



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

August 28, 2008

MEMORANDUM

Subject: Second Transmission of Background Materials and Charge to the FIFRA Scientific Advisory Panel for the September 16 - 18, 2008 Meeting: "The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos"

To: Sharlene Matten, Ph.D., Designated Federal Official
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A first transmittal of documents for the September 16 - 18, 2008 meeting of the FIFRA SAP entitled, "The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos" was provided on August 21, 2008. This memo transmits the remaining supporting documents for this meeting, including Appendices B (Acetylcholinesterase inhibition) and D (Epidemiology) and additional benchmark dose analyses. In addition, the charge questions to Panel have been re-transmitted in this memo. One charge question, **5b**, has been changed. All other charge questions remain the same.

Documents & Files Provided to the Panel

The Agency has provided a number of documents and files for the Panel as part of this review. All the documents are considered DRAFT and should not be cited or quoted. The Agency has not yet made any final determinations on the updated chlorpyrifos hazard and dose response assessment.

- The Issue Paper, provided in the August 21, 2008 submission, contains the proposed updates to the chlorpyrifos hazard assessment and integrated summaries of key studies on metabolism, acetylcholinesterase (AChE) inhibition, toxicities related to effects on the developing brain, and epidemiology studies in mothers and children.

The Issue Paper is supported by seven appendices.

- Appendices A-D include detailed summaries on metabolism, acetylcholinesterase (AChE) inhibition, toxicities related to effects on the developing brain, and epidemiology. These four appendices contain varying degrees of discussion on the summarized information.
 - ***In this submission, Appendices B and D are included.***
Appendices A and C were provided in the previous submission.
- Appendix E, provided in the August 21, 2008 submission, contains an analysis of toxicokinetic and toxicodynamic data for purposes of developing data-derived extrapolation factors for inter- and intra-species extrapolation.
- Appendix F, provided in the August 21, 2008 submission, contains the results of benchmark dose analyses conducted on selected AChE studies. ***A supplement to Appendix F in this submission provides BMD analyses for additional studies not included previously. An updated BMD table with all analyses is also provided (file name Chlorpyrifos_ RevisedBMDTable).***
- Appendix G, provided in the August 21, 2008 submission, contains study reviews, also called data evaluation records or DERs, for the deliberate dosing studies in human subjects.

The Agency has also provided the following files to the Panel for informational purposes:

- Study reviews for the chlorpyrifos developmental neurotoxicity (DNT) and companion study (file names: DNT review & DNT companion review),
- EPA's 2000 human health risk assessment (file name: HED RA),
- EPA's 2000 hazard and dose-response assessment (file name: HIARC2000), and
- IPSC Guidance on Chemical Specific Adjustment Factors (2005) (file name: IPSC 2005 CSAF).
- ***Two additional informational documents are provided in this submission. These files represent slide presentations presented to EPA by Drs. Robin Whyatt and Virginia Rauh of Columbia University. These presentations are referenced by the Agency in Appendix D and are provided as supplemental information. The files are named: "VRslidesEPAmeeeting 4_23_08" and "WhyattNYCEPA meeting 4_23_08disclaimer".***

Charge to the Panel

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro -2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide. Chlorpyrifos is one of the most widely used OPs in the U.S. In 2000, nearly all residential uses were voluntarily cancelled by Dow AgroSciences but agricultural use remains. Since 2000, there has been extensive research on various aspects of chlorpyrifos, particularly on effects in animals and humans from gestational and post-natal exposure. Many new studies in rats on different toxicities including AChE inhibition and on the developing brain are available. In addition data from three cohorts of mothers and children exposed to OPs are available. At this time, the Agency is re-evaluating the extent to which toxicity endpoints and extrapolation/uncertainty factors for chlorpyrifos require updating based on new information. The Agency's issue paper and associated appendices contain the proposed updates and the scientific foundation for the proposed revisions. The contents and conclusions drawn in the issue paper and appendices are preliminary in nature. The ultimate goal of the Agency's on-going work is to improve the scientific support for the Agency's risk assessment by 1) evaluating new data on potentially susceptible subpopulations and 2) incorporating improved approaches like benchmark dose modeling instead of reliance on no-observed-adverse-effect levels (NOAELs) for points of departure and extrapolation factors based on data instead of reliance on default factors to account for differences in animals and humans and among humans. The Agency has progressed to a point in the review that feedback from the FIFRA SAP would be helpful.

