ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2005–0162; FRL–8797–6]

Carbofuran; Order Denying FMC's Objections and Requests for Hearing

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: In this order, EPA denies objections to, and requests for hearing on, a final rule revoking all pesticide tolerances for carbofuran under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The objections and hearing requests were filed on June 30, 2009, by the National Corn Growers Association, National Sunflower Association, National Potato Council, and FMC Corporation (''Petitioners'').

DATES: This final order is effective November 18, 2009.

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2005–0162. To access the electronic docket, go to *http://www.regulations.gov,* and search for the docket number. Follow the instructions on the regulations.gov Web site to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, *e.g.,* Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic docket at *http://www.regulations.gov,* or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

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SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

In this document EPA denies objections and hearing requests by the National Corn Growers Association, National Sunflower Association, National Potato Council, and FMC Corporation (''Petitioners'') concerning EPA's final rule revoking all pesticide tolerances for carbofuran. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Access Electronic Copies of this Document?

In addition to accessing an electronic copy of this **Federal Register** document through the electronic docket at *http://www.regulations.gov,* you may access this **Federal Register** document electronically through the EPA Internet under the **Federal Register** listings at *http://www.epa.gov/fedrgstr.* You may also access a frequently updated electronic version of EPA's tolerance regulations at 40 CFR part 180 through the Government Printing Office's pilot e-CFR site at *http://www.gpoaccess.gov/ecfr.*

C. Acronyms

The following is a list of acronyms used in this order:

AChE—Acetylcholinesterase
aPAD—Acute Population Adjusted Dose
BMD—Bench Mark Dose
BMDL—Bench Mark Dose Level
CCA—Comparative Cholinesterase Assay
CNS—Central Nervous System
CRA—Cumulative Risk Assessment
CSFII—Continuing Survey of Food Intakes by Individuals
CWA—Clean Water Act
CWS—Community Water System
DEEM–FCID—Dietary Exposure Evaluation Model-Food Commodity Intake Database
ECG—Electrocardiogram
EDWC—Estimated Drinking Water Concentration
EPA—Environmental Protection Agency
FACA—Federal Advisory Committee Act
FDA—Food and Drug Administration
FIFRA—Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA—Federal Food, Drug, and Cosmetic Act
FQPA—Food Quality Protection Act of 1996
HSRB—Human Studies Review Board
HUC–8—8-digit hydrologic unit code
IRED—Interim Reregistration Eligibility Decision
LD_{50}—Lethal Dose for 50% of a population
LOAEL—Lowest Observable Adverse Effect Level
NAWQA—National Water Quality Assessment Program
NHEERL—National Health and Environmental Effects Laboratory
NMC CRA—N-Methyl Carbamate Cumulative Risk Assessment
NOAEL—No Observable Adverse Effect Level
NOIC—Notice of Intent to Cancel
NRDC—National Resources Defense Council
OP—Organophosphate
ORD—Office of Research and Development
PAD—Population Adjusted Dose
PCA—Percent Cropped Area
PCT—Percent Crop Treated
PDP—Pesticide Data Program
PND—Post-Natal Day
PNS—Peripheral Nervous System
PoD—Point of Departure
ppb—parts per billion
ppm—parts per million
PRZM–EXAMS—Pesticide Root Zone Model-Exposure Analysis Model System
RBC—red blood cell
RED—Reregistration Eligibility Decision
RfD—Reference Dose
SAP—Scientific Advisory Panel
SDWA—Safe Drinking Water Act
USDA—United States Department of Agriculture
USGS—United States Geological Survey
WARP—Watershed Regression for Pesticides

