## Part A

# Abandonment of the 10X Is Legally and Scientifically Indefensible

Section 408 of the FQPA requires that "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." The law further states that a different margin of safety may be used "only when, on the basis of reliable data" the alternative will be safe for infants and children. (FFDCA Sect. 408 (b)(2)(C)) EPA drops the tenfold margin of safety for chlorpyrifos, using a 3X factor instead. The agency's rationale for doing so is flawed.

### A) Chlorpyrifos Toxicology Data Remain Incomplete

First, EPA incorrectly interprets the 10X provision of the FQPA. The 10X provision was written into FQPA due to the findings of the 1993 National Research Council report, *Pesticides in the Diets of Infants and Children*.[1] In short, the NRC found that the differences in metabolism in children, as well as their immature protective mechanisms and the inherent vulnerability of rapidly developing organs meant that children had greater *potential* susceptibility to toxic exposures than did adults. In addition, the NRC concluded that EPA's existing testing requirements and protocols (essentially unchanged today) were inadequate for providing a reasonable certainty of no harm to infants and children. The NRC exact words were:

> "The committee reviewed current EPA requirements for toxicity testing by pesticide manufacturers…In general, the committee found that current and past studies conducted by pesticide manufacturers are designed primarily to assess toxicity in sexually mature animals. Only a minority of testing protocols have supported extrapolation to infant and adolescent animals. Current testing protocols do not, for the most part, adequately address the toxicity and metabolism of pesticides in neonates and adolescent animals or the effects of exposure during early developmental stages and their sequelae later in life."[2]

In a 1998 study, *Putting Children First: Making Pesticide Levels in Food Safer for Children*, NRDC identified specific kinds of toxicity to developing animals not fully assessed by the tests currently required by EPA as part of its core battery for registering new pesticides.[3] (A copy of the report is attached to these comments.) For example, EPA's core tests:

- Fail to assess all food-use pesticides for neurotoxicity.
- Fail to assess even neurotoxic pesticides (let alone other food-use pesticides) for their toxicity to the developing brain and nervous system.
- Fail to assess pesticides for toxic effects on the function of the developing or adult immune system. (Subchronic studies were changed recently to include changed weighing and pathological exam of the spleen and thymus, but this cannot substitute for functional testing.)
- Fail to include any assessment for potential to disrupt the endocrine system.
- Fail, as a whole, to include any assessment of toxic effects on the function of an immature animal's organ systems after birth, apart from reproductive organs.

Congress wrote an additional margin of safety into the FQPA specifically to account for these inadequacies of EPA's existing testing requirements for pesticides generally, and to account for children's likely higher exposures, discussed later. However, Congress included additional

protection for children in the law by making any departure from this extra margin of safety for a particular pesticide contingent on the existence of complete exposure data for infants and children as well.

Though the law did not spell out exactly what constitutes the "complete" data on toxicity and exposure needed before EPA can change the presumptive additional 10X margin of safety in assessing pesticide risks, it is clear that completeness of the data must be determined relative to the law's explicit health standard. In other words, completeness of the data (for the purposes of changing the additional 10X) must be judged on whether an alternative margin of safety could still provide a "reasonable certainty" of no harm to infants and children.

***EPA Core Toxicology Requirements Are Incomplete With Respect to Children's Health.*** Instead of judging the "completeness of the data" relative to children's health, EPA's policy has been to judge the completeness of toxicity data for particular pesticides — like chlorpyrifos — largely with respect to its little-changed, inadequate core testing requirements. For chlorpyrifos, the agency asserts:

> "There are no data gaps for the assessment of the effects of chlorpyrifos following *in utero* and/or postnatal exposure. In addition to the core studies submitted to the Agency, a Developmental Neurotoxicity Study has been submitted and reviewed for chlorpyrifos."[4]

To be fair, there are more toxicology data for chlorpyrifos than for most other pesticides registered on food. However, EPA still lacks specific toxicological studies that are quite relevant to the health of infants and children. For example, FQPA requires EPA to have begun screening all pesticides — including chlorpyrifos — for effects on the endocrine system by August 1999, yet this testing has not been performed for chlorpyrifos. The endocrine disrupting potential of chlorpyrifos, therefore, has not been adequately assessed. Yet there is limited evidence in adult ewes that chlorpyrifos administration may affect levels of the hormones, thyroxine and cortisol.[5]

Neither chlorpyrifos, nor virtually any other pesticide, has been tested for immunotoxicity using EPA's validated protocol. Immunotoxicity may involve immune system suppression or hypersensitization. Miller and Metzel recently reported 37 cases where overexposure to organophosphates led to chemical sensitivity, half of which reportedly involved chlorpyrifos.[6] From 1984 to 1990 chlorpyrifos was the leading pesticide named among calls to the National Pesticides Telecommunications Network involving pesticide sensitivity problems, accounting for 15% of the 1,022 total calls.[7] Asthma often involves a hypersensitivity or allergic response of the lower airways to airborne irritants. Dr. Sheldon Wagner, of Oregon State University, recently described a case where a single house treatment with chlorpyrifos apparently triggered the new onset and persistence of asthma in a 22 month-old child with no previous history of allergy or asthma.[8]