1. Metabolism & Toxicokinetics (Issue Paper Section 3.1, Appendix A):

The Agency has performed a literature review of *in vivo* and *in vitro* studies on the metabolic profile and toxicokinetic (TK) properties of chlorpyrifos with particular focus on age-dependent and lifestage sensitivity.

- a. The Agency has concluded that age-dependant sensitivity, at least in part, is derived based on toxicokinetic (TK) differences between juveniles and adults. These TK differences lead to reduced ability to detoxify chlorpyrifos or the oxon in juvenile animals. Please comment on the Agency's conclusion and the scientific support for or against this conclusion.
- b. There are limited data on the metabolic capacity of pregnant animals and pregnant humans. These limited data on metabolism are supported by some toxicity data in rats. The Agency believes these studies suggest that pregnant animals and humans may be somewhat more sensitive to chlorpyrifos than non-pregnant adults to chlorpyrifos. Please comment on the Agency's preliminary conclusion and the scientific support for or against this conclusion.

2. Cholinesterase Inhibition (Issue Paper Section 3.2, Appendix B):

The Agency has reviewed numerous studies submitted for pesticide registration and from the literature in animals and human on the AChE-inhibiting effects of chlorpyrifos in blood and in the peripheral and central nervous system.

- a. Regarding inhibition of AChE, the Agency has preliminarily concluded that post-natal studies in rat support the conclusion that juveniles are more sensitive than adults. The Agency has further concluded that sensitivity is greatest in younger pups and decreases as pups mature towards adulthood. Please comment on these Agency's preliminary conclusions and the scientific support for or against these conclusions.
- b. There are multiple gestational studies available which provide AChE data in dams and/or fetuses. These gestational studies have consistently shown that AChE inhibition observed in the dam is greater than in the fetus. These studies suggest that the dam serves to protect the fetus. However, TK gestational studies have shown that fetal tissues have similar or higher levels of chlorpyrifos and/or its metabolites than the dam. In addition, multiple studies have shown that recovery from AChE inhibition is more rapid in juveniles compared to adults. This rapid recovery combined with production of the AChE enzyme as the rats mature leads to less AChE inhibition observed in the juveniles. The Agency has preliminarily concluded that AChE inhibition data from repeated dosing gestational studies showing less inhibition in fetuses may not reflect the true potential toxicity to the fetus. Please comment on the Agency's preliminary conclusions and the scientific support for or against this conclusion.

3. Laboratory Studies on the Developing Brain (Issue Paper Section 3.3, Appendix C):

The Agency has performed a literature review of *in vivo* and *in vitro* studies on the effects of chlorpyrifos on the developing brain.

- a. From a review of laboratory animal studies, the Agency has preliminarily concluded that gestational and early postnatal exposure at sufficiently high exposures to chlorpyrifos can lead to neurochemical and behavioral alterations persisting into adulthood after any initial AChE inhibition has reversed. The Agency has put particular emphasis on the behavioral data because studies are available from multiple laboratories. Please comment on the Agency's preliminary conclusions and the scientific support for or against this conclusion.
- b. Consideration of the mode of toxic action is an important component of risk assessment. The International Programme of Chemical Safety (IPCS) and International Life Sciences Institute Risk Science Institute (ILSI RSI) have developed a Mode of Action (MOA)/Human Relevance Framework which provides structure and transparency to MOA analyses (Meek et al., 2003 ; Seed et al 2005 and Boobis, et al, 2006). IPCS have combined and extended these components to produce a unified Human

Cancer Relevance Framework (IPCS HRF). In this approach, involvement of a series of key events in the MOA is established on weight-of-evidence, using criteria based on those described by Bradford Hill, taking account of factors such as dose-response and temporal concordance, biological plausibility, coherence and consistency. Other MOAs that logically present themselves also should be considered. Once an MOA is established, qualitative and quantitative comparison of each key event between the experimental animal and humans enables a conclusion as to likely relevance of the MOA for human risk. In the case of chlorpyrifos, the Agency has considered the available mechanistic data but has not evaluated these data in the context of MOA/human relevance framework. It has been initially determined that there are insufficient data to develop a series of supportable key events (as in a mode of action analysis¹) for neurodevelopmental toxicities other than AChE inhibition. The Agency notes a particular lack of data on dose response and temporal concordance which are critical in a MOA framework analysis. There may be other mechanisms which lead to effects on the developing brain but a supportable mode of action(s) can not be elucidated at this time. Please comment on the Agency's preliminary conclusions and whether there is sufficient scientific information to merit a full mode of action framework analysis. If a mode of action framework analysis is pursued, what would be the biologically plausible hypotheses to evaluate?