II. Introduction

A. What Action Is the Agency Taking?

Exposure to the pesticide carbofuran resulting from existing legal uses is unsafe—unsafe for the general

population, and particularly unsafe for infants and children. EPA reached this conclusion in 2006 after an exhaustive multi-year review of the data on carbofuran as part of its effort to determine whether carbofuran should be reregistered under the Federal Insecticide, Fungicide, and Rodenticide Act (''FIFRA''), and whether the tolerances allowing carbofuran residues on certain foods met the revised safety standard in section 408 of the FFDCA. This multi-year review included multiple opportunities for public participation, including no less than four formal public comment periods. Following EPA review of yet more carbofuran data submitted by FMC, the carbofuran registrant, and the review of EPA's science findings by the FIFRA Scientific Advisory Panel (SAP)—an independent scientific peer review panel—EPA again reached the same conclusion in its July 31, 2008 proposal to revoke the carbofuran tolerances (73 FR 44864 (July 31, 2008)). In response to this proposed revocation, FMC submitted comments challenging many of EPA's science findings and also requesting the cancellation of the registration of carbofuran on several crops and the restriction of where, and the manner in which, carbofuran could be used in the United States on its remaining registered crop sites. Finding FMC's science arguments to be flawed and its proposed amendments to the carbofuran registration to be insufficient, EPA finalized the rule revoking carbofuran tolerances on May 15, 2009 (74 FR 23046 (May 15, 2009)).

Pursuant to the procedures of the FFDCA, on June 29, 2009 objections to the final revocation rule were filed by the National Corn Growers Association, National Sunflower Association, National Potato Council, and FMC Corporation (''Petitioners''). The Petitioners also requested a hearing on their objections. Coupled with these objections, FMC filed on the same day yet another series of proposed amendments to its carbofuran registration. These proposed modifications contained new application and geographic restrictions as well as an unprecedented non-governmental scheme for preventing the use of carbofuran in any one area of the country above a small percentage of that area's agricultural acreage. The Petitioners relied on these proposed carbofuran registration amendments as central to, and inextricably intertwined with, their objection to EPA's prior determination in the final rule that carbofuran tolerances are unsafe. Specific challenges raised by the Petitioners involved EPA's decision on the appropriate level of the additional safety factor to protect infants and children, EPA's estimate of carbofuran levels in drinking water, EPA's consideration of the time needed to recover from exposure to carbofuran, and EPA's refusal to consider a human toxicity study conducted with carbofuran.

Today's order denies all of the Petitioners' objections and requests for hearing. A principal flaw in the Petitioners' objections is that they have objected to EPA's determination in the final rule on the safety of carbofuran based on the FIFRA registration amendments that FMC filed with EPA 45 days after the safety determination was made. As such, the Petitioners' objections are irrelevant, and thus immaterial, to the determination EPA made in the final rule. FMC has the statutory right under FIFRA to request amendment of its carbofuran registration. What Petitioners may not do is prolong the FFDCA tolerance revocation process by challenging EPA's safety determination based on proposed FIFRA registration changes not before EPA at the time of its final revocation decision.

It should be noted that EPA's decision on the carbofuran tolerances is not a determination on FMC's proposed registration amendments. FMC may continue to pursue these amendments and also the re-establishment of carbofuran tolerances in light of the amendments. Further, FMC may seek administrative review, and potentially an administrative hearing, with regard to any adverse decision issued by EPA on its proposed amendments. But that process must be played out in the future, a future in which any decision about the safety of carbofuran is made prior to the re-introduction of carbofuran residues in food and water, rather than concurrent with the continued exposure of infants and children to levels of carbofuran residues that EPA has found to be unsafe.