***Complete Data on Chlorpyrifos Must Include Its Metabolites, Contaminants, Inerts and Possible Stereoisomers of these Compounds.*** Finally, EPA's chlorpyrifos risk assessment fails to adequately consider chlorpyrifos metabolites, contaminants, inert ingredients, and possible stereoisomers, or metabolites that are stereoisomers. Children exposed to Dursban, for example, are not exposed to a single product but rather to a complex mixture which includes chlorpyrifos, its inert ingredients and impurities, including sulfotepp — another

organophosphate;[9] and trichloropyridinol (TCP), the feed stock for producing chlorpyrifos but also a contaminant and the chief metabolite of chlorpyrifos, as well as of chlorpyrifos methyl.[10] Chlorpyrifos oxon is another short-lived but toxicologically active metabolite of chlorpyrifos.

EPA has determined either implicitly or explicitly that these compounds are not of toxicological concern to a chlorpyrifos risk assessment. We assert that FQPA directs EPA to conduct the chlorpyrifos risk assessment in a manner which accounts for children's actual exposures, including metabolites, contaminants, inerts and/or other ingredients of chlorpyrifos. Because EPA has failed to do this, it constitutes a toxicological data gap.

***Inadequacy of the Chlorpyrifos DNT Study.*** EPA presents the Dow-submitted DNT study as supportive of the agency's 10X determination for the chemical. However, the agency's toxicology chapter describes the DNT study as "core grade: not acceptable guideline"[11] (presumably due to the fact that maternal adverse effects occurred at all doses administered). This is notable, but also confusing since later in the risk assessment EPA labels the same study as "acceptable guideline."[12] However, as part of its review of the DNT study EPA also states that "due to inadequate presentation of the statistical data analysis, it was not possible to determine the definitive developmental neurotoxicity NOAEL and LOAEL for the offspring."[13] NRDC questions whether even this new statistical analysis can make the study adequate. If the new analysis renders a NOAEL, or no-observed-adverse-effect level, the study cannot meet the safety standard of the FQPA because it is clear from the legislative history that Congress intended for EPA's regulatory decisions under FQPA to be based upon NOELs (no-observed-effects-levels) or LOELs (lowest-observed-effect-levels) and not NOAELs and LOAELs.[14] In some cases, the difference between a NOAEL and a NOEL could be tenfold or more.

***Summary.*** From the above discussion, it is clear there are many questions about the completeness of chlorpyrifos' toxicology dataset for providing a reasonable certainty of no harm to children. These include the failure of tests within EPA's core toxicology dataset to assess all endpoints of concern to children, including immunotoxicity and endocrine disruption; the agency's failure to consider children's exposures to all the metabolites, contaminants, inerts and perhaps stereoisomers that make up real world exposure to chlorpyrifos products; and the inadequacy of the Dow-submitted DNT study to meet FQPA and EPA guideline requirements. All of these are grounds for retaining the FQPA mandated additional 10X margin of safety to protect children.

## B) Chlorpyrifos Exposure Data Remain Incomplete

While the information and data presented in this risk assessment provide abundant cause for concern about children's current levels of exposure to chlorpyrifos, age-specific data are lacking to fully characterize and quantify these exposures across all routes. The FQPA clearly establishes this incompleteness of children's exposure data as grounds for retaining the full added 10X margin of safety to assure that children will remain protected while age-relevant exposure data are collected. EPA risk assessments currently lump together children age 1-6, and presume that calculations made using an average body weight for this group will protect all children. This ignores the enormous variation in size, eating patterns and behavior within this important age group. EPA needs better age-specific, actual, recent dietary consumption data for pregnant women and each major age group of infants and children (e.g. 0-6 months, 6-12 months, one–year age groupings for ages 1-6, and data for pre-adolescent and

adolescent children, another critical period of vulnerability to toxic injury. Each group may have distinct consumption and behavior patterns masked by aggregation of these subsets into larger groups. Toxicologists are increasingly recognizing that the old adage "the dose makes the poison" may not apply to developing organisms. Instead, for fetuses, infants, children and adolescents, it appears that the *timing* of the exposure makes the poison.

Specific examples of exposure data gaps are presented below:

***Biomonitoring Data for Children.*** EPA reports preliminary data from the recent Minnesota Children's Exposure Study finding measurable levels of TCP in the urine of 92% of the 89 children tested; mean levels of urine TCP in these children were nearly four times higher than the mean value for nearly 1,000 adults tested as part of the NHANES III.[15] TCP is a metabolite common to both chlorpyrifos and chlorpyrifos methyl. While the urine biomonitoring results indicate widespread exposure to one or both chemicals, more data must be collected to indicate the upper bound of the range of TCP values in the urine of children throughout the country. In the interim, retention of the additional 10X margin of safety for both chlorpyrifos methyl and chlorpyrifos will help ensure that children's exposure to TCP and its parent compounds is not increased.