4. Epidemiology Studies in Children and Mothers (Issue Paper Section 3.4, Appendix D):

The Agency has evaluated epidemiology studies from three major cohorts: the study sites are: (1) Columbia University, NYC, (2) Mt Sinai, School of Medicine, NYC, both with multi-ethnic urban low income women and infants, and (3) University of California at Berkeley (Center for Health Assessment of Mothers and Children of Salinas, CHAMACOS) with women and their children from farm worker populations.

- a. The Agency believes that all three studies provide valuable information on the effects in children of high exposures to pesticides, particularly OPs. For purposes of evaluating human health effects of chlorpyrifos, the Columbia University studies provide more robust information for evaluating the human health effects of chlorpyrifos because it measured chlorpyrifos rather than a metabolite in both environmental (air) and biologic media (maternal and cord blood) and showed that chlorpyrifos was significantly associated with birth outcomes (low birth weight and length) and neurodevelopmental outcomes that were no longer present when the residential uses were cancelled (i.e., conducted a pre- and post-residential cancellation analysis). Although the results reported by the Mount Sinai group are informative with regard to evaluating the relevance of PON1 status in health outcomes, this study is limited because the neurodevelopmental outcomes were linked to non-specific OP maternal urinary metabolites (DAP, DEP and DMP), rather than the chlorpyrifos-

¹For information on the Mode of Action Framework, see U.S. EPA ,1999, 2005;, Sonich-Mullin et al., 2001; Meek et al., 2003 ; Seed et al 2005 and Boobis, et al, 2006

specific metabolite TCP. The exposure of the CHAMACOS to many OPs reduces its usefulness in the chlorpyrifos risk assessment because the outcomes can not be specifically linked to chlorpyrifos exposure.

Please comment on the Agency's preliminary conclusions on each of the three cohorts regarding the degree to which the data informs the chlorpyrifos human health risk assessment. Please also comment on the scientific support for or against these preliminary conclusions.

- b. Data from Whyatt et al. (2003) show that 100% of air samples detected three AChE inhibiting pesticides (chlorpyrifos, diazinon and propoxur). Similarly, all three pesticides were found in 48-49% of umbilical cord samples at lower levels than chlorpyrifos. The investigators reported that chlorpyrifos was significantly associated with decreased birth weight and length, even after statistically controlling for these two OPs; a similar analysis has not been conducted for the neurodevelopmental outcomes. The Agency can not rule out that exposures to all three AChE-inhibiting pesticides in combination resulted in the neurodevelopmental health outcomes reported in the studies. However, this possibility does not rule out the potential role of chlorpyrifos in contributing to the reported health outcomes, particularly given the reported findings pre- and post-voluntary cancellation. In balance, given, that 1) measured levels of chlorpyrifos have been statistically associated with multiple birth and neurodevelopmental outcomes; 2) these associations are correlated in time prior to the cancellation of indoor uses of chlorpyrifos when exposures were much greater (and thereby show some degree of dose-response); and 3) there are animal data which supports neurobehavioral effects resulting from gestational exposure, the Agency has preliminarily concluded that chlorpyrifos likely played a role in these outcomes. Please comment on the Agency's preliminary conclusion and the scientific support for or against this conclusion.

5. Human Information Available for Risk Assessment:

Ultimately, the Agency will assess potential risk to humans from current exposures to chlorpyrifos. Thus, data in humans provide a valuable tool for considering human outcomes, metabolism, and dose response. Under this context, the Agency has considered the extent to which data in the epidemiology studies and the deliberate dosing studies can be used quantitatively in the chlorpyrifos risk assessment (See Issue Paper, Section 2.3).