Despite the fact that a central aspect of the Petitioners' objections is based on a flawed conception of the objection process (*i.e.,* the notion that the objection process presents the opportunity for a complete reformulation of the matter in dispute, rather than a chance for a review of the accuracy of EPA's earlier determination), EPA has undertaken a comprehensive analysis of the merits of each of the Petitioners' objections and hearing requests. That analysis shows, as is exhaustively set out in Unit VI, that none of the Petitioners' requests for hearing meets the regulatory standard for granting a hearing and none of the Petitioners' objections has merit. There are numerous reasons for these conclusions, but two related themes running throughout EPA's analysis are the Petitioners' failure to timely raise issues or submit supporting documents during the public comment process on the proposed rule and the Petitioners' failure to object to how EPA, in the final rule, resolved the issues the Petitioners did raise in the comment process. EPA considers issues untimely raised to be waived—as EPA clearly warned at the proposal stage—and finds recycled comments on the proposed rule to be irrelevant to the detailed determinations made in the final rule. The rulemaking phase of the revocation process has a purpose, and parties treat it lightly at their peril. Finally, EPA notes that an additional problem with the Petitioners' objections is that once the newly proposed registration amendments are stripped from the objections, it is not at all clear that any remaining issues, even if concluded in the Petitioners' favor, would result in lowering carbofuran's estimated risks—which EPA has estimated as far exceeding the safety standard—to an acceptable level. For all of these reasons, the Petitioners' objections and hearing requests are denied.

B. What Is the Agency's Authority for Taking This Action?

EPA is taking this action pursuant to the authority in FFDCA section 408(g)(2)(C), which requires the Agency to issue a final order resolving the objections to its final rule, issued pursuant to 408(b)(1)(b), 408(b)(2)(A), and 408(e)(1)(A). 21 U.S.C. 346a(b)(1)(b), (b)(2)(A), (e)(1)(A), (g)(2)(C).)

III. Statutory and Regulatory Background

In this Unit, EPA provides background on the relevant statutes and regulations governing the Petitioners' objections and requests for hearing as well as on pertinent Agency policies and practices.

A. FFDCA/FIFRA and Applicable Regulations

1. *In general.* EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food under section 408 of the FFDCA (21 U.S.C. 346a). Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is ''adulterated'' under section 402 of the FFDCA and may not be legally moved in interstate commerce (21 U.S.C. 331,

342). Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration (''FDA'') and the U.S. Department of Agriculture (''USDA''). Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (''FQPA''), which added the provisions discussed below establishing a detailed safety standard for pesticides, additional protections for infants and children, and the process for establishing or revoking tolerances (Pub. L. 104–170, 110 Stat. 1489 (1996)).

EPA also regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (''FIFRA'') (7 U.S.C. 136 *et seq.*). While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, FIFRA requires the approval of pesticides prior to their sale and distribution (7 U.S.C. 136a(a)), and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law (7 U.S.C. 136j(a)(2)(G)). In the FQPA, Congress integrated action under the two statutes by requiring that the safety standard under the FFDCA be used as a criterion in FIFRA registration actions as to pesticide uses that result in dietary risk from residues in or on food (7 U.S.C. 136(bb)), and directing that EPA coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA. (21 U.S.C. 346a(l)(1)).

2. *Safety standard for pesticide tolerances.* Section 408(b)(2)(A)(i) of the FFDCA requires EPA to modify or revoke a tolerance if EPA determines that the tolerance is not ''safe'' (21 U.S.C. 346a(b)(2)(A)(ii)). Section 408(b)(2)(A)(ii) of the FFDCA defines ''safe'' to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.'' This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(D) directs EPA, in making a safety determination, to:

Consider, among other relevant factors—* * *

(vi) Available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources;

EPA must also consider, in evaluating the safety of tolerances, ''safety factors which * * * are generally recognized as appropriate for the use of animal experimentation data.'' (21 U.S.C. 346a(b)(2)(D)(ix).)

Risks to infants and children are given special consideration. Specifically, section 408(b)(2)(C) states that EPA:

> Shall assess the risk of the pesticide chemical based on—* * *
>
> (II) Available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of in utero exposure to pesticide chemicals;

(21 U.S.C. 346a(b)(2)(C)(i)(II) and (III)). This provision also creates a presumptive additional safety factor for the protection of infants and children. Specifically, it directs that ''[i]n the case of threshold effects, * * * 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'' (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to ''use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children'' (Id.). The additional safety margin for infants and children is referred to throughout this order as the ''children's safety factor.''

