NRDC
THE EARTH'S BEST DEFENSE

NATURAL RESOURCES DEFENSE COUNCIL

April 29, 2002

Public Information and Records Integrity Branch
Information Resources and Services Division (7502C)
Office of Pesticide Programs
Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave., NW
Washington, DC 20460
Docket Number: OPP-00759

RE: Draft Science Policy Document, "Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity," OPP-00759.

Dear Sir or Madam:

We submit the following comments on behalf of the Natural Resources Defense Council (NRDC), World Wildlife Fund (WWF), Physicians for Social Responsibility (PSR), Institute for Environment and Agriculture (IEA), Institute for Agriculture and Trade Policy (IATP), and Consumers Union (CU). The Natural Resources Defense Council's purpose is to safeguard the Earth: its people, its plants and animals and the natural systems on which all life depends. NRDC uses law, science, and the support of more than 500,000 members nationwide to protect the planet's wildlife and wild places and to ensure a safe and healthy environment for all living things. NRDC has no direct or indirect financial or fiduciary interest in the manufacture or sale of pesticides.

I. INTRODUCTION AND SUMMARY OF COMMENTS

A. Summary of Application of Uncertainty Factors.

The standard uncertainty factors comprise a combined 100-fold default factor, which OPP believes should be applied in a cumulative risk assessment routinely to account for uncertainty in extrapolating from experimental animal data to estimate potential human risk among a diverse American population (Draft Policy at 7). These UF's are as follows:

- Intraspecies differences (between humans), UF_H
- Interspecies differences (between animals and humans), UF_A.

The draft policy document states that traditional uncertainty factors must be applied to the cumulative risk assessment to adjust for data limitations or deficiencies in the toxicity database that apply to the group of chemicals as a whole (Draft Policy at 10). These UF's are as follows:

- Subchronic data in lieu of chronic data, UF_S
- LOAEL in lieu of NOAEL, UF_L
- Absence of key toxicological data (database deficiencies), UF_{Db}

- Modifying factors not addresses by the other factors, MF

All the above standard and traditional UF's are used to derive the reference dose, RfD (NOAEL/UF standard x UF traditional = RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (Barnes and Dourson,1988).

The FQPA safety factor takes into consideration special susceptibility unique to the FQPA: "potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." (FFDCA § 408(b)(2)(C)). This is comprised of consideration of the completeness of the toxicity database, the potential for pre- and post-natal toxicity to infants and children, and the completeness of the exposure database. The population adjusted dose (PAD) is derived from dividing the RfD by the FQFA safety factor (RfD/FQPA factor = PAD).

B. Summary of Our Concerns.

A recent report by the World Health Organization (WHO) states that, "up to 40% of the global burden of disease attributable to environmental factors is estimated to fall on children under the age of 5 years. As developing organisms, children are particularly vulnerable to the impact of environmental pollution"[1]. The report states that this is so for a variety of reasons, including the following:

- early exposure has long-term consequences;
- children have a unique susceptibility to specific chemicals, and are exposed to substances in their immediate environment (such as soil and toys), particularly through their practice of picking things up and putting them into their mouths; and
- in proportion to their body weight, children breathe, drink and eat more than adults, with a consequently higher uptake of potentially toxic substances.[2]

While the unique vulnerability of fetuses, infants, and children is recognized by scientists, public health professionals, the World Health Organization, and the US EPA, it is not adequately addressed in this guidance policy. EPA's draft science policy document addressing application of the FQPA safety factor in cumulative risk assessments (hereinafter "Draft Policy"), does not provide adequate guidance for implementation and is internally inconsistent and nebulous throughout. As a legal matter, the Draft Policy misinterprets and misapplies the requirements of the FQPA. A number of scientific concerns are also evident. Primarily, the Draft Policy does not adequately provide guidance on:

- incorporation of studies from the published (open) literature
- consideration of studies submitted by registrants under FIFRA 6(a)(2)
- determination of relative potency factors based on data from immature animals, in addition to adult animals
- determination of potential for pre- and postnatal toxicity for the cumulative assessment group (CAG), based on developmental toxicity of individual CAG members
- consideration of all toxic endpoints, including those not considered for the relative potency determination

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[1] World Health Organization, "WHO Regional Office for Europe and European Environment Agency Present Children's Health And Environment: A Review of Evidence," April, 2002 (available at http://org.eea.eu.int/documents/newsreleases/our_childrens_health-en).

[2] *Id.*

- consideration to toxicity of degradates and metabolites
- consideration of all possible routes of exposure, including:
  - violative residues
  - public health uses
  - non-agriculture sources in drinking water
  - residues on food from home gardens and farmers markets
- consideration of seasonal peak exposures, maximum allowable use rates, and seasonal peak eating patterns
- consideration of farm and rural children as a high-exposure group
- consideration of uncertainty within the cumulative risk assessment

All the above points are discussed in detail in these comments.

II. STATUTORY REQUIREMENTS

As discussed below, implementation of EPA's draft 10X CRA policy would violate the FQPA.

