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Neurodevelopmental Disorders and Agricultural Pesticide Exposures

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We read with interest the analysis by Shelton et al. (2014) of the relationships between maternal proximity to insecticide application and autism spectrum disorders (ASDs) and developmental delay (DD) in children. Although we commend the investigators' efforts to identify, recruit, and enroll parents of children with ASDs or DD, absent is any confirmation of exposures or that the active ingredients drifted onto the residences or were inhaled or ingested, let alone at dose levels that might be adverse to the fetus (Williams and DeSesso 2014).

The authors noted other sources of potential exposure, including diet and nonagricultural applications that were unmeasured in their assessment. However, there are many factors that reduce the opportunity for participant exposures. Importantly, the inherent properties of each pesticide determine its volatilization and solubility. The method of application and whether the formulation is a liquid or granule also influences drift potential. For example, an orchard air-blast application has a very different exposure potential than a drip-line irrigation application of the same quantity of pesticide to the same crop at the same distance (U.S. EPA 2013a, 2013b). Weather conditions and wind direction influence whether an active ingredient is carried toward or away from a residence (U.S. EPA 2013b). Furthermore, Caldwell and Wolf (2006) found that amounts of ground-spray drift deposited 0.4 km downwind in windy conditions were 0.001% of the applied amounts. Last, being inside, outside, or away from home all factor into human exposures.

Proximity to agricultural pesticide application has not been found to translate to corresponding levels of the pesticide in household dust (Curwin et al. 2005; Fenske et al. 2002; Ward et al. 2006). The California Pesticide Use Registry was evaluated by Nuckols et al. (2007). Although they confirmed agreement of pesticide applications with crop maps, they also recommended biological sampling to validate exposure assumptions for each active ingredient. Correlations of pesticide concentrations in household dust and urinary pesticide metabolite levels in children have been suggested (Lu et al. 2000) but not confirmed (Fenske et al. 2002; Morgan et al. 2008). Several studies of farmers and their

families concluded that behavior patterns were more predictive of urinary pesticide concentrations than proximity to the field (Alexander et al. 2006; Arbuckle and Ritter 2005; Thomas et al. 2010).

In their recent review of geographic models in epidemiological studies, Chang et al. (2014) discuss many of these exposure-related issues. The U.S. Environmental Protection Agency has begun to evaluate residential exposures to agricultural pesticides from spray drift and volatilization (U.S. EPA 2014), and there is a growing understanding of off-target drift for each active ingredient. This understanding has permitted the agency to publish a quantitative methodology for assessing residential exposure and risk resulting from spray drift and volatilization of conventional pesticides (U.S. EPA 2014). Risk is the result of the interaction between exposure and toxicity; unfortunately, Shelton et al. (2014) confuse the occurrence of a distant application with exposure. In light of critical weaknesses in exposure characterization in the present case, any relationship between pesticide exposure and the occurrence of ASDs and DD is unknown, and an association between exposure and occurrence is speculation.

C.J.B. and C.L. are employees of companies that manufacture and sell pesticides. S.Z.C. owns an environmental consulting firm that includes among its clients pesticide users and producers, as well as those impacted by pesticide users and producers.

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Neurodevelopmental Disorders and Agricultural Pesticide Exposures: Shelton and Hertz-Picciotto Respond

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Burns et al. (2015) question whether residential proximity to agricultural pesticide applications can serve as a surrogate for actual exposures in research on autism spectrum disorders (ASDs) and neurodevelopmental delay. Previous work has consistently demonstrated that pesticide drift results in elevated levels of these compounds in both indoor air and house dust in residences located near agricultural applications (Fenske et al. 2002; Gunier et al. 2011; Harnly et al. 2005; Ward et al. 2006; Wofford et al. 2014). For example, Wofford et al. (2014) intensively

monitored ambient air concentrations for 40 active ingredients or degradation products of pesticides in a California Central Valley city. Air concentrations of the organophosphates chlorpyrifos, diazinon, phosmet, and malathion increased after recent applications within 8 km of the city boundary. Notably, these associations were found despite mitigating factors such as those named by Burns et al. (2015), for example, weather conditions, wind direction, type of formulation, and application method. The temporal correspondence between applications and measured concentrations in air was particularly strong for chlorpyrifos (Wofford et al. 2014), which we found to be associated with an elevated prevalence of ASDs among children exposed *in utero* (Shelton et al. 2014).

Burns et al. (2015) also assert that levels reaching homes are inadequate to induce adverse effects on the fetus. In fact, between 1996 and 2008 pesticide drift or off-target spraying was associated with 2,945 cases of acute pesticide illness in 11 U.S. states, of which 14% were children under 15 years of age (Lee et al. 2011). Furthermore, one-third of acute pesticide illnesses occurring in U.S. schools in 1998–2002 were attributed to drift exposure from farmland (Alarcon et al. 2005). Thus, considerable evidence shows biologically harmful exposures can and do occur in areas surrounding agricultural fields where pesticides are applied.

With chlorpyrifos detectable in 70.5% of pregnant mothers living in an agricultural area in California (Huen et al. 2012), fetal exposure is surely widespread. Because the fetus cannot metabolize organophosphate chemicals as well as its adult mother can (Chen et al. 2003; Furlong et al. 2006), there is a compelling biological basis for more severe effects once the compound passes through the placenta. Given greater fetal and neonatal vulnerability, these aforementioned results raise quite reasonable concerns for parents and warrant research

utilizing proximity to pesticides as an exposure indicator when biological samples are unavailable (Harnly et al. 2005).

Finally, Burns et al. (2015) include several misrepresentations of the scientific literature. For example, a review of behavioral impacts of chlorpyrifos exposure in rodent studies (Williams and DeSesso 2014) is cited to support the argument that doses reaching pregnant women neighboring agricultural fields are too low to cause harm to the human fetus. It is unclear how Burns et al. (2015) extrapolated to draw this conclusion or what assumptions they made regarding comparability of rodent versus human dosing.

Burns et al. (2015) also reference work by Ward et al. (2006), who used a spatial model to predict household carpet dust levels of agricultural pesticides. Ward et al. (2006) reported, “Increasing acreage of corn and soybean fields within 750 m of homes was associated with significantly elevated odds of detecting agricultural herbicides [in house dust] compared with homes with no crops within 750 m.” Yet Burns et al. (2015) state to the contrary, “Proximity to agricultural pesticide application has not been found to translate to corresponding levels of the pesticide in household dust (Curwin et al. 2005; Fenske et al. 2002; Ward et al. 2006).” Other results from these cited articles also are misrepresented: Fenske et al. (2002) reported higher chlorpyrifos in house dust for homes in closer proximity ($p = 0.01$), and Curwin et al. (2005) detected higher levels in farm homes than in nonfarm homes.

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