***Dietary And Drinking Water Exposures to Children.*** EPA fails to include three significant sources of dietary exposure in the chlorpyrifos dietary risk assessment: dietary exposure to chlorpyrifos from consumption of contaminated fish, ingestion of contaminated well water due to termiticide use of the pesticide, and consumption of food known to contain chlorpyrifos residues but which lack of chlorpyrifos tolerance — including several foods highly consumed by children such as carrots, spinach, squash, and potatoes. These are described more fully in Part B.

***Residential and Other Non-Dietary Exposures To Children.***
EPA acknowledges the lack of chlorpyrifos-specific data for all but one of the nine scenarios for homeowner use of the chemical; instead the agency largely relies on assumptions contained its still-draft Residential Standard Operating Procedures (SOPs).[16] Using these assumptions, the risks from homeowner use of chlorpyrifos exceeded EPA's levels of concern under eight of the nine scenarios. See Part C.

EPA fails even to attempt to quantify chlorpyrifos exposure and risk under several other likely exposure scenarios, citing the lack of chemical use data or chemical-specific exposure data. These scenarios also are described in Part C. They include, for example, residents exposed to chlorpyrifos following the professional application of insecticidal dust products;[17] travelers exposed following label use of chlorpyrifos in vehicles (i.e., planes, trains, automobiles, buses, boats); and other labeled "residential" uses such as treatment of supermarkets, restaurants, and theaters.[18] Despite its failure to characterize these exposures, EPA's registers "concern" for them based on the other scenarios the agency does assess.

EPA's risk assessment also fails to assess residential exposures resulting from *agricultural* applications of chlorpyrifos, including exposures from pesticide drift as well as other "take home" exposures. Take home exposures occur when pesticides are exhaled from parents' lungs, or are tracked home from treated lawns or fields on pets, shoes or clothing. For farmworker children, and other sentinel populations who live in a pesticide–rich environment,

these "secondary" sources of exposure may account for the majority of the risk from chlorpyrifos, even where there have been no registered residential uses.

***"Take home" exposures to fetuses and newborns***

Take home exposures also include the exposures faced by the fetuses of female pesticide workers (discussed further below), and exposures in breast milk to nursing infants. Mothers who are working in the fields and are exposed to pesticides can accumulate chemical residues in their breast milk. In reviewing the submitted developmental neurotoxicity study for chlorpyrifos, Makris, *et al*, state that "Notably, milk concentrations of chlorpyrifos [in dams] on lactation day 1 and 5 were at lesat 10-fold greater than blood concentrations in all dose groups."[19] In addition to the active ingredient, some volatile organic solvents used as "inert" ingredients in pesticides have been detected in breast milk.[20] As discussed above, interaction between chlorpyrifos and "inert" ingredients in a wide variety of formulations remains a possibility, with potentially devastating effects for newborn and other nursing infants.

Under FQPA, known exposures to labeled uses, as well as other likely exposures of fetuses and children of pesticide workers such as from drift and take-home exposures, must at least be estimated. EPA's failure to incorporate these real-world exposures into its chlorpyrifos risk assessments will tend to understate that risk. If data are lacking to quantify such exposures, the FQPA allows for the use of an additional 10X margin of safety to assure that continued use of the chemical is consistent with a reasonable certainty of no harm to fetuses, infants and children until more precise data can be generated. Congress clearly intended this provision to apply to the fetuses of pregnant workers since it states that the additional 10X margin of safety shall be applied "to take into account potential *pre- and post-natal toxicity* and completeness of the data" (emphasis added)

***Harm to Fetuses Through Exposure of Pregnant Farmworkers***

In setting, modifying or revoking tolerances, the FQPA directs the Administrator to consider, *inter alia*, "available information concerning the effects of *in utero* exposure to pesticide chemicals."[21] EPA must retain the 10X in cases where this data is inadequate to protect fetuses. In explaining its method of implementing the tenfold safety factor to the March 1998 meeting of the Science Advisory Panel (SAP), however, the EPA expressly stated that it would not consider prenatal exposures to the unborn children of pregnant farmworker women because such exposures are "occupational" and hence not within the contemplation of the FQPA.[22] The statutory language which directs the EPA to consider the effects of "in utero" or "prenatal" exposures to pesticides makes no exception for occupational exposures. Nor could such an exception make sense since a fetus or unborn child cannot work.

Indeed, in an analogous context, the California Supreme Court recently held that a child who was injured in utero when his pregnant mother was exposed to carbon monoxide at work could not be prevented from filing suit in tort by the workers compensation bar which prohibits an employee from suing his or her employer.[23] The Court dismissed the notion that the unborn child could be deemed an "employee" as "wholly without merit." The Court also noted that every other court had reached the same conclusion (except one lower California court whose decision was now overruled). Since an unborn child cannot be an "employee," its pesticide exposure cannot be "occupational." Thus, any prenatal exposure to farm children (carried both by workers and by workers' family members) must be considered in applying the 10-fold safety factor and in determining whether a pesticide is safe for infants and children.