A. The 10X FQPA Safety Factor.

The FQPA requires EPA to give special consideration to the health of infants and children in regulating pesticides, and EPA must "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue." (FFDCA § 408(b)(2)(C)(ii)(I)). In assessing the risks of pesticide exposure of infants and children, EPA must evaluate "available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity." (FFDCA § 346a(b)(2)(C)(i)(III)). As EPA acknowledges in its draft 10X CRA policy, FFDCA paragraph 408(b)(2)(C) "mandates that, in making the reasonable certainty of no harm finding, EPA apply an additional tenfold margin of safety to take into account potential pre- and postnatal toxicity and completeness of the toxicity and exposure databases." (Draft Policy at 2). EPA can use a different margin of safety "only if, on the basis of reliable data, such margin will be safe for infants and children." (FFDCA § 408(b)(2)(C)).

B. The Draft 10X CRA Policy Improperly Combines Several Distinct Safety Factors into the Definition of the FQPA Safety Factor.

Throughout the draft 10X CRA policy, EPA inappropriately attempts to conflate a number of safety factors that should be applied separately. The plain text of the FQPA – as well as the legislative history – makes clear that the FQPA safety factor is "an *additional* tenfold margin of safety." (FFDCA § 408(b)(2)(C)(i) (emphasis added)). Yet the EPA states that "there is a large degree of overlap between the FQPA safety factor and traditional Agency practice as to the use of uncertainty factors to account for incomplete characterization of a chemical's toxicity." (Draft Policy at 2). This unsupported proposition is contrary to the statute's mandate of an "additional" 10X safety factor. As the legislative history clarifies: "[w]hen data relating to infants and children are incomplete, and also to account for potential pre- and post-natal toxicity, the Administrator is to apply, under new Section 408(b)(2)(C), an *additional* tenfold margin of safety for infants and children." (H.R. Rep. No. 104-669, Pt. 2, at 43 (July 23, 1996)). Yet EPA also claims that "[e]ncompassed with the FQPA safety factor are traditional uncertainty factors used to account for use of a Lowest-Observed-Adverse-Effect-Level (LOAEL) to estimate a No-Observed-Adverse-Effect-Level (NOAEL), use of a subchronic NOAEL to estimate a chronic

NOAEL and deficiencies in the toxicity database; and special FQPA safety factors used to address residual concerns for children's health risks." (Draft Policy at 4). This interpretation essentially strikes the FQPA 10X safety factor from the statute by folding it in to other safety factors that are already being applied.

In passing the FQPA in 1996, Congress overhauled the pesticide regulatory framework. In so doing, Congress had the opportunity to decide that traditional safety factors used by EPA adequately accounted for the unique risks to infants and children posed by pesticide exposure. Congress did not do so. Instead, acknowledging that infants and children were insufficiently protected under preexisting law, Congress mandated an additional tenfold safety factor to address these risks. EPA's attempt to weaken this provision by claiming that risks to infants and children are generally mitigated under "traditional Agency practice" flouts the plain language of the FQPA and Congress' clear intent.

C. The Draft 10X CRA Policy Improperly Reverses the Presumption of the FQPA and Declares that the Default 10X FQPA Safety Factor Can Be Overturned Even in the Absence of Reliable Data.

The statute requires that 10X must be applied unless there are "reliable data" to justify using a different safety factor. (FFDCA § 408(b)(2)(C)). Although paying lip service to this mandate in summarizing the statutory background (Draft Policy at 2), the EPA approach outlined in the rest of the draft policy document turns the statutory presumption on its head. For example, EPA says that the "absence of data that pertains to the common mechanism of toxicity does not automatically warrant the application of a database uncertainty or safety factor. When data deficiencies exist pertaining to the common mechanism of toxicity, *the risk assessor should consider the general, overall value of the missing study* to the cumulative risk assessment." (Draft Policy at 10 (emphasis added)). With respect to pre- and postnatal toxicity, EPA also states that, even if "there is evidence of a high degree of concern for the [cumulative assessment group] chemicals, the risk assessor should evaluate whether the standard approach of applying traditional uncertainty factors to the relative potency factors or the Point of Departure for the Index Chemical provides assurance that infants and children will be adequately protected." (Draft Policy at 11).

This policy forwarded by EPA is plainly contrary to the FQPA, which presumes that a tenfold safety factor be applied unless reliable data support deviation. EPA's approach essentially presumes the opposite – if there are no reliable and convincing data to affirmatively justify a tenfold safety factor, EPA will apply a lower factor or no safety factor at all. As EPA states: "It should be emphasized that OPP does not believe that the safety of infants and children requires retention of a special additional safety factor for a group of pesticides that share a common mechanism of toxicity whenever the common toxic effect involves some increased susceptibility of the young. Risk assessors should focus on the *degree of concern* and the residual uncertainties raised by increased susceptibility in evaluating what safety factor would be protective of infants and children." (Draft Policy at 11-12 (emphasis added); *see also id.* at 13 ("The risk assessor should evaluate the potential significance of any excluded exposure scenario.")). Congress concluded that prenatal and postnatal toxicity and incomplete data on exposure and toxicity provide the requisite "degree of concern" to require 10X, and codified that conclusion in the FQPA. EPA seeks to supplant that determination by authorizing individual risk assessors to substitute their own conclusions and override Congress.

