Coullery R, Pacchioni AM, Rosso SB. Exposure to glyphosate during pregnancy induces neurobehavioral alterations and downregulation of Wnt5a-CaMKII pathway. Reprod Toxicol. 2020; 96:390-398

[15] Manservisi F, Lesseur C, Panzacchi S, Mandrioli D, Falcioni L, Bua L, Manservigi M, Spinaci M, Galeati G, Mantovani A, Lorenzetti S, Miglio R, Andrade AM, Kristensen DM, Perry MJ, Swan SH, Chen J, Belpoggi F. The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on development and endocrine system. Environ Health. 2019; 18(1):15

Widespread exposure to glyphosate from dietary and ambient sources, combined with the latest research showing the impact of glyphosate on fetal development, point to the need to prioritize glyphosate for further review and assessment under Proposition 65, for potential listing as a developmental toxicant.

Manganese

Growing scientific evidence indicates that exposure to manganese during pregnancy and childhood can impair learning, memory and behavior in children. Manganese is a naturally occurring mineral found in both food and water, and necessary for health in small amounts. However, as noted by both primary research studies and reviews, early-life exposure to manganese negatively affects the nervous system.[16,17] The impact of manganese on the nervous system development may depend on gender, as suggested by epidemiological studies and studies in laboratory animals.[18,19]

Manganese is commonly found in drinking water supplies across California. Drinking water testing data published by California Water Boards (https://sdwis.waterboards.ca.gov/PDWW/) indicate that hundreds of water systems in the state have manganese. Health effects data, combined with extensive exposure, support the prioritization of manganese for further review as a potential developmental toxicant.

Bisphenol S (BPS)

Recent research found that bisphenol S, a plasticizer introduced as a replacement for bisphenol A (BPA), has hormone-disrupting effects similar to those of BPA. Bisphenol S is also structurally similar to BPA, which was listed on Proposition 65 in 2015 due to effects on the female reproductive system. Cantonese and Vandenberg (2017) reported that BPS exposure during pregnancy and lactation in mice negatively affected nursing behavior and maternal care.[20] BPS-dosed mouse pups were less likely to initiate nursing, and BPS-treated mothers had to spend more time actively nursing, and these effects could be related to BPS-induced changes mammary

[16] Sanders AP, Claus Henn B, Wright RO. Perinatal and Childhood Exposure to Cadmium, Manganese, and Metal Mixtures and Effects on Cognition and Behavior: A Review of Recent Literature. Curr Environ Health Rep. 2015; 2(3):284-94.
[17] Liu W, Xin Y, Li Q, Shang Y, Ping Z, Min J, Cahill CM, Rogers JT, Wang F. Biomarkers of environmental manganese exposure and associations with childhood neurodevelopment: a systematic review and meta-analysis. Environ Health. 2020; 19(1):104.
[18] Madison JL, Wegrzynowicz M, Aschner M, Bowman AB. Gender and manganese exposure interactions on mouse striatal neuron morphology. Neurotoxicology. 2011;32(6):896-906.
[19] Riojas-Rodríguez H, Solís-Vivanco R, Schilmann A, Montes S, Rodríguez S, Ríos C, Rodríguez-Agudelo Y. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. Environ Health Perspect 2010;118(10):1465-70.
[20] M.C. Catanese and L. N. Vandenberg. Bisphenol S (BPS) Alters Maternal Behavior and Brain in Mice Exposed During Pregnancy/Lactation and Their Daughters. Endocrinology 2017; 158(3):516–530.

glands. BPS also caused stunted pup growth and development. Another publication showed that BPS disrupts the normal development of the female reproductive tract in mice exposed to BPS during early development.[21] Overall, these studies indicate that BPS should be prioritized for further review.

Closing recommendations

EWG also supports the prioritization for further review and hazard analysis for neonicotinoid pesticides (acetamiprid, clothianidin, imidacloprid, thiamethoxam), diethyl phthalate and benzophenone-3 (also called oxybenzone), a chemical commonly used as a UV filter in sunscreens. Epidemiological evidence suggests an association between neonicotinoid exposure and increased risk of adverse developmental and neurological effects, including anencephaly, preterm birth, autism spectrum disorder and IQ decrements in children.[22,23,24] Epidemiological studies support evidence of female reproductive and developmental effects associated with diethyl phthalate, including alterations of infant/toddler physical development and behavioral problems.[25,26] Benzophenone-3 is readily adsorbed into the body and is commonly detected in people in biomonitoring studies conducted under the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (NHANES) studies.[27] Benzophenone-3 shows evidence of hormone disruption, with both estrogenic and anti-androgenic effects,[28] and these endocrine effects, as well as widespread exposure, warrant prioritization for further review.

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[21] C. E. Hill et al., Developmental exposures to bisphenol S, a BPA replacement, alter estrogen-responsiveness of the female reproductive tract: A pilot study. Cogent Medicine, 2017, 4(1).
[22] Cimino AM1, Boyles AL, Thayer KA, Perry MJ. Effects of Neonicotinoid Pesticide Exposure on Human Health: A Systematic Review. Environ Health Perspectives. 2017 Feb;125(2):155-162. doi: 10.1289/EHP515. Epub 2016 Jul 6.
[23] Ling C, Liew Z, von Ehrenstein OS, Heck JE, Park AS, Cui X, Cockburn M, Wu J, Ritz B. Prenatal Exposure to Ambient Pesticides and Preterm Birth and Term Low Birthweight in Agricultural Regions of California. Toxics. 2018 Jul 21;6(3). doi: 10.3390/toxics6030041
[24] Gunier RB, Bradman A, Harley KG, Kogut K1, Eskenazi B. Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children. Environmental Health Perspectives. 2017 May 25;125(5):057002. doi: 10.1289/EHP504
[25] Kay VR, Chambers C, Foster WG. Reproductive and developmental effects of phthalate diesters in females. Crit Rev Toxicol. 2013 Mar;43(3):200-19.
[26] Braun, J. M., Sathyanarayana, S., & Hauser, R. (2013). Phthalate exposure and children's health. *Current opinion in pediatrics, 25*(2), 247–254.
[27] Matta MK, Florian J, Zusterzeel R, Pilli NR, Patel V, Volpe DA, Yang Y, Oh L, Bashaw E, Zineh I, Sanabria C, Kemp S, Godfrey A, Adah S, Coelho S, Wang J, Furlong LA, Ganley C, Michele T, Strauss DG. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. JAMA. 2020; 323(3):256-267. Zamoiski RD, Cahoon EK, Michal Freedman D, Linet MS. Self-reported sunscreen use and urinary benzophenone-3 concentrations in the United States: NHANES 2003-2006 and 2009-2012. Environ Res. 2015; 142:563-7.
[28] Ghazipura M, McGowan R, Arslan A, Hossain T. Exposure to benzophenone-3 and reproductive toxicity: A systematic review of human and animal studies. Reprod Toxicol. 2017;73:175-183.

Finally, EWG agrees with OEHHA's approach, which combines epidemiological studies with toxicological data from laboratory animal studies to identify evidence of adverse developmental or reproductive effects. These two lines of evidence provide supporting information regarding the developmental and reproductive toxicity and, together with mechanistic evidence from *in vitro* studies, should all be jointly considered for hazard identification.

Submitted on behalf of the Environmental Working Group,

Tasha Stoiber, Ph.D.
Senior Scientist
EWG California Office
500 Washington St., Suite 400
San Francisco, CA 94111

Bill Allayaud
California Director of Government Affairs
EWG Sacramento Office
910 K Street, Suite 300
Sacramento, CA 95814