## Part A: Abandonment of the 10X

### C) Chlorpyrifos is a Developmental Neurotoxicant

Beyond its failure to meet the letter of the law in retaining the 10X for data gaps, EPA fails scientifically to acknowledge abundant evidence that chlorpyrifos is a developmental neurotoxicant — evidence which should preclude any change in the additional FQPA margin of safety. The human brain is by far the most sophisticated organ in all of nature, and its development is highly sensitive to toxic injury.

*In vitro* and *in vivo* animal studies of chlorpyrifos, studies of the chlorpyrifos metabolite, TCP, and case reports of chlorpyrifos-exposed children, all suggest that chlorpyrifos and/or TCP disrupts the normal development of the brain and nervous system. In other words, chlorpyrifos is a developmental neurotoxicant. When a chemical can be shown to exert toxicity on the developing brain in a manner that is unique to fetal or postnatal development — having no counterpart in the adult, this constitutes solid grounds for retaining the full additional tenfold margin of safety for the protection of children.

Further, even the most sophisticated developmental neuritoxicity studies in rodents can easily fail to identify the low levels of exposure that cause toxic effects in humans, even with an extra tenfold margin of safety. Calabrese and Baldwin found that, depending on the level of confidence desired in the results, variability in extrapolation, for example, from dogs or rats to humans could reasonably be expected to reach 65 to 100-fold.[24]

Developmental neurotoxicity appears to vary greatly between species. Historical experience with lead, methylmercury and PCBs illustrates the tragic consequences of relying solely on rodent testing. Studies with these compounds in adult rodents missed the human neurotoxic no effect level by a minimum of three orders of magnitude.[25] Even developmental neurotoxicity studies in rodents may not be sensitive enough to protect the developing brain. Rodent developmental neurotoxicity studies with PCBs produced NOAELs 1,000 to 10,000 times higher than the NOAEL for human in-utero exposure. Rodent developmental studies for methymercury produced NOAELs 100 times higher than the neurotoxic NOAEL in infants and children. Even if EPA used extremely sophisticated developmental neurotoxicity and learning protocols in rodents such as those used for some lead studies, researchers have found LOELs that could result in an RfD about 5 times less protective of children than needed, and even then only if they applied an additional 1,000-fold factor to the LOEL.[26] EPA has no such sophisticated studies for chlorpyrifos.

***Animal Studies in the Scientific Literature***. Abundant data show that chlorpyrifos is a developmental neurotoxicant. EPA acknowledges a wealth of studies suggesting that neonates exposed to oral chlorpyrifos may be more sensitive *vis a vis* cholinesterase inhibition and behavioral effects. These studies point to specific effects of chlorpyrifos on the developing brain of neonates.[27,28] These data alone are sufficient to preclude EPA from dropping the children's 10X margin of safety while still finding, with "reasonable certainty," that children will remain protected.

More specifically, Brimijoin and Koenigsberger cite evidence that chlorpyrifos may "be able to disturb *multiple* neurotransmitter pathways in the developing nervous system," not only directly through effects on cholinesterase inhibition but also through subsequent reduction in adenylyl cyclase expression and impairment signaling cascades involving G-protein.[29] Through these and other little-understood pathways, the authors postulate that "anticholinesterase pesticides

like chlorpyrifos might harm immature organisms by hindering the architectural development of their nervous systems."[30]

Other animal studies also support the hypothesis that chlorpyrifos, as well as other cholinesterase-inhibiting pesticides, can disrupt the finely-tuned process of brain development. When two week-old rats were treated with just 1 mg/kg of chlorpyrifos, they demonstrate a loss of neurons in the forebrain.[31] Similarly, day-old rats given 2 mg/kg chlorpyrifos subcutaneously showed depressed DNA synthesis throughout the brain.[32] Slotkin notes that DNA synthesis can be persistently inhibited with low doses of chlorpyrifos that reduced cholinesterase by only 20%, and that were a devoid of signs of overt or systemic toxicity.[33] EPA acknowledges in its risk assessment that "several studies in the literature indicate that chlorpyrifos affects the developing brain of neonates during cell division."[34]

Slotkin further points out that chlorpyrifos affects DNA synthesis initially not through cholinergic mediation, but through a noncholinergic effect.[35] Slotkin emphasizes that these noncholinergic mechanisms may play the critical role in chlorpyrifos' adverse effects on brain development: "Conversion of chlorpyrifos to its oxon metabolite and the consequent inhibition of cholinesterase may not be the essential factors in determining neurobehavioral teratology by this compound or potentially for other insecticides as well."[36] Thus, a risk assessment focused solely on cholinesterase inhibition may miss a significant source of potential harm, and therefore cannot provide a reasonable certainty of no harm to infants and children.

***Dow-submitted Study of Developmental Neurotoxicity.*** Unlike for most organophosphate insecticides, the chlorpyrifos registrant (DowAgroSciences) has submitted a developmental neurotoxicity (DNT) study to EPA, a study based upon the agency's validated DNT protocol. In addition, Dow submitted a companion study that determined plasma, RBC and brain cholinesterase levels in dams and offspring once during gestation and five times postnatally; further, the study looked at levels of chlorpyrifos, chlorpyrifos oxon and TCP in the blood of both dams and offspring, and in the milk of dams. None of these parameters are measured in a typical DNT study.