These purported justifications for EPA's failure to apply the 10X children's safety factor violate the FQPA and EPA's own stated policy on proper application of the 10X safety factor. (Office of

Pesticide Programs, U.S. Environmental Protection Agency, *Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*, Feb. 28, 2002, at 11 ("Risk assessors . . . should presume that the default 10X safety factor applies and should only recommend a different factor, based on an individualized assessment, when reliable data show that such a different factor is safe for infants and children.")). Under EPA's proposed approach in the draft 10X CRA policy, the removal of the safety factor is based not upon the statutorily demanded "reliable data," but upon the risk assessor's subjective expectations—his or her intuition or professional judgment. For example, EPA claims that "the exposure database for a cumulative risk assessment should be considered adequate if the risk assessor is confident that the exposure estimate did not understate the potential exposure," apparently even in the presence of significant exposure data gaps. (Draft Policy at 12). EPA's proposed underprotective approach is untenable.

D. The Lack of Information on Exposure of Farm Children Is a Significant Exposure Data Gap.

EPA has failed to review data on the cumulative exposure of farm children. Farm children should be deemed to comprise an especially vulnerable population. The FQPA requires that EPA consider exposure not just to consumers as a whole, but also to "major identifiable subgroups of consumers." (FFDCA § 408(b)(2)(D)). In establishing tolerances, EPA must consider, among other relevant factors, "available information concerning the dietary consumption patterns of consumers (and major identifiable subgroups of consumers); . . . available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers);" and "available information concerning the variability of the sensitivities of major identifiable subgroups of consumers." (FFDCA §§ 408(b)(2)(D)(iv); (vi); (vii)). Farm children are a major identifiable subgroup under these statutory provisions, and their unique dietary consumption patterns, aggregate exposure levels, and sensitivities to exposure should be assessed by EPA in conducting cumulative risk assessments. (*See generally* NRDC et al., *Petition for a Directive that the Agency Designate Farm Children As a Major Identifiable Subgroup and Population at Special Risk to be Protected under the Food Quality Protection Act,* Oct. 22, 1998). Until EPA has done so, that significant exposure data gap prevents EPA from overturning the presumption of applying the 10X safety factor in conducting cumulative risk assessments.

E. The Draft 10X CRA Policy Is Self-Contradictory and Fails to Provide Useful Guidance to OPP Staff.

As an intended resource to "serve as a guide for OPP risk assessors to facilitiate consistent implementation of the children's FQPA safety factor provision in cumulative risk assessments," the draft 10X CRA policy ultimately fails to provide clear or helpful guidance. (Draft Policy at 1). The draft policy does set forth the required statutory standard but simultaneously offers techniques to circumvent it. Furthermore, EPA's insistence that the value judgments of an individual risk assessor can overturn the default 10X safety factor – despite prenatal and postnatal toxicity and significant data gaps on toxicity or exposure – will undoubtedly hinder EPA's stated goal of achieving consistency in implementation of 10X.

The draft 10X CRA policy also paints a confusing picture of the intent and necessity of the tenfold safety factor. EPA states that "OPP believes that it is critical to the protection of infants and children that it not rely on and not apply a default value or presumption in making decisions under Section 408 where reliable data are available that support use of a different safety factor in the assessment of risk." (Draft Policy at 5). This phrasing of OPP's position implies the curious and disturbing conclusion that infants and children will be better off the more often OPP deviates downward from 10X. It is certainly true that, if reliable data indicate that 10X is too low to

protect infants and children, protection of children's health requires either that a higher safety factor be applied or that no tolerance be granted. But it is hard to understand how it could be "critical" to the protection of infants and children to apply a safety factor lower than 10X. This draft policy would greatly benefit from a clear and unequivocal declaration by EPA that the FQPA tenfold safety factor is an invaluable tool for the protection of vulnerable infants and children from the harmful and long-lasting effects of pesticide exposure.

III. THE SCIENCE: APPLICATION OF THE FQPA FACTOR

EPA has failed to provide in its Draft Policy a framework for the Agency to evaluate scientific data, determine the uncertainty, and consistently apply uncertainty factors – including the FQPA factor – to comply with the law and provide the proper margin of safety. The FQPA requires that the Agency evaluate scientific data to make determinations as to an adequate protective margin of safety. Yet the guidance policy provides no guidance on what constitutes "good" data or what constitutes a complete database. Notably, the following omissions, inconsistencies, and inadequacies must be amended before this document can provide the framework that it promises.