3. *Procedures for establishing, amending, or revoking tolerances.* Tolerances are revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Section 408(e) of the FFDCA, 21 U.S.C. 346a(e), authorizes EPA to modify or revoke tolerances on its own initiative.

In issuing a regulation on its own initiative, EPA must first publish a notice of proposed rulemaking, and must generally provide at least 60 days to allow the public to comment on the proposed regulation. After considering comments submitted during this comment period, EPA issues a final rule.

Once EPA issues a final rule, any person may file objections with EPA and, if desired, request an evidentiary hearing on those objections (21 U.S.C. 346a(g)(2)). Objections must specify ''with particularity the provisions of the regulation * * * deemed objectionable and stating reasonable grounds therefore'' (21 U.S.C. 346a(g)(2)(A); 40 CFR 178.25(a)). Objections and hearing requests must be filed within 60 days (Id.). The statute provides that EPA shall ''hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections'' (21 U.S.C. 346a(g)(2)(B)). EPA regulations make clear that hearings will only be granted where it is shown that there is ''a genuine and substantial issue of fact;'' the requestor has identified evidence ''which, if established, will resolve one or more of such issues in favor of the requestor,'' and the issue is ''determinative'' with regard to the relief requested (40 CFR 178.32(b)). After consideration of any objections, EPA must issue a final order stating the action taken in response to each objection, including a determination as to whether any hearing is appropriate (21 U.S.C. 346a(g)(2)(C)). The final order also establishes any revisions to the final regulation EPA deems to be warranted based on the objections. Id. EPA's final order on the objections is subject to judicial review in the Court of Appeals, within 60 days of the publication of the order (21 U.S.C. 346a(h)(1)).

4. *Tolerance reassessment and FIFRA reregistration.* EPA revoked the carbfuran tolerances to implement the Agency's findings made during the reregistration and tolerance reassessment processes.

The FQPA required that EPA reassess the safety of all pesticide tolerances existing at the time of its enactment. (21 U.S.C. 346a(q)). EPA was given 10 years to reassess the approximately 10,000 tolerances in existence in 1996. In this reassessment, EPA was required to review existing pesticide tolerances under the new ''reasonable certainty that no harm will result'' standard set forth in section 408(b)(2)(A)(i). (21 U.S.C. 346a(b)(2)(A)(i)). This reassessment was substantially completed by the August 3, 2006 deadline. Tolerance reassessment was generally handled in conjunction with a similar program involving reregistration of pesticides under FIFRA. (7 U.S.C. 136a–1). Reassessment and reregistration decisions were generally combined in a document labeled a Reregistration Eligibility Decision (RED).

B. EPA's Human Research Rule

EPA decisions regarding the use of human studies in pesticide regulatory decisions are governed by the Protection for Subjects in Human Research final rule (''Human Research rule''), which significantly strengthened and expanded protections for subjects of human research (71 FR 6138 (February 6, 2006)). The framework of the Human Research rule rests on the basic principle that EPA will not, in its actions, rely on data derived from unethical research. The rule divides studies involving intentional dosing of human subjects into two groups: ''new'' studies—those initiated after April 7, 2006 (the effective date of the rule)—and ''old'' studies—those initiated before April 7, 2006. The Human Research Rule forbids EPA from relying on data from any ''new'' study, unless EPA has adequate information to determine that the research was conducted in substantial compliance with the ethical requirements contained therein (40 CFR 26.1705). These ethical rules are derived primarily from the ''Common Rule,'' (40 CFR part 26), a rule setting ethical parameters for studies conducted or supported by the federal government. In addition to requiring informed consent and protection of the safety of the subjects, among other things, the rule specifies that ''[r]isks to subjects [must be] reasonable in relation to * * * the importance of the knowledge that may reasonably be expected to result [from the study].'' (40 CFR 26.1111(a)(2)). In other words, a study would be judged unethical if it did not have scientific value outweighing any risks to the test subjects.