- a. The epidemiology studies provide important information about potential human outcomes related to the potential effects of OPs on the developing brain. Moreover, they provide data which supports the human relevance of outcomes observed in animal studies. However, at this time, they have not been proposed for use in directly deriving the PoDs or UFs.

Each of the cohorts has been exposed to chlorpyrifos to some extent. However, in addition to chlorpyrifos, each cohort has been exposed to multiple pesticides, including other OPs. Determining the quantitative contribution of chlorpyrifos to the reported outcomes separate from the

other OPs is challenging. This determination would be highly uncertain given the current state of the science on the dose response relationships for mechanisms (other than AChE inhibition) leading to effects on the developing brain. As the science evolves in this area, the understanding of TK and TD factors which impact toxicity to the developing brain will improve as will the dose response information in animals. With this improved understanding, the Agency may, in the future, be able to better characterize the linkage between blood or urinary levels of chlorpyrifos and/or its metabolites with health outcomes. At this time, the Agency has used the reported levels of chlorpyrifos and its metabolites simply as markers of exposure without an attempt to estimate actual exposure or dose to the tissues. The Agency is aware of an effort by Drs. Dale Hattis and Robin Whyatt to develop a physiologically-based pharmacokinetic (PBPK) model which includes a placental compartment for assessing tissue dosimetry to the fetus and which accounts for intra-species TK variability. The investigators then plan to use that model to estimate a human PoD from the blood biomarker reported in Whyatt et al (2003). This work has only just begun and will likely take several years. Please comment on the Agency's conclusion to use the epidemiological studies primarily for purposes of hazard characterization and not for dose response assessment. Please also comment on the scientific support for or against this preliminary conclusion.

- b. Three deliberate dosing studies in adult (non-pregnant) humans are available which measure AChE activity and urinary levels of chlorpyrifos and/or its metabolites (See Appendix G). The Agency has determined that the deliberate dosing studies in adults are not appropriate for use in PoD or UF derivation in the current proposal. This determination is based on several factors.
- There are experimental laboratory animal data that indicate that the susceptibility of the developing nervous system to chlorpyrifos may be related to cholinergic and noncholinergic mechanisms. Findings in epidemiology studies in children support the animal studies. The human studies do not include the potentially susceptible populations being evaluated in the current effort, namely pregnant woman and children and thus do not consider toxicity endpoints other than AChE inhibition (and related clinical signs).
 - Nolan et al (1982) and Griffin et al (1999) only include a single dose group for a particular route (a study design issue previously criticized by the Human Studies Review Board (HSRB) with respect to other human studies).
 - Griffin et al (1999) report no changes in AChE inhibition and in Kisicki et al (1999) changes were only seen in one person leading to the characterization of these studies as NOAEL only studies (a type of study not supported by the HSRB for use in risk assessment since absence of an effect (LOAEL) raises questions

about whether the investigators were able to detect an effect or that it was possible given the study design).

However, the Agency has determined that the human studies do provide valuable information on correlating oral or dermal exposure with levels of chlorpyrifos and/or TCP in blood and urine. In addition, these studies also provide information on time course of absorption, metabolism, and excretion. Kisicki et al (1999) also includes PON1 genotype information. Due to the availability of quality TK information, these studies have been used in the past by the Agency to aid in interpreting biomonitoring data. Specifically, results from Nolan et al (1982) have been used previously by the Agency in estimating (i.e., back-calculating) chlorpyrifos exposure based on urinary levels of TCP. Nolan et al (1982) has also been used to derive a dermal absorption factor in humans.

If the Agency wishes to continue this use of the human studies to assist in characterizing and interpreting epidemiology and biomonitoring data, the studies will be brought to the Agency's HSRB for review of their scientific and ethical conduct. To assist the Agency in preparing for this review by the HSRB, please comment on the clarity and completeness of the Agency's scientific analysis of the human studies. In particular, please focus on whether the Agency has identified the key scientific issues and whether other information or studies are available that should be considered in formulating the Agency's preliminary conclusion to use these studies for purposes of characterizing and interpreting the epidemiology and biomonitoring data and not for deriving PoDs or UFs.