A. Use of FQPA Factor for Completeness of Toxicity Database.

1. The Agency must appropriately incorporate information from the published literature on pesticide toxicity.

The Draft Policy should provide a framework for incorporation of published data, or application of compensating uncertainty factors reflecting an incomplete database. The Agency has traditionally relied on toxicology studies provided by the chemical manufacturers, most of which are unavailable in the public domain, for its determination of no-effect levels and potency factors. These studies have not undergone peer review and are not available for public scrutiny; without this they lack scientific credibility as defined by the scientific community. The Agency has not made any serious attempt to incorporate the scientific knowledge of pesticide toxicity that is freely available in the published literature. This rich database remains virtually untapped by the Agency. A cumulative risk assessment that does not consider the published literature cannot be said to represent the current scientific understanding of pesticide toxicity. We therefore consider this to be a deficiency in the limited database upon which the risk assessment is based, and that the Agency either incorporate, in a quantitative and meaningful way, the published literature on pesticide toxicity, or make appropriate adjustments for this omission through the use of traditional and FQPA database uncertainty factors, for database limitations and uncertainties.

2. The Agency should consider studies submitted under FIFRA § 6(a)(2).

Section 6(a)(2) of FIFRA requires that "[i]f at any time after the registration of a pesticide the registrant has additional factual information regarding unreasonable adverse effects on the environment of the pesticide, the registrant shall submit such information to the Administrator." This submission requirement applies equally to epidemiological and animal data. The Agency recognizes that this information is of importance, and it should therefore be considered quantitatively in the risk assessment. If it is not, then its impact must be estimated with an uncertainty factor.

The Draft Policy should provide a framework for incorporation of studies submitted by the registrant under FIFRA § 6(a)(2), or application of compensating uncertainty factors, reflecting an incomplete toxicity database. Studies submitted under FIFRA § 6(a)(2) may have great relevence to the assessment of potency, risk, and special vulnerability of immature organ systems.

For example, registrant studies submitted to the Agency demonstrate differences in cholinesterase inhibition ranging from 2-fold to over 20-fold, between adults and pups given equivalent doses of malathion[3]. Most dramatic, two hours after a single oral dose of technical grade malathion administered to young adult rats and PND11 pups, the adult brain cholinesterase levels were inhibited 3-4% (male and female), compared with controls. However, brain cholinesterase activity was inhibited in the pups by 81-84% (female and male), compared with controls, a 20-fold difference compared with the adult response. Clearly, these data demonstrate that consideration of data submitted by the registrant under FIFRA6(a)(2) is important to consider when making a determination of the toxicity of a chemical compound.

B. Use of FQPA Factor for Potential Pre- and Post-Natal Toxicity to Fetuses, Infants, and Children.

1. When relative potency determination is based on toxicology data derived from adult animals, extrapolation to fetuses, neonates, and juveniles requires an FQPA factor of at least 10-fold.

The Draft Policy should provide a framework for incorporation of data on immature animals, or require the application of a compensating FQPA factor. Considering that the impetus of cumulative risk assessment is the FQPA, which mandates the re-evaluation of pesticide exposure with specific attention to the effects on fetuses, infants, and children, it is an obvious, egregious omission to disregard these life stages in the final quantitative determination of relative potency. This omission is especially enormous when the individual chemicals have not undergone appropriate neurotoxicity, immunotoxicity, or endocrine toxicity testing on immature animals.

It is well established in the scientific literature that the body is extremely vulnerable to chemical assault during development of target organs and systems. During neural development the nervous system is acutely vulnerable to neurotoxic assault, and exposures may result in long-term or permanent destruction or dysfunction[1]. This is equally true for the developing immune system, endocrine system, and reproductive system. Data from adult animals cannot adequately describe the risk to fetuses, infants, and children without the application of an uncertainty factor to provide an adequate margin of safety to protect people during these especially vulnerable developmental stages.

2. When some members of the CRA group have demonstrated developmental effects (i.e. immature animals are more sensitive than adults), then all members must be presumed to have such effects, unless chemical-specific data demonstrates otherwise.

The Draft Policy should require that, unless data demonstrates otherwise, if any members of a CAG are shown to be developmentally toxic, then all members of the group should be considered similarly toxic. The Agency must presume that the developing organ systems are more vulnerable than the adult to toxic assault. Presuming all neurotoxic, immunotoxic, and hormonally-disruptive chemicals to be developmentally toxic is consistent with current scientific understanding of embryology and toxicology. In fact, the Draft Policy states the opposite position, that the potential for pre- or postnatal toxicity of the CAG should "not be predetermined" based on

[3] Letter from Cheminova, submitted by Jellinek, Schwartz, and Connolly, Inc. Re: Malathion: Preliminary data from a developmental neurotoxicity study. February 13, 2001. EPA LIN#L0000617.

whether individual members of the CAG have demonstrated pre-or postnatal toxicity (Draft Policy at 12). This is appalling, illogical, scientifically unjustifiable, and a violation of FQPA. A recent report by the WHO states that, "children under the age of 10 are among the groups most vulnerable to food- and waterborne diseases. The possible health consequences of exposure to pesticide residues and chemicals potentially present in the environment, food and water include immunological effects, endocrine disruption, neurotoxic disorders and cancer"[4]. For example, a number of organophosphate pesticides have been shown to be especially harmful to immature animals, even at low doses[2-6]. This is expected, given that the organophosphates are designed specifically to disrupt cholinesterase levels, thereby affecting synaptogenesis, neurite outgrowth (axonal and dendritic), arborization, and kindling. Functionally, this has been demonstrated to result in permanent disruptions in learning, memory formation, cognitive ability, and behavior.

