

## **Appendix 6. Columbia Center for Children’s Environmental Health (CCCEH) Epidemiology Data Acquisition “Raw Data” Request**

### **I. ACTION REQUESTED**

To fulfill identified information needs for the purposes of incorporating the Columbia Center for Children’s Environmental Health (CCCEH) epidemiology data into the Human Health Risk Assessment (HHRA) for chlorpyrifos, the agency sought to obtain certain “raw data” from CCCEH researchers. Specifically, EPA requested the original analytic data file used to support analyses presented in the peer-reviewed, published epidemiology studies concerning *in utero* chlorpyrifos exposure (V. Rauh et al., 2011; V. A. Rauh et al., 2006; Whyatt et al., 2004). CCCEH researchers did not agree to provide these data, however, the researchers met with EPA and discussed the agency’s questions about the data to help determine whether further review of the raw data might assist EPA in resolving uncertainties. As a result of new information gathered through an on-site meeting and other sources, EPA is no longer pursuing the request for the original analytic data file from CCCEH researchers. This memorandum details the new information gained that resolves or renders unobtainable the previously identified information needs.

### **II. BACKGROUND**

EPA considers many different types of scientific information when performing a human health risk assessment (HHRA) of pesticide exposure in the human population. Traditionally, EPA uses toxicology, product and residue chemistry, and industrial hygiene studies as well as measured and modeled human and environmental exposure information to support assessment of environmental risks. In its preparation of the HHRA for chlorpyrifos, the agency has evaluated environmental epidemiology studies of the potential risk of long-term neurodevelopmental effects such as delayed motor skill acquisition or reduced intelligence quotient (IQ) measures among children who experienced pesticide exposure during gestational development. There are three prospective birth cohort studies in the U.S. that examine pesticide exposure (as well as other environmental toxicants) to the pregnant mother and fetus, and then measure neurological and neurodevelopmental performance in children as they grow older. EPA has provided some of

the funding support for each of these studies. Authors hypothesize that *in utero* and early life exposure may influence brain development and effect neurological functioning in children. These studies include the CHAMACOS study in the Salinas Valley, CA, the Mt. Sinai children's environmental health study (Mt. Sinai study), and the Columbia Center for Children's Environmental Health (CCCEH).

The CCCEH study is the only one of the three studies that measures maternal and fetal exposure to chlorpyrifos specifically; the other two cohorts measure exposure to organophosphate pesticides generally. Authors with the CCCEH study reported reduced birth weight and birth length among neonates more highly exposed to chlorpyrifos during gestation (as measured by cord blood concentration of chlorpyrifos) (Whyatt et al., 2004). Similarly, authors observed slower motor skill acquisition and reduced mental capacity among infants who were more highly exposed to the chemical *in utero* (V. A. Rauh et al., 2006). In 2011, authors from all three birth cohort studies concurrently reported evidence of reduced measures of intelligence (Wechsler intelligence scale scores) by increasing *in utero* chlorpyrifos and/or organophosphate exposure (M. F. Bouchard et al., 2011; Engel et al., 2011; V. Rauh et al., 2011).

Given the value of this information to the agency's HHRA for chlorpyrifos, EPA requested the FIFRA SAP to provide external peer review of the strengths and limitations of the epidemiology data for use in the chlorpyrifos HHRA (FIFRA SAP September 2008 and April 2012). The agency identified two major areas in which additional information was needed to fully incorporate these data into the HHRA: additional measures of environmental exposure to chlorpyrifos in the CCCEH cohort to discern whether acetyl cholinesterase inhibition was likely to have occurred in connection with reported adverse outcomes, and also the role of other environmental chemicals (lead, polycyclic aromatic hydrocarbon (PAH), other organophosphate pesticides) in the observed adverse neurological effects reported in relation to *in utero* chlorpyrifos exposure.