As to ''old'' studies, the Human Research Rule forbids EPA from relying on such data if there is clear and convincing evidence that the conduct of the research was fundamentally unethical or significantly deficient with respect to the ethical standards prevailing at the time the research was conducted (40 CFR 26.1704). EPA has indicated that in evaluating ''the ethical standards prevailing at the time the research was conducted'' it will consider the Nuremburg Code, various editions of the Declaration of Helsinki, the Belmont Report, and the Common Rule, as among the standards that may be applicable to any particular study (71 FR at 6161). Further, reflecting the concern that scientifically invalid data are ''always unethical,'' (71 FR at 6160), the rule limits the human research that can be relied upon by EPA to ''scientifically valid and relevant data'' (40 CFR 26.1701).

Whether the data are ''new'' or ''old,'' the Human Research rule forbids EPA from relying on data from any study involving intentional exposure of pregnant women, fetuses, or children subject to a very limited exception (40 CFR 26.1703, 1706).

To aid EPA in making scientific and ethical determinations under the Human Research rule, the rule established an independent Human Studies Review Board (HSRB) to review both proposals for new research (new studies) and reports of completed human research (old studies) on which EPA proposes to rely (40 CFR 26.1603). The rule directs that the HSRB shall be comprised of non-EPA employees ''who have expertise in fields appropriate for the scientific and ethical review of human research, including research ethics, biostatistics, and human toxicology'' (40 CFR 26.1603(a)). If EPA decides to rely on the results from ''old'' research conducted to identify or measure a toxic effect, EPA must submit the results of its assessment to the HSRB for evaluation of the ethical and scientific merit of the research (40 CFR 26.1602(b)(2)).

EPA has established the HSRB as a federal advisory committee under the Federal Advisory Committee Act (FACA) to take advantage of ''the benefits of the transparency and opportunities for public participation'' that accompany a FACA committee (71 FR at 6156). The HSRB, as appointed by EPA, contains approximately 16 distinguished experts in the fields of bioethics, biostatistics, human health risk assessment and human toxicology, primarily from academia (Ref. 10).

IV. EPA's Approach to Dietary Risk Assessment

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. A short summary is provided below to aid the reader. For further discussion of the regulatory requirements of section 408 of the FFDCA and a complete description of the risk assessment process, see *http://www.epa.gov/fedrgstr/EPA-PEST/1999/January/Day-04/p34736.htm*.

To assess the risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps: (1) Identification of the toxicological hazards posed by a pesticide; (2) determination of the exposure ''level of concern'' for humans; (3) estimation of human exposure; and (4) characterization of human risk based on comparison of human exposure to the level of concern.

A. Hazard Identification and Selection of Toxicological Endpoint

1. In General. Any risk assessment begins with an evaluation of a chemical's inherent properties, and whether those properties have the potential to cause adverse effects (*i.e.,* hazard identification). EPA then evaluates the hazards to determine the most sensitive and appropriate adverse effect of concern, based on factors such as the effect's relevance to humans and the likely routes of exposure.

Once a pesticide's potential hazards are identified, EPA determines a toxicological level of concern for evaluating the risk posed by human exposure to the pesticide. In this step of the risk assessment process, EPA essentially evaluates the levels of exposure to the pesticide at which effects might occur. An important aspect of this determination is assessing the relationship between exposure (dose) and response (often referred to as the dose-response analysis). In evaluating a chemical's dietary risks EPA uses a reference dose (RfD) approach, which involves a number of considerations including:

- A 'point of departure' (PoD)—the value from a dose-response curve that is at the low end of the observable data and that is the dose that serves as the 'starting point' in extrapolating a risk to the human population;
- An uncertainty factor to address the potential for a difference in toxic response between humans and animals used in toxicity tests (*i.e.*, interspecies extrapolation);
- An uncertainty factor to address the potential for differences in sensitivity in the toxic response across the human population (*i.e.*, intraspecies variability); and
- The need for an additional safety factor to protect infants and children, as specified in FFDCA section 408(b)(2)(C).