Cancer in childhood is rare and has potentially dramatic outcomes. The WHO reported recently that in European countries, 1 out of 500 children are estimated to be diagnosed with cancer before the age of 15. This WHO report states that "although the role of environmental exposure in childhood cancer is limited, children are more prone to biological events potentially related to the development of cancer (multistage carcinogenesis) because exposure to carcinogens during childhood can lead to cancer later in life, as in the case of excessive exposure to ultraviolet radiation causing melanoma"[5].

The WHO report expresses concern that, if not adequately tested, the assessment of the developmental toxicity of pesticides which are endocrine disruptors is inadequate. For example, the report states, "dieldrin, toxaphene, chlordane and DDT have been found to be estrogenic, as has endosulfan, a pesticide still used in agriculture (Soto *et al*., 1994[7]). Interactions of pesticides with specific endocrine receptors during fetal and infant development may have profound effects on the morphological and functional development of the child. Certain estrogenic chemicals, such a nonylphenol (a nonionic detergent/surfactant), elicit uterotrophic response in young animals at a lower dose than in adult animals[8]. In addition, there is increasing evidence that exposure to certain synthetic compounds, including dioxins and polychlorinated biphenyls, during the perinatal period can impair normal thyroid function and also learning, memory and attentional processes in offspring (Hauser *et al*., 1998[9]). This raises the question whether the current toxicological database for pesticides is sufficient to fully assess potential developmental adverse effects."[6] 10

The WHO report expresses similar concerns regarding immunotoxic pesticides. The report states, "Numerous pesticides, including dieldrin, aminocarb, captan, carbaryl, lindane, malathion and dichlorophos, can induce changes in the immune system (US NRC, 1993; Barnett and Rogers, 1994). In 1993 the NRC concluded that the immune systems of infants and children showed an increased sensitivity to the toxic effects of chemicals. It has been recommended that in the context of risk assessment for infants and young children, immunotoxicity to infants and children needs to be addressed since some chemicals may interfere with the developing immune system and give rise to persistent adverse effects, such as reduced ability to respond to immune challenge (EU SCF, 1998; Wallinga, 1998)."[7]

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[4] *See supra* note 1.
[5] *Id.*
[6] *Id.* at 156.
[7] *Id*.

The organophosphate pesticides (OP's) are a common-mechanism group, they target a common enzyme, they induce a common set of effects, and therefore, by all scientific criteria, if any are shown to be fetotoxic, then all should be presumed to be fetotoxic, unless data shows otherwise. However, developmental neurotoxicity testing (DNT), specifically designed to detect the impact of neurotoxins on the immature nervous system, has been completed for only a handful of over 25 OP's currently under cumulative risk assessment by the EPA. Malathion is a commonly used OP pesticide. Registrant studies submitted to the Agency demonstrate differences in inhibition ranging from 2-fold to over 20-fold, between adults and pups given equivalent doses of malathion[8]. Most dramatic, two hours after a single oral dose of technical grade malathion administered to young adult rats and PND11 pups, the adult brain cholinesterase levels were inhibited 3-4% (male and female), compared with controls. However, brain cholinesterase activity was inhibited in the pups by 81-84% (female and male), compared with controls, a 20-fold difference compared with the adult response. Chlorpyrifos is another common OP pesticide. In his publications, Dr. Slotkin points out that numerous animal studies demonstrate that immature animals are far more susceptible to acute toxicity of chlorpyrifos, despite the fact that they recover from cholinesterase inhibition more quickly than adults[5, 6], presumably due to multiple mechanisms of toxicity of chlorpyrifos. These findings were supported by the DNT results, which demonstrated evidence of neuropathology and increased vulnerability of fetuses when exposed to chlorpyrifos (Chlorpyrifos IRED p. 16; Makris et al.[9]). Most concerning, in these experiments neuropathology was seen in the neonates at the lowest dose tested; these studies were unable to identify an offspring NOAEL in the DNT (Chlorpyrifos IRED p. 16-17). In the cumulative risk assessment for OP's the EPA is evaluating neurotoxic pesticides, in the absence of DNT data. The organophosphate pesticides are a common-mechanism group, they target a common enzyme, they induce a common set of effects, and therefore, by all scientific criteria, if any are shown to be fetotoxic, then all should be presumed to be fetotoxic, unless data shows otherwise. Clearly, the OP's that were rigorously tested, using appropriate study designs (such as DNT studies) were shown to be especially harmful to the developing nervous system.

Clearly, in the absence of substantial data, it is scientifically sound to presume that fetuses, infants, and children are more vulnerable to toxic assault than adults.

3. Assessment of critical effects is necessary, even those that occur at doses below those used to calculate relative potency or PoD.