To fulfill these information needs for the purposes of incorporating the epidemiology data into the chlorpyrifos HHRA, the agency sought to obtain certain "raw data" from the Columbia Center for Children's Environmental Health (CCCEH) study. Specifically, EPA requested the

original analytic data file used to support analyses presented in the peer-reviewed, published epidemiology studies concerning *in utero* chlorpyrifos exposure (V. Rauh et al., 2011; V. A. Rauh et al., 2006; Whyatt et al., 2004). CCCEH did not agree to provide the data based upon these initial inquiries and they asserted that because EPA did not fund the pesticide exposure component of their cohort study EPA was not legally entitled to review their underlying data. CCCEH did agree, however, to meet and discuss EPA's questions about the data to help determine whether further review of the raw data might assist EPA in resolving uncertainties. As a result on April 15<sup>th</sup>, 2013, EPA scientists and CCCEH researchers held an all-day meeting at the CCCEH data center (Mailman School of Public Health, New York City, NY) to discuss EPA's information needs and whether acquisition of the full analytic data would be necessary or valuable to EPA's assessment. Addendum 1 delineates the questions EPA posed to CCCEH study staff at this all-day meeting.

### **III. RESOLUTION OF INFORMATION NEEDS**

#### **A. EPIDEMIOLOGY STUDY EXPOSURE CHARACTERIZATION**

The primary rationale supporting EPA's request for "raw data" from the CCCEH researchers relates to the agency's need to determine whether the levels of chlorpyrifos exposure in the environment (apartments, apartment building or other outdoor environment, or dietary exposure) of CCCEH study participants were above or below levels that may elicit a greater than 10% inhibition of acetylcholinesterase enzyme levels, the current regulatory endpoint. During the April 2013 meeting, EPA learned that this type of information is neither available nor obtainable. CCCEH researchers estimated relative pesticide exposure using several different exposure methods including 48-hour air sampling with personal monitor, 2-week integrated stationary air monitoring, maternal urinary concentration of TCPy (urinary metabolite of chlorpyrifos) during the last trimester of pregnancy, maternal urinary concentration of TCPy at delivery, and umbilical cord blood and meconium at delivery. To determine whether a significant change in acetyl cholinesterase levels may have occurred as a result of actual environmental exposure, temporal concordance between pesticide use and the chlorpyrifos measurement is needed, *i.e.*, exposure estimation at the time of pesticide application is optimal. The CCCEH study design did not incorporate pre- and post-pesticide use/exposure measurement in the study protocol.

Therefore, this information was not collected and is not retrospectively obtainable.

In addition, EPA requested any additional information obtained by researchers as to specific pesticide products used to better understand the pattern and frequency of organophosphate pesticide use among cohort participants. This information was solicited from participants in a written questionnaire administered during a follow-up period (unpublished copy of questionnaire obtained by EPA Oct. 2012). In response to the EPA inquiry, researchers recalled that the Whyatt (2002) publication described the challenges of collecting pesticide product information in etiologic epidemiology studies, and in the on-site meeting in April 2013 confirmed that the information quality in the CCCEH written questionnaire responses is very low. This information was deemed of such poor quality by CCCEH data analysts that the data were not coded or entered into the analytic data file. Therefore, EPA learned that this specific request for “raw data” concerning pesticide product use is not available.

As a surrogate for this information, CCCEH researchers suggested EPA contact the New York City Department of Health to obtain a linked dataset of CCCEH study participant residential address and public housing pesticide usage. The linked dataset provides aggregated pesticide usage data at the cohort participant building-level only. EPA has obtained and reviewed these data (June 2013) and determined that pursuing a data reconstruction exercise is the most appropriate way to estimate environmental pesticide exposure that would have to occur among CCCEH study participants. EPA has conducted such analysis and included it in the revised human health risk assessment.

## **B. CO-EXPOSURE TO OTHER ENVIRONMENTAL CONTAMINENTS**

A second major concern raised by EPA, FIFRA SAP peer reviewers, and public commenters is the ability of the CCCEH study authors to accurately measure and statistically model the relationship between other environmental chemicals (lead and PAH, specifically) or other pesticides (diazinon, propoxur) that may influence fetal brain development and childhood neurodevelopmental performance, and also be related to chlorpyrifos exposure (these are “potentially confounding” exposures). EPA’s concern stems from the understanding that if these

other exposures are not sufficiently considered in the epidemiological analysis, then an incorrect inference and conclusion may result (*i.e.*, a potential false positive association). For example, prenatal and early life exposure to lead in the environment has been causally linked to adverse neurodevelopmental outcomes similar to those measured in the CCCEH cohort study including intelligence measures. EPA was concerned about the potential error in the CCCEH study if lead levels were not appropriately considered, *i.e.*, the apparent chlorpyrifos effect on neurodevelopment observed in the study may have been due to the lead exposure.