The chlorpyrifos DNT study indicated exposure-related effects on nervous system development including delayed physical development (delayed sexual maturation and incisor development), altered startle reflex, statistically significant decreases in brain weight when measure on post-natal day 11, and alterations in brain morphology that persisted from postnatal day 11 at least through postnatal day 62 and which were pervasive across several different brain regions.[37] Makris et al. note that decreased brain weight in the early postnatal period, but not later, may reflect an early reduction in the number of neurons that is then masked by the later addition of brain mass through other processes such as cell growth and myelination.[38]

Like the scientific literature, DowAgroScience's DNT study shows chlorpyrifos to be a developmental neurotoxicant. Moreover, EPA acknowledges "studies of increased susceptibility of young rats compared to adults reported in the scientific literature that can not be discounted."[39] Yet, ironically, EPA cites the positive DNT study itself as a reason for not retaining the additional FQPA tenfold margin of safety — an extra safety margin Congress explicitly prescribed "to account for potential pre- or postnatal toxicity." It is inconceivable that Congress intended for EPA to drop this additional safety buffer for children as soon as a

chemical's potential for disrupting development is confirmed, as soon as there is evidence at hand that an extra safety margin is in fact needed.

EPA gives as a primary reason for reducing the 10X safety factor the fact that there is a lack of "*quantitative* evidence of increased susceptibility in the developmental neurotoxicity study" (emphasis added.)[40] But this ignores the Scientific problem that developmental toxicity often cannot be compared *quantitatively* to toxicity in adults because the developmental endpoints are unique. By definition, developmental toxicity occurs during development. A developing brain is vulnerable to developmental neurotoxicity because of the incredibly intricate and tenuous sequence of events that must take place to produce a brain that performs to its potential. So how can one compare the possible effects of a developmental neurotoxin on a child with its effects on an adult whose brain is already mature? At a more detailed level, even if a chlorpyrifos DNT study and an adult neurotoxicity study were both to yield NOELs based on cholinesterase inhibition, these NOELs might not be quantitatively comparable, since the role of acetylcholine in the developing nervous system is probably unique, as Brimijoin and Koenigsberger and Slotkin have recently illustrated.

Further, while qualitative findings from the Dow DNT study confirm concern about early life exposure to chlorpyrifos, the DNT protocol itself probably is not a sensitive enough measure of the neurobehavioral endpoints of greatest relevance to children to draw *quantitative* conclusions from its results. On the one hand, according to EPA scientists the DNT protocol does include unique endpoints not examined in any other standard toxicity testing protocol.[41] On the other hand, EPA scientific advisors have determined that the protocol in its current form may be inadequate to appreciate in advance all neurobehavioral effects in children stemming from exposure to developmental neurotoxicants.[42] At the same time, the scientific literature clearly documents experience with several neurotoxic chemicals — most notably lead, methylmercury, PCBs, ethanol and some epilepsy drugs — showing that exposure can produce neurobehavioral effects in developing animals and children at levels that do not cause toxicity in adults.[43] Therefore, while a DNT study using this protocol may offer affirmative evidence of developmental neurotoxicity, negative findings cannot assure the absence of developmental neurotoxicity. Because the current DNT protocol may not be sensitive enough to appreciate the full spectrum of neurobehavioral effects of concern, positive findings from this study cannot necessarily be compared quantitatively to results from tests of adult toxicity.

Finally, EPA's insistence on quantitative evidence of increased susceptibility to chlorpyrifos from the DNT study demonstrates a basic lack of understanding of the FQPA. The law directs EPA to use an additional margin of safety under the presumption, made explicit in the 1993 NAS study, that infants and children already are more susceptible to injury, absent any chemical-specific data to the contrary.[44] Therefore, any lack of evidence noted by EPA must mean there was insufficient evidence to remove this additional presumptive margin of safety for protecting children.

## Part A: Abandonment of the 10X

***Temporary Cholinesterase Inhibition During Development May Have Irreversible Effects***
EPA states that, "Chlorpyrifos is a reversible inhibitor of cholinesterase (ChE)." But the agency fails to demonstrate this statement's veracity or relevance in the context of the developing brain and nervous system. As previously discussed, single doses of chlorpyrifos given to day-old rats and two week-old rats lead to the loss of neurons in the forebrain and depressed synthesis of DNA throughout the brain, respectively. And Slotkin has emphasized that DNA synthesis can be persistently inhibited by low doses of chlorpyrifos without any signs of overt toxicity.