The Draft Policy should provide a framework for incorporation of data on effects that occur at doses below those used to determine the relative potency, or else require the application of a compensating FQPA factor reflecting the potential for pre- or post-natal toxicity. The risk assessor must quantitatively compare all clinical endpoints associated with the CRA mode of action (MOA), and indicate where clinical effects occur in the absence of MOA indicators, or below the level of concern/detection. Behavioral and cognitive testing, including learning and memory tests, reflex tests, and others, are key to assessing the true toxic effects of any neurotoxic and fetotoxic chemicals. Most importantly, with any developmental neurotoxic chemical, effects are the result of more than the magnitude of the dose. Rather, the effect is dependent on the dose, the duration of dose and effect, and the stage of development at which the exposure takes place.

[8] letter from Cheminova, submitted by Jellinek, Schwartz, and Connolly, Inc. Re: Malathion: Preliminary data from a developmental neurotoxicity study. February 13, 2001. EPA LIN#L0000617. Obtained by NRDC, Jennifer Sass, by FOIA RIN-0283-02

[9] 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.

Exposures at key windows of susceptibility during neural development, even at very low doses, are most likely to have permanent, devastating effects on neural function, including behavior and cognition. Exclusion of these critical effects represents a very serious gap in the understanding of the toxic effects, particularly to fetuses, infants, and children. It is appropriate to apply a database uncertainty factor to the CRA group, in this case, as suggested in the guidance document (Draft Policy at 10). Although the Draft Policy mentions this point, it does not adequately provide a framework for either assessing such endpoints, or using the full 10X FQPA factor, as is required by law.

4. Toxic degradates and metabolites should be considered in a cumulative risk assessment.

The Draft Policy should provide a framework for incorporation of data on the toxic impact of degradates and metabolites, or else require the application of a compensating FQPA factor reflecting the potential for pre- or post-natal toxicity. NRDC recommends using data on toxic degradates where available, such as some water monitoring and food data. Where such data are not available, the EPA should estimate exposure and risk based on chemical structure, mobility, degradation rate, and other known characteristics of the degradates. Though EPA has abundant data for dietary exposure to some pesticides, its PDP databases (USDA's pesticide data program) only include monitoring data for residues of the parent compound. Likewise, toxic degradates/metabolites and treatment byproducts are often not available or not included in the water assessment. It is not scientifically justifiable to presume, without data, that metabolites act like parent compounds. The omission of proper consideration of degradates results in an underestimation of exposure, and if they are to be omitted, then the magnitude of difference in toxicity, persistence, or mobility must be estimated, and adjusted for with sufficient uncertainty factors.

Many pesticides have toxicologically significant metabolites and stereoisomers. For example, malaoxon — the bioactivated form of malathion — inhibits acetylcholinesterase about 1,000–fold more strongly than does malathion. Similarly, EPA acknowledges that dimethoxon, a significant metabolite of dimethoate, is 75-100 times more potent than dimethoate in inhibiting acetylcholinesterase. Moreover, this metabolite is found under field conditions on food crops. The primary degradate of ethyl parathion, paraoxon, is five times more easily absorbed than parathion and 40 to 50 times more toxic. One of the chief metabolites of chlorpyrifos, chlorpyrifos oxon, inhibits cholinesterase more strongly than the parent compound, but appears to be very short-lived. It breaks down to TCP; compared with chlorpyrifos, TCP is stated to be "more mobile and significantly more persistent in many soils, especially under anaerobic conditions" (chlorpyrifos IRED p.20).

C. Use of FQPA Factor for Completeness of Exposure Database.

1. Consideration of newborns, young children, and teenagers as distinct sensitive subpopulations is necessary.

The Draft Policy should provide a framework requiring data on fetuses, infants, children, and the elderly, or else require the application of a compensating FQPA factor reflecting the potential for special sensitivity of these vulnerable age groups. Consideration of the age-specific dietary, occupational, and behavioral patterns of various age groups, in addition to their age-specific developmental or health status, is necessary to a complete cumulative risk assessment[11]. Particularly, inclusion of ages 0-11 months, 6-12 years, 13-19 years, and over 56 years and

distinct age groups, with distinct behaviors or health statuses, is relevent. To omit any of these age groups, or to merge such age groups so as to "average" out distinct behavior or health patterns, would weaken a CRA substantially. In particular, fetuses, infants, and children are the intended targets of the FQPA, and without considering the risks associated with these distinct groups the requirements of the FQPA have not been met.

2. All routes of exposure should be considered.

a. Violative residues.

The Draft Policy should provide a framework for incorporation of data on violative residues, or else require the application of a compensating FQPA factor reflecting a gap in the exposure database. To ensure that tolerances are set at a safe level, EPA must account for all pathways of exposure, including exposures from legal and illegal behavior that results in violative residues. These data are available to the EPA, and should be incorporated appropriately. Violative residues may be either residues detected on food for which no tolerance is issued, or which exceed the tolerance. In either case, these are extremely important, and may indicate a widespread and very dangerous problem. If residues exceed the tolerance routinely, seasonally, or even occasionally the CRA must consider these "real world" residues. It is unacceptable for the Agency to disregard these data as "outliers" without providing evidence that they are flatly incorrect or of inconsequential health impact. If these "violative" residues are the result of spray drift, illegal applications, or machinery residues, they must be considered indicative of widespread exposure and a contributor to exposure. In any case, the Agency must provide data as to the frequency, spatial and temporal pattern (if any exists), and magnitude of the "violations." The absence of these monitoring data is a considerable data gap that likely underestimates exposure and warrants use of an uncertainty factor.

b. Public health applications.