However, EPA has confirmed with study authors that lead levels and chlorpyrifos levels in cord blood are not statistically associated in this population. Plotting blood lead levels against cord blood chlorpyrifos levels illustrates that the two exposures are extremely weakly (linearly) correlated in this cohort ( $\rho < 1\%$ ) (V. A. Rauh et al., 2006). Further, EPA learned from unpublished, supplemental analyses performed by CCCEH researchers upon EPA request that postnatal blood lead levels and prenatal chlorpyrifos levels are also not strongly statistically associated (Andrews, January 21, 2013). This is plausible because of intensive lead abatement programs on-going in New York City during the time period of this study. According to the New York City Department of Health, the number of children with elevated blood lead levels declined 92% between 1995 and 2008.<sup>1</sup> Therefore, because the two exposures are not related, it is not likely that pre- or postnatal blood lead exposure could explain the observed association with chlorpyrifos.

Furthermore, during the April 2013 meeting CCCEH researchers pointed out that based upon available information it appears that lead and chlorpyrifos may affect the brain differently. It is well understood that lead affects the neurodevelopmental sub-domain leading to outward motivation and aggression; while research within the CCCEH cohort indicates chlorpyrifos may affect inward motivation, information processing and organization (V. Rauh et al., 2011; V. A. Rauh et al., 2006; Wright et al., 2008). Additionally, MRI imaging studies of lead affected persons and preliminary brain imaging studies of chlorpyrifos affected persons show different MRI patterns, grey matter as opposed to white matter compositional patterns, respectively (Brubaker, Dietrich, Lanphear, & Cecil, 2010; Brubaker et al., 2009; Cecil et al., 2008; Cecil et

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<sup>1</sup> <http://www.nyc.gov/html/doh/html/data/stats-childlead.shtml>

al., 2011; V. A. Rauh et al., 2012). Therefore, given that neither pre- nor postnatal lead levels and chlorpyrifos levels are not statistically associated with one another in the CCCEH study, and the different ways through which lead and chlorpyrifos appear to influence neurodevelopmental domains EPA concludes that lead exposure did not likely confound (bias or render incorrect) the observed association between chlorpyrifos exposure and neurodevelopment in this study population.

Peer review panelists participating on the April 2012 FIFRA SAP panel identified the concern that authors had not fully considered the long-term effects of polycyclic aromatic hydrocarbon (PAH) exposure, a ubiquitous air pollutant in inner-city areas such as NYC, in the observed association between chlorpyrifos and neurodevelopmental outcomes. Specifically, panelist argued that ‘a shift in environmental exposures over time’ such that postnatal PAH exposure may have combined with the measured *in utero* pesticide exposure to result in the observed ND outcomes. During the April 2013 meeting, authors clarified that the study design did not include a repeat measure of exposures over time, so an analysis of postnatal PAH exposures is not possible. In the published studies, authors were able to control for the effect of prenatal PAH through statistical adjustment. In addition, authors examined the possible modifying role of prenatal PAH in this epidemiological association and did not observe any evidence of a different risk estimate between chlorpyrifos and ND among those more highly exposed to PAH. Concerning the role of postnatal environmental exposures, CCCEH researchers also stated their belief that their overall study results illustrate that it is gestational exposure, and not early life exposure, that influences neurodevelopment in the study population. They state that the longitudinal analyses of infant and child neurodevelopment in relation to *in utero* chlorpyrifos exposure illustrates a persistent effect of the prenatal environment (M. Bouchard et al., 2003; M. F. Bouchard et al., 2011; Engel et al., 2007; Engel et al., 2011; Eskenazi et al., 2004; Eskenazi et al., 2007; V. Rauh et al., 2011; V. A. Rauh et al., 2006; Whyatt et al., 2004). EPA concluded that CCCEH researchers utilized best practices in statistical analysis of epidemiological data concerning the role of prenatal PAH in neurodevelopmental outcomes, and that a study of repeated, postnatal PAH exposure was beyond the scope of the current CCCEH study, and would require a follow-up study not yet undertaken.