EPA uses the chosen PoD to calculate a safe dose or RfD. The RfD is calculated by dividing the chosen PoD by all applicable safety or uncertainty factors. Typically in EPA risk assessments, a combination of safety or uncertainty factors providing at least a hundredfold (100X) margin of safety is used: 10X to account for interspecies extrapolation and 10X to account for intraspecies variability. Further, as required by FFDCA section 408(b)(2)(C), in evaluating the dietary risks for pesticide chemicals, an additional safety factor of 10X is presumptively applied to protect infants and children, unless reliable data support selection of a different

factor. In implementing FFDCA section 408, EPA also calculates a variant of the RfD referred to as a Population Adjusted Dose (PAD). A PAD is the RfD divided by any portion of the children's safety factor that does not correspond to one of the traditional additional uncertainty/safety factors used in general Agency risk assessment. The reason for calculating PADs is so that other parts of the Agency, which are not governed by FFDCA section 408, can, when evaluating the same or similar substances, easily identify which aspects of a pesticide risk assessment are a function of the particular statutory commands in FFDCA section 408. For acute assessments, the risk is expressed as a percentage of a maximum acceptable dose or the acute PAD (*i.e.*, the acute dose which EPA has concluded will be ''safe''). As discussed below in Unit V.C., dietary exposures greater than 100 percent of the acute PAD are generally cause for concern and would be considered ''unsafe'' within the meaning of FFDCA section 408(b)(2)(B). Throughout this document general references to EPA's calculated safe dose are denoted as an acute PAD, or aPAD, because the relevant point of departure for carbofuran is based on an acute risk endpoint.

2. Acetylcholinesterase Inhibition. Carbofuran is a member of the class of pesticides called *N*-methyl carbamates (NMCs). The primary toxic effect caused by NMCs, including carbofuran, is neurotoxicity resulting from inhibition of the enzyme acetylcholinesterase (AChE). The toxicity profile of these pesticides is characterized by rapid time to onset of effects followed by rapid recovery (minutes to hours). Consistent with its mechanism of action, toxicity data on AChE inhibition from laboratory rats provide the basis for deriving the PoD for carbofuran.

AChE inhibition is a disruption of the normal process in the body by which the nervous system chemically communicates with muscles and glands. Communication between nerve cells and a target cell (*i.e.,* another nerve cell, a muscle fiber, or a gland) is facilitated by the chemical, acetylcholine. When a nerve cell is stimulated it releases acetylcholine into the synapse (or space) between the nerve cell and the target cell. The released acetylcholine binds to receptors in the target cell, stimulating the target cell in turn. As EPA has explained, ''the end result of the stimulation of cholinergic pathway(s) includes, for example, the contraction of smooth (*e.g.,* in the gastrointestinal tract) or skeletal muscle, changes in heart rate or glandular secretion (*e.g.,* sweat glands) or communication between nerve cells in the brain or in the autonomic ganglia of the peripheral nervous system.'' (Ref. 78 at 10).

AChE is an enzyme that breaks down acetylcholine and terminates its stimulating action in the synapse between nerve cells and target cells. When AChE is inhibited, acetylcholine builds up prolonging the stimulation of the target cell. This excessive stimulation potentially results in a broad range of adverse effects on many bodily functions including muscle cramping or paralysis, excessive glandular secretions, or effects on learning, memory, or other behavioral parameters. Depending on the degree of inhibition these effects can be serious, even fatal.

EPA's cholinesterase inhibition policy statement explains EPA's approach to evaluating the risks posed by AChE-inhibiting pesticides such as carbofuran (Ref. 78 at 10). The policy focuses on three types of effects associated with AChE-inhibiting pesticides that may be assessed in animal and human toxicological studies: (1) Physiological and behavioral/functional effects; (2) AChE inhibition in the central and peripheral nervous system; and (3) AChE inhibition in red blood cells and blood plasma. The policy discusses how such data should be integrated in deriving an acceptable dose (RfD/PAD) for a AChE-inhibiting pesticide.

