Clinical Article

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Organophosphate insecticide exposure: A clinical consideration of chlorpyrifos regulation

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ABSTRACT

Background and purpose: In March 2017, the Environmental Protection Agency (EPA) reversed course on a proposal to ban the agricultural use of the organophosphate (OP) insecticide chlorpyrifos (CPF). The purpose of this article is to examine the evidence leading to this controversial decision and provide clinically applicable health promotion guidance for nurse practitioners on CPF exposure and risk reduction measures.

Methods: Environmental Protection Agency documents on CPF regulation and corresponding research referenced within the EPA reports are reviewed. Evidence-based health promotion strategies obtained through PubMed, CINAHL, Center for Disease Control and Prevention, and National Institutes of Health sources are summarized.

Conclusions: Available data suggest a potential association between CPF exposure and adverse neurodevelopmental outcomes. Particularly vulnerable populations are pregnant women, children younger than two years, and agricultural workers. There may be genetic variability in susceptibility to environmental toxins.

Implications for practice: Because of the extensive use of the OP CPF in agriculture and other community-based settings throughout the United States, nurse practitioners should be knowledgeable of the evidence regarding CPF exposure and be prepared to provide health promotion guidance to patients in clinical practice. Nurse practitioners should also consider their role in advocacy for healthy environments and the protection of vulnerable populations as it relates to agricultural insecticide exposure.

Keywords: Environmental health; health promotion; rural health; chlorpyrifos exposure; nurse practitioners.

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Regulatory background

On March 29, 2017, Scott Pruitt, head of the Environmental Protection Agency (EPA) under the Trump administration, rejected a petition by the National Resources Defense Counsel and Pesticide Action Network North America to ban agricultural use of the organophosphate (OP) insecticide chlorpyrifos (CPF) in the United States (EPA, 2017). This decision is a significant policy shift from the 2015 Obama administration proposal to add an agricultural ban of CPF to previously enacted residential use prohibitions (EPA, 2015). Obama administration EPA recommendations for a CPF ban were primarily supported by research associating exposure to CPF with neurodevelopmental disorders in children (U.S. EPA, 2014). The successive Trump administration ruling was predicated on a determination that the current science on CPF was inconclusive and did not meet the EPA criteria for revocation by demonstrating that the product was unsafe (EPA, 2017). Further study on the human impact was declared necessary before a complete ban on CPF could be justified (Schipani, 2017). However, in accordance with the standard EPA review cycle, the safety of CPF is not expected to be reevaluated before the year 2022 (EPA, n.d. b). Legal challenges to the current EPA ruling on the use of CPF have been initiated including a federal appeal in the Ninth Circuit Court in San Francisco (League of United Latin American Citizens vs. Scott Pruitt, U.S. Court of Appeals, Ninth Circuit, 17-71636) (Biesecher, 2017). In addition, the Protect Children, Farmers & Farmworkers from Nerve Agent Pesticides Act of 2017 (SB 1624) introduced in the U.S. Senate would ban the use of CPF on food products and require further study on the effects of OP exposure on vulnerable populations (Earthjustice, 2017).

Organophosphate insecticides

Organophosphates are a broad class of manufactured phosphorus-based chemicals with a variety of commercial formulations, applications, and widely ranging toxic properties (Roberts & Routt Reigart, 2013). Predominantly

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applied as a produce and feed crop insecticide, other registered nonagricultural use includes golf course turf, greenhouse and nursery production, veterinary care, industrial building pest control, wood preservation treatment, mosquito fumigation, roach bait, and fire ant mound treatment (U.S. EPA, 2014; Roberts & Routt Reigart, 2013).

The lethal mechanism of action of OPs is triggered by the phosphorylation of acetylcholinesterase enzyme (AChE), resulting in an irreversible inhibition of acetylcholinesterase responsible for the breakdown of acetylcholine (ACh) within neural synapses (Roberts & Routt Reigart, 2013). At toxic doses, OP insecticides cause an excessive accumulation of ACh, resulting in acute cholinergic overstimulation within the central and peripheral nervous system. Symptoms of acute ACh toxicity in humans may include the following: pupillary constriction, headache, confusion, muscle twitching and weakness, gastrointestinal distress, cardio/respiratory dysfunction, seizures, loss of consciousness, and death (Roberts & Routt Reigart, 2013). The most toxic OPs can be formulated as nerve gas used in chemical warfare, the devastating human effects of which were evident in the aftermath of the 2017 suspected Syrian sarin gas attacks (Center for Disease Control and Prevention, 2015).