6. Points of Departure (PoD) for Risk Assessment (Issue Paper, Section 2.5):

- a. Based on the results of the extensive literature review, the Agency has proposed updated PoDs derived from the laboratory animal studies for extrapolating human risk. The Agency has posed three options for the PoDs for chlorpyrifos in the issue paper. When the Agency derives PoDs for assessing the risk from exposures to pesticides, it needs to consider all relevant routes (oral, dermal, inhalation), durations (ranging from acute to chronic), and all exposed populations (including adult, pregnant women of child bearing age and children).

The first option proposes to use the PoDs which were based on rat RBC and plasma ChE inhibition in the 2000 risk assessment for acute oral exposures and blood AChE for chronic oral exposures. The 2000 risk assessment included a weight of the evidence discussion primarily on adult rat and dog AChE guideline studies and adult data from Zheng et al (2000). This option would involve application of the no-observed-adverse-effect-levels (NOAELS) for blood AChE inhibition from route specific studies (oral, dermal, inhalation) in rats or dogs to all populations. The acute oral PoD would be 0.5 mg/kg/day and the repeated oral PoD would be 0.03 mg/kg/day. The dermal and inhalation NOAELS would be 5 and 0.1 mg/kg/day, respectively.

The second option proposes to use a value of 0.1 mg/kg/day derived from multiple studies and lifestages. This proposed PoD would be applied to all populations and all durations. The proposed value of 0.1 mg/kg/day was derived using benchmark dose estimates from brain and RBC AChE in young pups (PND1 and 12) following acute dosing and from peripheral (heart) AChE following repeated gestational studies with dams. As such, multiple lifestages are considered in the proposed PoD: pregnant dams, PND1 pups, and PND12 pups. Furthermore, the proposed value is 3 to 10 fold lower than causing effects on the developing brain reported in other laboratory animal studies and thus is expected to be protective for those effects.

The third option is a blend of options 1 and 2. This option proposes to use a value of 0.1 mg/kg derived from the acute post-natal rat brain and RBC AChE data for all populations but only for the acute duration for oral exposures. Exposure scenarios involving repeated exposures would use the PoD of 0.03 mg/kg/day from the 2000 risk assessment for oral exposures. The value of 0.03 mg/kg/day was derived for the 2000 risk assessment based on blood AChE from multiple adult rat and dog studies. The lower PoD for repeated exposures in option 3 is proposed to account for potential accumulation of toxicity which can occur following repeating doses of chlorpyrifos in adult studies.

Please comment on the strengths and weaknesses of each proposed approach. Is there another option or a variation of one of the three options that the Agency should consider?

- b. Route specific data are preferred because such data accounts for potential differences in absorption, distribution, or metabolism. In the case of chlorpyrifos, dermal and inhalation studies are available which identify NOAELs for these routes in adult rats. With respect to inhalation exposure, there are two nose only studies with vapor chlorpyrifos which provides a NOAEL of 287 ug/m³ or 20 ppb (0.1 mg/kg/day). Similarly, there are two dermal studies which together provide a dermal NOAEL in adult rats of 5 mg/kg/day. These studies do not include pregnant dams, fetuses or post-natal pups and therefore do not consider potentially susceptible populations. In the absence of data in these groups, the Agency will continue to use route specific studies, as appropriate. An alternative for dermal exposure is to use an oral PoD derived from susceptible populations (as discussed above) with a dermal absorption factor. Specifically, the Agency could use a dermal absorption of 3% from human subjects (Nolan et al, 1982).

Please comment on the strengths and weaknesses associated with use of the adult dermal and inhalation studies in the chlorpyrifos human health risk assessment. The Agency also requests the SAP to provide suggestions on potential toxicity and/or toxicokinetic studies (if any) in pregnant dams, fetuses, and/or post-natal pups which could be conducted to better inform the dermal and inhalation risk assessments.

7. Extrapolation/Uncertainty Factors (Issue Paper, Section 2.6, Appendix E):

In risk assessment, once PoDs are selected, extrapolation from animals to humans (inter-species) and within human variability is performed. Historically, the Agency has used default 10-fold factors to account for inter- and intra-species extrapolation. More recently, emphasis on the derivation of extrapolation factors from TK and toxicodynamic (TD) data instead of default factors has increased. With the intent of improving the scientific basis for the chlorpyrifos risk assessment, in this issue paper the Agency has considered the availability of current PBPK models, TK, and TD data for chlorpyrifos to use in animal to human and within human extrapolations. Overall, the available PBPK models, although well-developed and supported for non-pregnant adults, do not include calculations for dose during pregnancy (e.g., no placental compartment) and for young children less than 5 years old and thus can not be used in a quantitative manner for this effort. As such, the Agency has used the 2005 IPCS guidance on Chemical-Specific Adjustment Factors to evaluate available TK and TD data in animals and humans and to determine the extent to which such data support data-derived or chemical-specific extrapolation factors.