These and other results support the observation by Brimijoin and Koenigsberger that anticholinesterase pesticides like chlorpyrifos may disrupt the architectural development of the brain and nervous systems, as well as the hypothesis that these disruptions might occur during very narrow developmental windows. Pharmacokinetic studies confirm that a single gavage dose of chlorpyrifos in adult rats at levels as low as 1 mg/kg will persistently inhibit plasma cholinesterase for at least twelve hours; at higher levels of exposure, brain cholinesterase also will be persistently inhibited for more than twelve hours.[45] Meanwhile, pharmacokinetic study of chlorpyrifos in *developing* animals (dosing from gestation day 6 through lactation day 10) indicates that significant plasma and RBC inhibition of cholinesterase continues at least 24 hours (and up to 12 days) after the last dose, even for the least exposed animals.[46]

The studies above show that a one to twelve day period of persistent cholinesterase inhibition in a neonatal animal may be sufficient to affect the development of the structure of the young brain. Thus, EPA's focus on the reversibility of cholinesterase inhibition is less relevant to children's health than is the duration of cholinesterase inhibition during brain development. Even temporary or "reversible" cholinesterase inhibition during the proper developmental window probably can lead to irreversible effects on the developing brain. The most recent science clearly demonstrates this to be true, even if the exact pathways involved have not yet been fully described.

***Studies of the Chlorpyrifos Metabolite, TCP.*** EPA has inappropriately excluded consideration of the chief chlorpyrifos metabolite, 3,5,6-Trichloro-2-Pyridinol's (TCP), from its risk assessment. Part E discusses this conclusion in depth.

In 1993, EPA decided that TCP was not of "toxicological concern" regarding tolerances for chlorpyrifos. This limited conclusion is outdated, especially in light of the 1993 NAS finding that children may be more vulnerable than adults to the toxic effects of pesticides, and the 1996 signing of FQPA into law. EPA must revisit it. By relying on its 1993 policy decision, EPA ignores the more recent scientific findings that are of utmost relevance to the safety of infants and children, and therefore relevant for making decisions about chlorpyrifos under the FQPA.

Mounting evidence suggests that TCP may be teratogenic, and a developmental neurotoxicant. While no one piece of evidence is conclusive, the body of evidence as a whole demands consideration in this chlorpyrifos risk assessment. These pieces are described in more detail in Part E, but include the following:

- A DowElanco Material Safety Data Sheet (MSDS) for TCP, dated August 2, 1991, which lists under the heading of Health Hazard Data: "Teratology (Birth Defects): Has been reported to cause birth defects in laboratory animals at doses nontoxic to the mother." The MSDS is based on an unpublished 1987 DowElanco study of TCP's developmental toxicity

in rabbits,[47] a study for which EPA's review later determined there to be an "increased # of fetuses and litters with hydrocephaly or hydrocephaly/dilated ventricles increased in 100 & 250 (mg/kg) groups."[48] Strangely, EPA's 1999 description of this same study makes no mention of these developmental effects.[49] Neither Dow nor EPA has sufficiently refuted or explained their earlier concerns about TCP's possible teratogenicity, or why those concerns are no longer discussed.

- There have been several case reports of children with birth defects following a history of *in utero* chlorpyrifos exposure.[50,51] In a 1999 study, Sherman describes the cases of eight children — 4 boys and 4 girls — and notes a concordant pattern of "unusual and uncommon" birth defects, including defects of the structure of the brain, eye and some endocrine mediated effects.[52] Sherman notes ventricular defects in 7 out of 8 cases, and hydrocephaly in 5 out of 8, which may be consistent with the DowElanco rabbit study. These cases are described in more detail in Part E.
- A report from EPA's Incident Data System concerning a child with severe birth defects, including brain damage and cerebral atrophy, allegedly following two uses of chlorpyrifos methyl in a residence for flea control while the child was *in utero*.[53] The brain damage reported for the case appears consistent with the hydrocephaly and severely dilated cerebral ventricles observed in the 1987 rabbit study described above. TCP is a common metabolite to both chlorpyrifos and chlorpyrifos methyl.

***Summary.*** EPA's chlorpyrifos risk assessment should utilize at least the additional 10X margin of safety. This is necessary because EPA has failed to rebut sufficiently the possible teratogenicity of TCP; because the DNT study for chlorpyrifos demonstrates developmental neurotoxicity, even though the protocol is acknowledged as being less than sensitive to the neurobehavioral endpoints of greatest concern to children — including learning and memory; and finally, because the scientific literature also suggests that chlorpyrifos is a developmental neurotoxicant through both cholinergic and noncholinergic pathways.

### D) Failure to Perform an Aggregate Exposure Assessment

EPA fails to perform an aggregate risk assessment for chlorpyrifos as part of the overall risk assessment. The agency states,

> "An aggregate risk estimate was not conducted for any duration (i.e., acute, chronic, short- or intermediate-term) because the total residential MOEs (dermal, inhalation, and inadvertent oral exposures) for all the residential post-application exposure scenarios, except mosquito use, alone exceed HED's level of concern." [54]

Aggregate exposure assessment is an explicit requirement for a safety determination (a reasonable certainty of no harm) under the FQPA. (FFDCA Sect. 408 (b)(2)(C)(ii)) Absent an aggregate exposure assessment, EPA certainly lacks the grounds for reducing the additional margin of safety to protect infants and children that is mandated by law.