EPA was also interested to learn more about the co-exposure to other organophosphate pesticides among CCCEH study participants. Specifically, EPA as well as external peer review panelists noted the uncertainty as to the degree to which exposure to multiple acetyl cholinesterase inhibiting pesticides exposures over time and/or concurrent in time may have influenced study results. CCCEH researchers agreed that a more clear understanding of the role of mixtures – exposure to multiple OP pesticides overall or concurrent in time – on these neurodevelopmental outcomes is desirable; however they also recognized that the current sample size is too small to perform this type of analysis. To better understand the role of exposure to a mixture of OP pesticides a new cohort study with a larger sample size and different design is required. Therefore, EPA concluded that co-exposure to multiple organophosphate mixtures is not currently obtainable.

For risk characterization purposes, EPA was also interested in understanding the relative contributions of various environmental exposures on ND outcomes, (*e.g.*, PAH, environmental tobacco smoke, chlorpyrifos). Researchers noted that a preliminary indication of the relative contribution of various risk factors for intelligence measures in these cohorts can be seen through examination of supplemental tables published by CCCEH researchers, *i.e.*, the beta-coefficients provided in published supplemental tables provide an indication of the relative contribution of each risk factor (V. Rauh et al., 2011). However, CCCEH researchers indicated that to gain a true reflection the causal model in the population a series of studies in other study populations is needed. EPA and CCCEH researchers agreed that these studies will likely accumulate over time, however they are not currently available.

#### **IV. CONCLUSIONS**

In the past, EPA sought to obtain the original analytic data file used to support certain epidemiological analysis of *in utero* exposure to chlorpyrifos and subsequent adverse neurodevelopmental health outcomes in children generated by the Columbia Center for Children's Environmental Health (CCCEH) to support the Human Health Risk Assessment (HHRA) of chlorpyrifos. EPA believed these data were important to both clarify the exposure-response relationship observed in the epidemiology study relative to the current regulatory

endpoint (acetylcholinesterase inhibition), and also to resolve uncertainties regarding study participants co-exposure to other environmental contaminants, among other areas of uncertainties. CCCEH researchers did not agree to provide these data, however, the researchers met with EPA and discussed the agency's questions about the data to help determine whether further review of the raw data might assist EPA in resolving uncertainties. As a result of this meeting and additional discussions with CCCEH staff, EPA concluded that access to the raw data would either not provide answers to EPA's questions or that the information EPA sought could be obtained without analyzing the raw data. Indeed, based on discussions in that meeting as well as further work conducted by agency staff, EPA has gained additional information to better clarify and characterize the major issue areas identified as uncertainties. For these reasons, EPA decided that it would not further pursue its request for the analytic data file from the CCCEH researchers.

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**Columbia University Epidemiology Studies**

**The agency is obligated to review and address peer review comments in support of regulatory decisions. The following is a list of key issues about the epidemiological studies carried out by researchers at Columbia University that were raised in peer review comments. These issues require EPA to have access to the raw data for additional analyses by the agency.**

**1) Further analysis of other chemical exposures (e.g., lead, PAHs, other pesticides) to address, if possible, their impact or contribution as modulating factors on the measured outcomes**