After clinical signs or symptoms, AChE inhibition in the nervous system provides the next most important endpoint for evaluating AChE-inhibiting pesticides. Although AChE inhibition in the nervous system is not itself regarded as a direct adverse effect, it is ''generally accepted as a key component of the mechanism of toxicity leading to adverse cholinergic effects'' (Id. at 25). As such, the policy states that it should be treated as ''direct evidence of potential adverse effects'' and ''data showing this response provide valuable information in assessing potential hazards posed by antiAChE pesticides'' (Id.). Unfortunately, useful data measuring AChE inhibition in the peripheral nervous system tissues has only been relatively rarely captured by standard toxicology testing, particularly for the NMC compounds. For central nervous system effects, however, more recent neurotoxicity studies ''have sought to characterize the time course of inhibition in * * * [the] brain, including brain regions, after acute and 90-day exposures'' (Id. at 27).

AChE inhibition in the blood is one step further removed from the direct harmful consequences of AChE-inhibiting pesticides. According to the policy, inhibition of blood AChEs ''is not an adverse effect, but may indicate a potential for adverse effects on the nervous system'' (Id. at 28). The policy states that ''[a]s a matter of science policy, blood AChE data are considered appropriate surrogate measures of potential effects on peripheral nervous system AChE activity in animals, for central nervous system (''CNS'') AChE activity in animals when CNS data are lacking and for both peripheral and central nervous system AChE in humans'' (Id. at 29). The policy notes that ''there is often a direct relationship between a greater magnitude of exposure [to a AChE-inhibiting pesticide] and an increase in incidence and severity of clinical signs and symptoms as well as blood AChE inhibition'' (Id. at 30). Thus, the policy regards blood AChE data as ''appropriate endpoints for derivation of reference doses or concentrations when considered in a weight-of-the-evidence analysis of the entire database * * *'' (Id. at 29). Between AChE inhibition measured in red blood cell (''RBC'') or blood plasma, the policy states a preference for reliance on RBC AChE measurements because plasma is composed of a mixture of acetylcholinesterase and butyrylcholinesterase, and inhibition of the latter is less clearly tied to inhibition of acetylcholinesterase in the nervous system (Id. at 29, 32).

EPA has relied on a benchmark dose (BMD) approach for deriving the PoD from the available rat toxicity studies. A BMD is a point estimate along a dose-response curve that corresponds to a specific response level. For example, a BMD_{10} represents a 10% change from the background; 10% is often used as a typical value for the response of concern (Ref. 76). Generically, the direction of change from background can be an increase or a decrease depending on the biological parameter and the chemical of interest. In the case of carbofuran, inhibition of AChE is the toxic effect of concern. Following exposure to carbofuran, the normal biological activity of the AChE enzyme is decreased (*i.e.,* the enzyme is inhibited). Thus, when evaluating BMDs for carbofuran, the Agency is interested in a decrease in AChE activity compared to normal activity levels, which are also termed ''background'' levels. Measurements of ''background'' AChE activity levels are usually obtained from animals in experimental studies that are not treated with the pesticide of interest (*i.e.,* ''negative control'' animals).

In addition to the BMD, a confidence limit was also calculated. Confidence limits express the uncertainty in a BMD that may be due to sampling and/or

experimental error. The lower confidence limit on the dose used as the BMD is termed the BMDL, which the Agency uses as the PoD. Use of the BMDL for deriving the PoD rewards better experimental design and procedures that provide more precise estimates of the BMD, resulting in tighter confidence intervals. Use of the BMDL also helps ensure with high confidence (*e.g.,* 95% confidence) that the selected percentage of AChE inhibition is not exceeded. From the PoD, EPA calculates the RfD and aPAD. Specific to carbofuran and the other NMCs, EPA the FIFRA SAP has reviewed and supported the statistical methods used to derive the BMD and BMDLs on multiple occasions (Refs. 34, 35, 36).