It is concern for the potential health effects of subacute environmental OP exposure from agricultural insecticide use that is driving the current CPF debate, particularly regarding the exposure of potentially vulnerable populations. Organophosphates can be absorbed through ingestion, inhalation, and dermal contact and are metabolized primarily in the liver (Agency for Toxic Substances & Disease Registry [ATSDR], 1997). Lipophilic OP compounds (including CPF) may bioaccumulate through fat cell storage (Roberts & Routt Reigart, 2013). Evidence suggests that chronic subacute exposure to OPs may result in changes in neuropsychological function including executive function, memory, mood, attention, psychomotor coordination, and sleep (ATSDR, 1997; Muñoz-Quezada et al., 2016). Although the EPA has identified CPF as unlikely to be carcinogenic, OP exposure has been linked to endocrine disruption, which has demonstrated an association with human reproductive disorders including infertility and cancer (EPA, 2017; Sifakis, Androutsopoulos, Tsatsakis, & Spandidos, 2017). Concerns have also been raised regarding possible associations with lung cancer (EPA, 2017). Organophosphates can cross the placental barrier into fetal circulation, and evidence suggests that prenatal exposure to OPs may disrupt fetal brain development (Rauh et al., 2012). A series of epidemiologic investigations have identified an association between the OP exposure and adverse neurodevelopmental outcomes in children, which is the crux of the current debate on the EPA CPF decision (EPA, 2017).

Chlorpyrifos

Chlorpyrifos has been on the market since 1965 and is the most commonly used agricultural OP insecticide in the United States (EPA, 2017). The EPA tolerance (detectable allowance) for CPF on agricultural and meat products ranges from 0.05 to 20 parts per million (ppm) depending on the product (U.S. Government Publishing Office, 2017). Agricultural products with approximately one third or more of the crops treated with CPF include cranberries (70%), sweet potatoes (65%), apples (55%), broccoli (45%), walnuts (45%), pecans (35%), onions (35%), lemons (35%), peaches (30%), cherries (30%), and almonds (30%) (Solomon et al., 2014). Although a significantly lower percentage of crops are treated, the largest application of CPF by pound are on corn (5% treated) and soybeans (<1% treated) accounting for approximately 50% of the CPF used in the United States. Substantial levels of pesticide exposure are present across the United States (**Figure 1**) with the highest concentration of CPF use in agricultural counties in California, Pennsylvania, and Georgia (Solomon et al., 2014). Applications of CPF occur throughout the year with some increase in use in the winter on nut bearing trees in California and field crops in the summer. As a result of regulatory restrictions including the residential ban in 2000 and the introduction of alternative insecticides, the use of CPF in the United States has declined to less than 50% of the estimated amounts used before 2000 (Solomon et al., 2014). Previous EPA agricultural restrictions have included a ban on tomato crop application (2000), restricted use on apples to prebloom and dormant application (2000), lowered tolerance levels on grapes (2000), limitations on citrus and nut tree applications (2002), limitations on agricultural pesticide application rates, and creation of "no-spray" buffer zones adjacent to agricultural production sites where the application of pesticide is prohibited to prevent community drift exposure (2012) (EPA, n.d.b).

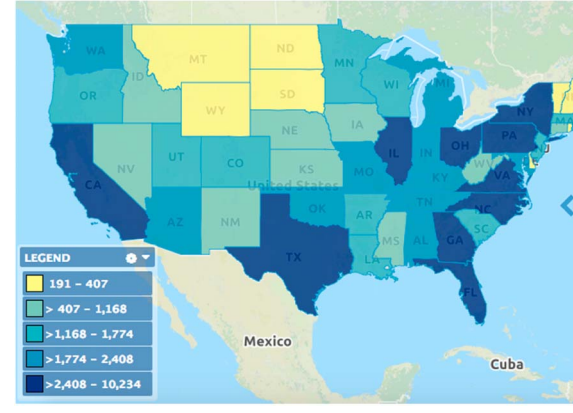

Figure 1. Pesticide exposure by state. Center for Disease Control and Prevention: National Environmental Public Health Tracking Network (2014). Number of reported exposures to all pesticides. https://ephtracking.cdc.gov/showHome.action.

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Chlorpyrifos has a short to moderate persistence in the environment, dissipated through volitalization, hydrolysis, photolysis, and microbial degradation (Giesy et al., 2014). A 2016 EPA Revised Human Health Risk Assessment for Registration Review applying refined analytic techniques identified potential CPF environmental exposure risk for humans from dietary sources and drinking water, particularly for children younger than 2 years (U.S. EPA, 2016). The report also identifies potential residential postapplication exposure risk, as well as risk for agricultural workers who mix, load, and apply CPF (U.S. EPA, 2016). Chlorpyrifos is classified as toxic to fish and birds; however, the actual kill risk with approved use is very small (Giesy et al., 2014). Chlorpyrifos is highly toxic to honey bees through direct contact exposure. Risks to honey bees may be mitigated through label precautions against CPF application during times when bees are flying or when flowering crops or weeds are present in the treatment area (Giesy et al., 2014).