The Draft Policy should provide a framework for incorporation of data resulting from the public health applications of pesticides, or else require the application of a compensating FQPA factor reflecting a gap in the exposure database. NRDC is concerned that emergency and public health uses may be of sufficient frequency and dose, or used in such close proximity to people, as to pose significant risk to exposed populations. While the benefits of pest control in urban areas is acknowledged, so must the health impacts of widespread urban spraying of pesticides be considered[12]. Such urban spraying will contaminate lawns, outdoor plants and flowers, home vegetable gardens, lawn furniture, children's outdoor toys, and cars, to name the obvious. Clearly, such contamination provides an obvious route of transmission to young children, in addition to the general population. It is therefore negligent to omit consideration of public health uses of pesticides from any cumulative risk assessment.

c. Non-agriculture contribution to water sources.

The Draft Policy should provide a framework for incorporation of pesticide residues in water originating from non-agriculture sources, or else require the application of a compensating FQPA factor reflecting a gap in the exposure database. Drinking water contamination can occur through public health uses of pesticides, in addition to leaching and runoff from golf courses, lawns and gardens, and other urban or residential uses. It is negligent to omit consideration of these routes of water contamination in a cumulative risk assessment which is attempting to accurately characterize the cumulative load on an exposed population.

d. Food purchased at farmers markets, farm stands,"U-Pick" farms, and from household gardens.

The Draft Policy should provide a framework for incorporating exposure data from farmers markets and farm stands, or else require the application of a compensating FQPA factor reflecting a gap in the exposure database. Without considering these exposures, EPA does not account for the dietary exposure of a significant number of consumers who purchase produce at farmers markets, farm stands, and "U-Pick" farming operations. Over 1.9 million people buy vegetable and fruits from nearly 13,000 farmers, at more than 2,000 community-based farmers markets and farm stands in the US. (National Association of Farmers' Market Nutrition Programs (http://www.nafmnp.org/)). These consumers include pregnant women, infants, and children, and must be protected. By ignoring this significant community of consumers, EPA vastly underestimates dietary exposure and cannot ensure that exposure to residues at the tolerance level will be safe. Not having the data does not justify ignoring the dietary exposure of potentially millions of consumers to residues of OP's at the tolerance level. EPA must ensure that the legal levels of pesticide chemical residues – the established tolerance levels – are themselves safe. (FFDCA § 408(b)(2)(A)).

3. Estimates of exposure based on "typical" exposure scenarios ignore peak exposure scenarios that are likely to be of significant risk to exposed populations.

The Draft Policy should provide a framework for incorporation of data on pesticide exposures from maximum allowable use rates, or else require the application of a compensating FQPA factor reflecting a gap in the exposure database. NRDC recommends to EPA that the water assessment be based on all available data of use rates, use patterns, and monitoring data where available, so that the CRA will adequately capture the population at highest risk. The water model (PRZM/EXAMS) used for the preliminary organophosphate CRA plots the distribution of daily residues over multiple years, and plots multiple sites rather than high-exposure sites; no point estimates were considered. This is a major departure from the individual risk assessments, where point estimates were used, to capture the 99.9^{th} percentile. Ignoring peak point estimates leads to a severe underestimation of risk, and ignores the potentially devastating effects of toxic pesticide exposures, even at very low doses, and even for short duration, on the developing nervous system. It is a further underestimate of risk to presume typical use rates and typical use patterns. This is a departure from the individual risk assessments, which assessed exposure based on maximum allowable label rates and maximum allowable use patterns; this more conservative approach, while still ignoring exposures that exceed allowable limits, at least attempts to protect those people who suffer allowable high-end exposures. The Draft Policy should provide guidance for considering a full distribution of real-world use rates and patterns, so that real-world exposure scenarios capturing peak exposures are considered in a cumulative risk assessment.

4. Estimates based on "typical" eating patterns are likely to underestimate exposures to certain populations.

The Draft Policy should provide a framework for determining gaps in the database on eating patterns, and guidance on application of a compensating FQPA factor reflecting a weakness in the exposure database. Risk assessors must determine if certain ethnic groups and their eating patterns are under-represented in the food consumption data (PDP data), and correct the impact of any possible bias on the risk assessment. For example, vegetarian diets, which are certainly very common, are likely to exceed the "typical" fruit and vegetable eating pattern, and exceed the

"typical" pesticide exposure profile. These real-world diets are consumed by pregnant women, breast-feeding women, children, teenagers, adults, and the elderly. These people must be represented in a cumulative risk assessment, and must be protected under the FQPA

5. Farm children are especially vulnerable to pesticide exposure.

The Draft Policy should provide a framework for incorporation of exposure to farm community children, or else require the application of a compensating FQPA factor reflecting a gap in the exposure database. Farm children should be deemed to comprise an especially vulnerable population, and their exposure to pesticides must be considered in establishing tolerances where data are available. The children of farmers, farmworkers and agricultural communities – including over 500,000 children under the age of six – are surrounded by a virtual sea of pesticides. They come in contact with pesticides through residues from their parents' clothing, dust tracked into their homes, contaminated soil in areas where they play, food brought directly from the fields to the table, family vehicles and farm equipment, and contaminated well water[13-17]. These children are likely to have the highest exposure to pesticides of any group of people in the country. Furthermore, farm children often accompany their parents to work in the fields, raising their pesticide exposures even higher. Many of the children with the greatest pesticide exposures are from migrant farmworker families, who are poor and usually people of color or recent immigrants.