In addition to the lack of an aggregate exposure assessment, this preliminary risk assessment appears to characterize risks inadequately, making it more difficult for Agency risk managers to make a tolerance determination with "reasonable certainty." Risk characterization should fully describe both the assumptions underlying the assessment, and the impact of those

assumptions on the final risk estimate. Moreover, estimates of risk must be communicated in the clearest possible way to the public.

### E) Use Of Studies That Prospectively Dose People With Pesticide Poisons

The EPA's November 1999 Joint SAB/SAP panel recommended against acceptance of any study involving the prospective dosing of humans with a neurotoxic pesticide, submitted solely for the purpose of helping to set a NOEL. Despite this recommendation, EPA has determined that two principal human studies for chlorpyrifos meeting this description could be considered "supplementary for risk assessment purposes," and could be compared with animal studies of chlorpyrifos to determine "the uncertainty factors and margins of exposure for dietary and occupational risk assessments, respectively."[55] More specifically, EPA uses these same human studies to help derive acute and chronic RfDs for chlorpyrifos.[56]

On page 5 of the HED assessment, it is clear that EPA also has used the human studies for making a 10X determination for chlorpyrifos. EPA notes that "Data from two human studies suggest that humans are similarly and possibly more sensitive than animals following acute and short-term oral exposure and acute dermal exposure based on plasma ChE inhibition and/or possible clinical signs."[57]

We question use of these studies on both moral and scientific grounds, especially for the purpose of relaxing safety margins for children. The ethical basis for prospectively dosing individuals with known nerve poisons, when they have no expectation of personal health benefit, is shaky. In the case of the 1972 Coulston et al. study submitted by Dow for chlorpyrifos, the study population was a small group of male New York prisoners. We remain unconvinced that this population could truly provide ethical and adequate informed consent.

On scientific grounds, (and while not conceding the ethical appropriateness of such tests), we question the ability of studies performed on healthy adult humans to provide data that are sufficiently relevant to fetuses and children to serve as grounds for abandoning one of two tenfold uncertainty factors traditionally used in risk assessment to fully account for interindividual and interspecies variability.

Additionally, to our knowledge neither EPA nor the companies performing these human pesticide studies have ever submitted an analysis of their statistical power. A human test using less than 20, or even less than ten people per dose group, likely will lack the statistical power to uncover the sort of subtle neurobehavioral effects that are most relevant to children exposed to the organophosphate insecticides — effects such as deficits in learning and memory. At the Joint SAB/SAP meeting, it was suggested by Dr. Needleman that a human study with adequate statistical power to set a NOAEL would have to include 2,5 participants.[58,59]

## Endnotes

[11] National Research Council (NRC), Pesticides in the Diets of Infants and Children, National Academy Press: Washington, D.C., 1993.

[2] Ibid., p. 4.

[3] Wallinga D, Putting Children First: Making Pesticide Levels in Food Safer for Children, Natural Resources Defense Council, April 1998.
[4] U.S. EPA Memorandum, Chlorpyrifos—Report of the FQPA Safety Factor Committee, Office of Prevention, Pesticides and Toxic Substances, April 5, 1999.
[5] Rawlings NC, Cook SJ, Waldbillig D, Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, lindane, triallate, trifluralin, 2,4-D, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes, *J Toxicol Environ Health,* 54:21-36, 1998.
[6] Miller C, Mitzel HC, Chemical sensitivity attributed to pesticide exposure versus remodeling*, Archives of Enviromental Health* 50:119-19, 1995, *as cited by* U.S. EPA Memorandum, Chlorpyrifos incident review update, Office of Prevention, Pesticides and Toxic Substances, September 27, 1999, p. 12.
[7] USEPA, September 27, 1999.
[8] Ibid., p. 11.
[9] Allender WJ, Keegan J, Determination of chlorpyrifos and its major breakdown products in technical formulation, *Bull Environ Contam Toxicol* 46: 313-319, 1991; Turle R and Levac, Sulfotepp in Diazinon and other organophosphorus pesticides, *Environ Contam Toxicol* 38:793-797, 1987.
[10] Sherman JD, Chlorpyrifos (Dursban) exposure and birth defects: report of 15 incidents, evaluation of 8 cases, theory of action, and medical and social aspects, *Eur J Oncol* vol 4(5) (in press), 1999.
[11] U.S. EPA Memorandum, Toxicology Chapter for Chlorpyrifos, Office of Prevention, Pesticides and Toxic Substances, September 28, 1999, Table 4, p.15.
[12] Ibid., Table 6, p. 19.
[13] Ibid., p. 24.
[14] Food Quality Protection Act of 1996 Report, 104th Congress, 2d Session, Rept. 104-669, part 2, p. 41.
[15] U.S. EPA Memorandum, HED Preliminary Risk Assessment for the Registration Eligibility (RED) Document, Office of Prevention, Pesticides and Toxic Substances, Washington, D.C., October 18, 1999, p. 4.
[16] U.S. EPA Memorandum, Occupational/Residential Handler and Postapplication Residential Risk Assessment, Office of Prevention, Pesticides and Toxic Substances, October 5, 1999, p. 6.
[17] U.S. EPA, October 18, p. 44
[18] U.S. EPA, October 5, 1999, p. 4.
[19] Makris S, Raffaele K, Sette W, Seed J, A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) draft, 11/12/98, p. 8.
[20] Wolff MS. Occupationally derived chemicals in breast milk. Am J Ind Med 1983; 4:259-81.
[21] 21 U.S.C. §346a(b)(2)(C)(i)(I–II).
[22] Presentation for the FIFRA Scientific Advisory Panel by Office of Pesticide Programs, Health Effects Division on FQPA Safety Factor for Infants and Children (March 24-25, 1998).
[23] *Synder v. Michael's Stores,Inc.,* 16 Cal.4th 991, 945 P.2d 781, 68 Cal.Rptr.2d 476 (1997).
[24] Calabrese EJ, Baldwin LA, A Toxicological Basis to Derive a Generic Interspecies Uncertainy Factor, *Environ Health Perspect*, 102(1), 1994.
[25] Rice DC et al, Lessons for Neurotoxicology from Selected Model Compounds: SGOMSEC Joint Report, *Environ Health Perspect* 104(2) (Suppl), 1996.
[26] Ibid.
[27] U.S. EPA, October 18, 1999, p. 6.
[28] U.S. EPA, September 28, 1999, p.6
[29] Brimijoin S, Koenigsberger C, Cholinesterases in Neural Development: New Findings and Toxicologic Implications, *Environ Health Perspect*, 107(Suppl 1), February 1999.
[30] Ibid.
[31] Campbell CG, Seidler FJ, Slotkin TA, Chlorpyrifos interferes with cell development in rat brain regions, *Brain Res Bull*, 43: 179-189, 1997
[32] Whitney KD, Seidler FJ, Slotkin TA, Developmental neurotoxicity of chlorpyrifos: cellular mechanisms, *Toxicol Appl Pharmacol*, 134: 53-62, 1994.