Chlorpyrifos and neurodevelopmental disorders in children

The EPA analysis of the association between neurodevelopmental disorders in children and CPF exposure, ultimately leading to the Obama administration recommendation for an agricultural ban on CPF, was largely based on epidemiologic investigations from three prospective birth cohorts: the Mothers and Newborn Study of North Manhattan and South Bronx conducted by Center for Children's Environmental Health (CCEH) at Columbia University, Mount Sinai Children's Environmental Health Study (MSEHS), and the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) from the University of California, Berkeley (U.S. EPA, 2016). A subsequent expanded EPA systematic review of the literature on OP exposure produced results consistent with the outcomes of these three robust cohort investigations resulting in the EPA conclusion that there is sufficient evidence of neurodevelopmental effects related to CPF exposure with currently approved use (U.S. EPA, 2016).

Columbia Center for Children's Environmental Health Study

The EPA CPF risk assessments related to neurodevelopmental outcomes primarily focused on data from the Columbia CCEH study. In this series of prospective cohort studies, prenatal CPF exposure was measured through the evaluation of neonate umbilical cord blood plasma in over 250 children born to African American or Dominican women beginning in 1998 (Rauh et al., 2006, 2011, 2012, 2015). Heavy exposure to indoor use of CPF was self-reported by this population largely for cockroach control in inner-city dwellings before the residential CPF ban (Rauh et al., 2006). Pediatric neurodevelopmental and cognitive outcome measurements included the Bayley Psychomotor Development Index (PDI), the Bayley Mental Development Index (MDI), the Child Behavior Checklist, the Weschler Intelligence Scale for Children, fourth edition (WSIC-IV), the full-scale IQ, and the Working Memory Index (Rauh et al., 2006, 2011). Covariates included maternal education and intelligence, measured using the Test of Nonverbal Intelligence, as well as the quality of the caretaking measured using the Home Observation for the Measurement of the Environment (HOME) instrument (Rauh et al., 2006).

Analysis of this data indicates that at 36-month children with high levels of prenatal CPF exposure were significantly more likely to demonstrate delays in cognitive (OR = 2.4; 95% CI = 1.1–5.1) and psychomotor development (OR = 4.9; 95% CI = 1.8–13.7). Children with the highest level of exposure to CPF also demonstrated a statistically significant increase in attention problems (OR = 11.26; 95% CI = 1.79–70.99), attention-deficit hyperactivity disorder (OR = 6.50; 95% CI = 1.09–38.69), and symptoms of pervasive developmental disorder (OR = 5.39; 95% CI = 1.21–24.11) at the age of 3 years (Rauh et al., 2006).

The WSIC-IV was again used to assess neurodevelopmental outcomes at the 7-year CCEH study evaluation (n = 265) (Rauh et al., 2011). The WISC-IV was selected as an outcome measure for this analysis as it has demonstrated sensitivity to detect cognitive effects of low dose neurotoxic exposures. Linear regression models suggest that for each standard deviation of CPF exposure (4.61 pg/g) working memory declined by 2.8% (1.6–3.7 points) and full-scale IQ declined by 1.4% (0.94–1.8 points) (Rauh et al., 2011).

A third examination of the CCEH data evaluated the effect of prenatal exposure to CPF on motor development and movement among children at 11 years of age (N = 263) (Rauh et al., 2015). The outcome measure for this study was the completion of hand-drawn Archimedes spirals as a test of motor function to detect the presence of tremor. The findings suggest a statistically significant increase in tremor in either arm (p = .03) and the dominant arm (p = .01) in children with the highest level of CPF exposure (Rauh et al., 2015).

A corollary investigation drawing from the original CCEH sample examined differences in the pediatric brain morphology between children with high exposure (upper tertile of umbilical cord blood CPF concentrations $\geq$ 4.39 pg/g) and low prenatal CPF exposure (Rauh et al., 2012). Twenty high exposure participants and 20 randomly selected low exposure participants between the ages of 5.9 and 11.2 years completed magnetic resonance imaging of the brain to examine differences in morphological characteristics. Morphologic changes in the brains of high CPF-exposed children corresponded with areas of the brain related to attention, receptive language, social cognition, reward, emotion, and inhibitory control (Rauh et al., 2012).