- **2012 SAP** -- “it should be noted that it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes.”
- **2012 SAP** -- “In an earlier examination of the same cohort, Perera *et al.* (2009) reported an association between a decrease in full-scale IQ and verbal IQ in 5-year-olds with prenatal polycyclic aromatic hydrocarbons (PAH) exposure rather than chlorpyrifos, thus, raising an issue of the shift in chemical exposure association with increase in age. In each of these analyses, statistical modeling showed that the exposures were independently associated with IQ, and no significant interaction was observed with the other chemical. While this is a statistically sound approach to determine independent responses, panel members noted that it is very difficult to identify the independent physiological effects of a single chemical in this type of multi-chemical exposure scenario.”
- **2012 Federal Peer Review** -- “even low levels of lead can impact neurodevelopment, and even that the observed neurobehavioral deficits are more pronounced at lower blood lead levels when compared with higher blood lead levels”.
- **2008 SAP** -- “In order to eliminate the possible causes of neurodevelopmental effects by other pesticides in the Columbia study, it is suggested that EPA should repeat the pre-post residential cancellation analysis done for chlorpyrifos using other pesticide measurements, such as malathion diacid (MDA), a specific metabolite of malathion. The outcomes from those additional analyses will either confirm or reject EPA’s preliminary conclusion that chlorpyrifos is likely to play a role in the neurodevelopmental outcomes.”
- **2008 SAP** -- ““It would be useful to examine the results of a statistical analysis that includes all three AChE-inhibiting insecticides in the analysis model as dichotomous variables (above or below LOD) in combination with continuous measurements for these variables. This type of analysis would likely not change

the results, but it could be helpful in illustrating threshold or dose response effects.”

**2) Further analysis and information to address and, if possible, better characterize uncertainty around outcome measures on learning/memory/IQ**

- **2012 SAP--** Alternative considerations for non-quantified samples: “little use was made of techniques to integrate non-quantified samples into the statistical test. . . . Various methods were reviewed by the July 2010 SAP that can be applied to either normally or lognormally distributed data that include a significant (even a majority) of non-detectable sample . . . . Specifically, the use of ‘probability plots’ was described that can yield an estimate of the geometric mean of the distribution [GM], the geometric standard deviation [GSD], and corresponding percentiles.”
- **Federal Peer Review --** “There is a scatterplot showing the raw scores for overall IQ and for each of the subtests, but it is not possible to obtain the necessary information to compare the distributions of these scores with the norms for the test or with any other study sample. Ideally, the means and standard deviations for these scores should be presented for either a non-exposed or a non-exposed combined with low exposed group and these should be compared to a moderate or high-exposed group as was done for the BSID-II in the Rauh et al., 2006 paper. Here the uncertainties stem from the assumptions that are made when regression analyses are performed. The main issue here is that outliers can greatly influence the slope of the function.”
- **Federal Peer Review--**A between group analysis using inferential statistics, as was done for the Bayley Scales of Infant Development II in the Rauh et al., 2006 paper, should be performed on each variable in both studies (i.e., the Child Behavior Checklist in Rauh et al., 2006, and the full scale IQ and subscales for the WISC-IV in the Rauh et al., 2011 study). This would be the most direct and least problematic method for determining whether exposure to chlorpyrifos resulted in significant decreases in IQ or significant increases in behavioral problems “ . . . . no information was provided regarding the qualifications of the individuals who administered and scored the tests. “

**3) Further analysis to assess, if possible, whether individual cohort members had the potential for exposure to chlorpyrifos and/or other acetylcholinesterase (AChE) inhibiting pesticides (e.g., diazinon, propoxur), prenatally and /or postnatally, at levels leading to greater than 10% AChE inhibition (the level used to derive the regulatory point of departure).**

- **2012 SAP--** recommended conducting a dose reconstruction analysis—“data on the concentration of chlorpyrifos in various media (*i.e.* house dust, air and water) while market basket data exists on the concentration of chlorpyrifos on food. These data provide the main tools for developing an effective exposure assessment and a subsequent reconstruction of potential dose.” The agency has begun such analysis but the current draft analysis is limited without data on the exposure information relevant to individual women such that environmental chlorpyrifos exposure can then be linked to measures of blood chlorpyrifos.
- **2012 SAP--** recommended the agency consider issues related to multiple chemical exposure (*i.e.*, mixtures) to chlorpyrifos and other key AChE inhibiting pesticides identified by the Columbia University studies (diazinon, propoxur). Assumptions of co-exposure will likely be grossly overestimated without access to the raw data; such raw data may enable the agency to evaluate actual co-exposure information for individuals from air monitoring samples and blood samples.