Children who live on or near farms are at risk from airborne pesticide drift when they spend any time outdoors. Fog samples gathered in suburban Maryland and in agricultural regions of California revealed up to 16 different agricultural pesticides. The pesticides detected included organophosphates, triazines, dinitroaniline (pendimethalin), and chloroacetanilides (alachlor, metolachlor). The levels of organophosphates and their oxygen analogues often exceeded 10 μg/liter: two or three orders of magnitude above levels reported in rain. The maximum measured level of the highly toxic parathion oxygen analogue (paraoxon) was 184 μg/liter – a level considered sufficient to cause significant cholinesterase inhibition. In addition, volatile, fat-soluble pesticides were found in fog at concentrations far greater than expected[18]. Pesticides sprayed outdoors may enter houses and concentrate in indoor air. A Minnesota study revealed that an application of two herbicides by ground-broom sprayer 50 meters upwind from a farmhouse resulted in a three- to four-fold elevated concentration of both chemicals in outdoor air adjacent to the farmhouse, and a 50% increase in the concentration of one of the herbicides inside the farmhouse. The herbicide in indoor air was attributed to infiltration of outdoor air.[10] Outdoor air concentrations of pesticides in agricultural regions may be extremely significant from a public health perspective. This is likely particularly true for pesticides applied via fumigation or broadcast spraying. Children who live in agricultural regions may receive significant airborne pesticide exposures when playing outdoors. Infiltration of homes by outdoor air may also result in airborne exposures inside the home. Protection of children necessitates routine, consistent monitoring of ambient air pesticide levels in agricultural regions. Because overexposures to organophosphates and soil fumigants have been documented, these categories of pesticides should receive particular scrutiny.

Epidemiology studies of farmworkers and people living in agriculture communities suggest that pesticide exposures are associated with numerous diseases, including Parkinson's Disease, non-Hodgkin's lymphoma, leukemia, and brain cancer[19-31]. These studies provide strong evidence

[10] Camann D, Geno P, Harding H, Giardino N, Bond A, al. e. A Pilot Study of Pesticides in Indoor Air in Relation to Agricultural Applications. Proc Indoor Air 1993; 2:207-212.

that exposure to pesticides is of extreme concern at current use rates and use patterns, especially to farmworkers and their families, and agricultural communities.

IV. UNCERTAINTY

A. Determination of uncertainty must consider both individual chemical data, and the cumulative assessment group as a whole.

Uncertainty factors must consider both individual chemical data and the CAG as a whole. The guidance document clearly states that the application of these traditional uncertainty factors to the cumulative risk assessment is in addition to the need for uncertainty factors for individual chemical members of the CAG (Draft Policy at 10). That is, both data limitations for individual chemicals, and data limitations for the CAG must be considered separately, and with the separate application of traditional uncertainty factors. This is an important point, which NRDC supports, and must be written more clearly, and with substantiation, in the guidance document. Consideration of the database deficiencies for individual chemicals may reveal any or all of the above named gaps (ie. UF_S, UF_L, UF_{Db}, and other gaps), which would compromise the scientific confidence in the assessment. Uncertainty factors are required to provide an adequate margin of safety. However, the same consideration of the database for the CAG as a whole is required, to adjust for such gaps as they apply specifically to common mechanism endpoints.

To adequately assess and quantify uncertainty in any cumulative risk assessment, the EPA must develop uncertainty distributions to capture population variability in exposure levels and patterns, and, in biological responses to a given exposure scenario. The Draft Policy should provide a framework for developing such uncertainty assessments, as well as providing guidance on what constitutes an adequate versus insufficient assessment of uncertainty.

B. Determination of uncertainty must consider the variations in experimental determinations of toxicity and relative potency.

The EPA receives all most or all of its toxicology data from registrants, who may provide the results of an experiment with little or no detail as to the protocols followed. Laboratories performing similar assays have been demonstrated to vary widely in procedures, sensitivity, and results[32]. The Draft Policy must provide a strong statement urging that all data which is used to assess a CAG for the determination of a benchmark dose and relative potency factors must come from experimental protocols which are scientifically rigorous, and are standardized in procedures and sensitivity. Similarly, protocols should be standardized for species and strain of animals. While demanding standardized, rigorous protocols for all data submissions, to limit variation in results as much as is humanly possible, the Agency must recognize that this is an ideal situation, and in reality some variation between laboratories will remain. Therefore, it is incumbent on the Draft Policy to demand the best science, and then provide guidance to assess and quantify uncertainty where it exists.

Thank you for consideration of these comments.

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