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Mount Sinai Children's Environmental Health Study

The MSEHS used a similar sample of multiethnic inner-city children born between the years of 1998–2002 (n = 404) to examine the effects of prenatal OP exposure on psychomotor and cognitive development (Engel et al., 2011). The CPF exposure biomarker used in this study was OP metabolites in third trimester maternal urine. Additional consideration was given to the influence of the Paraoxonase 1 (PON1) genotype, known to be a key enzyme in the metabolism of OPs and hypothesized to be potentially associated with neurodevelopmental outcomes related to CPF exposure (Engel et al., 2011).

Results of this study reflect poorer MDI scores among black and Hispanic children at 12 months when associated with higher maternal concentrations of OP urinary metabolites (Beta = −3.29; 95% CI = −5.88 to −0.70); however, a reverse effect was found among white participants with an increase in MDI related to higher CPF exposure (Beta = 4.77; 95% CI = 0.69–8.86). At 24 months, exposure to CPF was inversely associated with MDI regardless of race/ethnicity (Beta = −2.08; 95% CI = −4.60 to 0.44). Prenatal urine metabolites were also associated with a slight decrease in full-scale IQ (Beta = −2.89; 95% CI = −6.15 to 0.36), perceptual reasoning (Beta = −3.51; 95% CI = −7.31 to 0.30), and working memory (Beta = −3.48; 95% CI = −7.29 to 0.34) in children aged between 6–9 years (Engel et al., 2011). Associations between PON1 maternal genotypes and pediatric neurodevelopmental outcomes support the hypotheses of a potential genetic link to environmental toxin susceptibility (Engel et al., 2011).

The Center for Assessment of Mothers and Children of Salinas

The EPA CPF risk assessments also included a consideration of data derived from the CHAMACOS study (U.S. EPA, 2016). The CHAMACOS project is a longitudinal birth cohort investigation assessing developmental effects of environmental exposures of children in the farmworker community of Salinas, California. Seventeen years of CHAMACOS data have contributed to numerous scholarly publications available on the CHAMACOS website: http://cerch.berkeley.edu/research-programs/chamacos-study.

One of the studies evaluated by the EPA including CHAMACOS data is a pooled analysis of four studies (n = 936) on the effects of OP exposure on pediatric neurodevelopment conducted by the Children's Environmental Health and Disease Prevention Research Center (Engel et al., 2015). Two of the centers, Mount Sinai (MSEHS) and Columbia (CCEH), sampled low-income urban communities as previously described. The Cincinnati Children's Environmental Health Center HOME study included both an urban and suburban sample, and the CHAMACOS study included low-income women and children residing in potentially high exposure agricultural regions.

The biomarker for prenatal OP exposure in all the studies was maternal urine OP metabolites. Associations with PON1 genotyping were also examined. In this analysis, only the CHAMACOS center birth cohort, demonstrating a 4.17 point decline in the MDI per 10-fold increase in OP metabolite, reached statistical significance for an association between OP exposure and MDI (Beta = −4.17; 95% CI = −7.00 to −1.33). Although the pooled estimates also signified an association between the OP exposure and lower MDI (Beta = −1.48; 95% CI = −2.77 to −0.19), inference from the pooled results is limited by significant heterogeneity of results between birth cohort research centers potentially related to design differences and confounding factors. Overall, the investigators conclude that results support the estimation that each 10-fold increase in prenatal exposure to OPs is associated with an approximate 1-point decrease in MDI at 24 months. No association was detected between OP exposure and PDI at 24 months in this investigation. When analyzed by race and ethnicity, the Hispanic sample population was found to have the strongest negative association between CPF exposure and MDI. Stronger negative associations were also found for carriers of the PON1 genotype, particularly among Blacks and Hispanics (Engel et al., 2015).

Evidence-based health promotion recommendations

Given the significant publicity and controversy surrounding the recent EPA CPF decision, it is foreseeable that patients will bring questions regarding pesticide exposure risks to their health care providers. Nurse practitioners (NPs) should be prepared to facilitate a conversation on the current state of the science on CPF and provide evidence-based health promotion recommendations regarding pesticide safety. Foremost, a review of the available literature suggests that it is reasonable to advise patients that human epidemiologic investigations and mammalian toxicity studies support a potential link between OP exposure and negative neurodevelopmental outcomes. Particularly vulnerable populations include pregnant mothers, children younger than 2 years, and agricultural workers.