[33] Dam K, Seidler FJ, Slotkin TA, Developmental neurotoxicity of chlorpyrifos: delayed targeting of DNA synthesis after repeated administration, *Dev Brain Res* 108:39-45, 1998, *as cited by* Slotkin TA, Developmental Cholinotoxicants: Nicotine and Chlorpyrifos, *Environ Health Perspect* 107 (Suppl 1), February 1999.
[34] U.S. EPA Memorandum, September 28, 1999, p.6.
[35] Slotkin, 1999.
[36] Ibid.
[37] Makris *et al*, 11/12/98.
[38] Ibid.
[39] Ibid., p. 7
[40] U.S. EPA Memorandum, October 18, 1999, p. 7.
[41] Makris et al., 1998, p. 20.
[42] Report: FIFRA Scientific Advisory Panel Meeting, December 8, 1998, held at the Sheraton Crystal Hotel, Arlington, VA, SAP Report No. 99-01B, January 22, 1999, p. 18.
[43] Makris et al., 1998, p. 20.
[44] NRC 1993, p. 9.
[45] U.S. EPA Memorandum, Chlorpyrifos — Replacement of Human Study Used in Risk Assessments — Report of the Hazard Identification Assessment Review Committee, June 2, 1999, p. 8.
[46] U.S. EPA, September 28, 1999, p. 24.
[47] Hanley TR Jr., Zielke GJ, Lomax LG, 3,5,6-trichloro-2-pyridinol: Oral teratology study in Fischer 344 rats, Mammalian and Environmental Toxicology Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland Michigan, July 23, 1987a, 215 pp.
[48] U.S. EPA Memorandum, Chlorpyrifos Registration Standard —Revision to Exclude TCP Metabolite from Existing Tolerances, Alan C. Levy, Office of Pesticides and Toxic Substances, December 15, 1988.
[49] U.S. EPA, September 28, 1999, Table 4, p.15.
[50] Sherman JD, Chlorpyrifos (Dursban) - associated birth defects: a proposed syndrome, report of four cases, and discussion of the toxicology, *Intern J Occup Med Toxicol* 4(4): 417-431, 1995.
[51] Sherman JD, Dursban Revisited: Birth Defects, U.S. Environmental Protection Agency, and Centers for Disease Control (editorial), *Archives of Environmental Health*, v. 52(5): 332-333, 1997.
[52] Sherman, 1999.
[53] U.S. EPA Memorandum, Review of Chlorpyrifos Methyl Incident Reports, Memo from Jerome Blondell, Ph.D., April 15, 1999.
[54] Ibid., p. 11.
[55] U.S. EPA, June 2, 1999.
[56] Ibid., pp 9-12.
[57] USEPA Memorandum, October 18, 1999, p. 5.
[58] U.S. EPA, Joint Meeting of the SAB/SAP,
[59] Risk Policy Report, EPA Science Advisors Support Use of Human Studies, With Restrictions, Inside Washington Publishers, December 17, 1999.