- a. Inter-species and Intra-species Toxicodynamic Extrapolation: The Agency has preliminarily concluded that with regard to TD characteristics, due to the likelihood of several possible modes of action of neurodevelopmental toxicity of chlorpyrifos and lack of identifiable and quantifiable key events for MOAs not related to AChE inhibition, the Agency can not confidently refine the TD component of the animal to human and within human variability factors (i.e., UF_{AD} and UF_{HD}). Please comment on the scientific support for or against the use of default factors of inter- and intra-species TD extrapolation.
- b. Inter-species and Intra-species Toxicokinetic Extrapolation: As discussed in detail in Appendix E, the Agency evaluated the extent to which data on carboxylesterases, P450s, and paraoxonase (PON1, or A-esterase) support development of DDEFs of inter- and intra- TK extrapolation (i.e., UF_{AK} and UF_{HK}). Based on differences in rat and humans with regard to maturation of metabolic processes, there are uncertainties surrounding appropriate metabolic parameters for animal to human extrapolation of juveniles. This uncertainty in combination with limited data precludes the development of a DDEF for inter-species TK extrapolation (i.e., UF_{AK}). Thus, the Agency proposes to apply the default 3X for UF_{AK} . Data on carboxylesterases are not sufficiently robust for intra-species TK extrapolation (i.e., UF_{HK}). Data on P450s are complicated by multiple enzymes each with its own maturation profile. Others have evaluated the P450 literature for use in derivation of child specific UFs with poor success (Ginsberg et al, 2004a). Please comment on the scientific support for or against the use of default factors of inter-species TK extrapolation. Please further comment on the Agency's preliminary conclusions on the utility of carboxylesterase and P450 data to refine the intra-species extrapolation factor.
- c. Intra-species Toxicokinetic Extrapolation (Within Human Variability): There are extensive data on PON1 from many populations worldwide and

for different age groups. Using these data, the Agency has performed a preliminary analysis for within TK human variability for PON1 activity. These calculations were done in a manner consistent with the IPSC CSAF guidance. The calculations show that the largest variability in PON1 activity is between newborns and their mothers and is thus likely related to age-dependant maturation.

There is some debate as to the extent to which PON1 status plays a role in toxicity at low environmental concentrations. Some have suggested that significant amount of OP must be present in the blood or brain for PON1 activity to affect toxicity based on generally low affinity (K_m , 0.1-10 mM). Others believe that PON1 status is a key determinant in chlorpyrifos toxicity. The Agency has evaluated the available *in vivo* and *in vitro* data from animals and humans relevant to this issue. The Agency has preliminarily concluded that the available data suggest that PON1 status can not be ruled out as a determinant in chlorpyrifos toxicity, particularly for the fetus or young child. However, uncertainties remain, particularly regarding the degree to which other metabolic pathways modulate potential deficits in detoxification capacity. Please comment on the science which does and does not support PON1 status as a determinant in toxicity at low environmental concentrations.

- d. The Agency's PON1 calculations have focused on the PON-152Q/R polymorphism based largely on the extensive data available. No calculations have so far been performed on other genotypes. Please comment on scientific support for or against focusing on the PON-152Q/R polymorphism.
- e. The Agency's calculations conducted on PON1 activity follow the 2005 IPSC CSAF guidance for developing intra-species extrapolation factors for TK. The preliminary analysis suggests that within human variability is larger than the default 3X when newborns and adults are considered together. Specifically a value of 12X has been calculated for chlorpyrifos oxonase activity. The Agency has proposed two options for these calculations: 1) use the value calculated for chlorpyrifos-oxonase derived from newborn and mother values in Holland et al (2006) and 2) use the default factor of 3X. Please comment on the strengths and weaknesses of each proposed approach. Please include comments on the statistical approach used in the analysis as a component of your response.