Controversy surrounding the interpretation of the CPF investigations related to human safety includes charges that the EPA did not appropriately calculate risks associated with PON1 genetic variability, that the EPA did not adequately address prenatal and early childhood safety factors, and that the EPA was overly reliant on chemical company industrial data. The complete response by the EPA to the petition to revoke all tolerances for CPF can be reviewed at regulations.gov, Federal Register # 2017-06777 (EPA, 2017). As investigations into CPF exposure safety and public debate continue, available evidence seemingly warrants evocation of the "Precautionary Principle." The Precautionary Principle simply stated is erring on the side of caution, particularly regarding the protection of

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Box 1. Precautionary Principle

The Precautionary Principle invoked by the American Nurses Association (ANA) and the American Public Health Association (APHA) "posits that in the absence of certainty, the appropriate course of action is to err on the side of caution" (Chaudry, 2008, p. 261).

vulnerable populations (Box 1) (Chaudry, 2008). In accordance with the Precautionary Principle, the current science on CPF justifies advocacy for ongoing scrutiny of OP safety. Nurse practitioners should consider their influential roles in the realm of local, state, and federal policy to advocate for safe environments and the protection of vulnerable populations. Those interested in a professional venue to further develop environmentally aware nursing practice, as well as policy engagement, are encouraged to participate in the Alliance of Nurses for Healthy Environments (http://envirn.org), a national organization of nurses from a range of specialties who are also specifically interested in environmental health.

In the clinical practice setting NPs are able to guide patients in an assessment of risk and the identification of personal risk reduction measures. To minimize potential OP exposure, patients should be advised to avoid application spray exposures in agricultural communities. Pesticide application regulations are largely controlled by individual states and information on location-specific regulations regarding spray restrictions, and notifications can be obtained from state or regional EPA offices (EPA, n.d. a). It is estimated that CPF may persist in the air after application from 4 to 11 hours (Christensen, Harper, Luukinen, Buhl, & Stone, 2009). Surface applications to soil have an estimated half-life of 7–15 days (Toxnet, 2014). Pesticide applicators are primarily responsible for the proper use of chemicals in accordance with label instructions and the management of drift. All pesticide applicators should wear personal protective clothing including gloves. Applicators should be trained, certified, and compliant with the use of appropriate cautionary signage. Patients can be advised to close windows and turn off air conditioners if pesticide applications occur within residential proximity. Specific levels of exposure risk for pregnant and breastfeeding women are unknown, as such preventable exposure and direct application of pesticides by pregnant and breastfeeding women should be avoided (National Institute for Occupational Safety and Health, 2017). The use of a respirator may reduce risk if pesticide exposure is unavoidable. Children should not be allowed to play in agricultural fields where pesticide residues may be present or around irrigation ditches where run off could occur. Children should not remain outside during pesticide spray application, and outdoor play equipment should be covered and then cleaned (Lucas & Allen, 2009).

Additional considerations in agricultural communities to reduce family exposure to pesticides include the following: "no shoe" policies in homes; use of walk-off mats at building/home entrances; showering immediately after work; frequent hand washing for children and adults, particularly before meals; thorough house cleaning with an attention to floors and other surfaces where chemicals may accumulate and increase exposure to young children; and washing farmworkers' clothing separately from other family members (Lucas & Allen, 2009). Patients should be advised that agricultural pesticides should never be used inside, and use of pesticide alternatives should be encouraged. Agricultural workers should avoid eating while in treated fields (Lucas & Allen, 2009). The most common laboratory testing for OP exposure is a blood analysis for reduced levels of plasma or red blood cell AChE. Testing may be indicated for individuals working directly with OPs (National Pesticide Information Center, 2009).

To decrease exposure to dietary OP residue, patients should be encouraged to purchase organic produce when feasible, particularly the fruits and vegetables with the highest potential for pesticide residues. The Environmental Working Group (EWG) has branded a list of products the "Dirty Dozen," including the following: strawberries, spinach, nectarines, apples, peaches, celery, grapes, pears, cherries, tomatoes, sweet bell peppers, and potatoes (EWG, 2017). Washing produce with a 12–15-minute 1% baking soda and water solution soak has demonstrated effectiveness in reducing residue from nonsystemic pesticides (Yang et al., 2017). Reduction of systemic pesticide exposure can be achieved by peeling fruits such as apples; however, the trade-off is a loss of dietary nutrients (Yang et al, 2017). Patients and health professionals who are interested in more information regarding toxin exposure can be directed to the EWG website at www.ewg.org or to the National Library of Medicine's Toxnet suite of evidence-based information and database. Patients should be encouraged to explore the available information on pesticide exposure and work with their health care providers to advocate for healthy families and communities.

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