In the Agency's BMD analysis for carbofuran, EPA used a response level of 10% brain AChE inhibition; this value represents the estimated dose where AChE is inhibited by 10%, compared to untreated animals. For the last several years EPA has used the 10% value to regulate AChE inhibiting pesticides, including organophosphorous pesticides (OPs) and NMCs. For a variety of toxicological and statistical reasons, EPA chose 10% brain AChE inhibition as the response level for use in BMD calculations. EPA analyses have demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies; is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity across the brain compartment; and is a response level close to the background (Refs. 34, 35).

B. Estimating Human Dietary Exposure Levels

Pursuant to section 408(b) of the FFDCA, EPA has evaluated carbofuran's dietary risks based on ''aggregate exposure'' to carbofuran. By ''aggregate exposure,'' EPA is referring to exposure to carbofuran by multiple pathways of exposure. EPA uses available data and standard analytical methods, together with assumptions designed to be protective of public health, to produce separate estimates of exposure for a highly exposed subgroup of the general population, for each potential pathway and route of exposure. For acute risks, EPA then calculates potential aggregate exposure and risk by using probabalistic [1] techniques to combine distributions of potential exposures in the population for each route or pathway. For dietary analyses, the relevant sources of potential exposure to carbofuran are from the ingestion of residues in food and drinking water. The Agency uses a combination of monitoring data and predictive models to evaluate environmental exposure of humans to carbofuran.

1. Exposure from Food. The level of human exposure to pesticide residues in food is a function of both the pesticide residues in food and the amount of food consumed. Data on the residues of carbofuran in foods are available from a variety of sources. One of the primary sources of data comes from federally-conducted surveys, including the Pesticide Data Program (PDP) conducted by the USDA. Further, market basket surveys, which are typically performed by registrants, can provide additional residue data. These data generally provide a characterization of pesticide residues in or on foods consumed by the U.S. population that closely approximates real world exposures because they are sampled closer to the point of consumption in the chain of commerce than field trial data, which are generated to establish the maximum level of legal residues that could result from maximum permissible use of the pesticide. In certain circumstances, when EPA believes the information will provide more accurate exposure estimates, EPA will rely on field trial data (see below in Unit VI.E.1).

EPA relies on USDA's Continuing Survey of Food Intake by Individuals (CSFII) for information on food consumption by the US population as well as 32 subgroups based on age, gender, ethnicity, and region. The latest CSFII was conducted in 1994–1996 and 1998. The 1998 survey was a special survey required by the FQPA to supplement the number of children survey participants. DEEM–FCID also contains ''recipes'' that convert foods as consumed (*e.g.,* pizza) back into their component raw agricultural commodities (*e.g.,* wheat from flour, or tomatoes from sauce, etc.). This is necessary because residue data are generally gathered on raw agricultural commodities rather than on finished ready-to-eat food. Data on residue values for a particular pesticide and the RfD or PADs for that pesticide are inputs to the DEEM–FCID computer program to estimate exposure and risk.

The DEEM–FCID computer program estimates exposure by combining data on human consumption amounts with residue values in food commodities. DEEM–FCID also compares exposure estimates to appropriate RfD or PAD values to estimate risk. EPA uses DEEM–FCID to estimate exposure for the general U.S. population as well as for 32 subgroups based on age, sex, ethnicity, and region. DEEM–FCID allows EPA to process extensive volumes of data on human consumption amounts and residue levels in making risk estimates. Matching consumption and residue data, as well as managing the thousands of repeated analyses of the consumption database conducted under probabilistic risk assessment techniques, requires the use of a computer.

For carbofuran's assessment, EPA used DEEM–FCID to calculate risk estimates based on a probabilistic distribution. DEEM–FCID combines the full range of residue values for each food with the full range of data on individual consumption amounts to create a distribution of exposure and risk levels. More specifically, DEEM–FCID creates this distribution by calculating an exposure value for each reported day of consumption per person (''person/day'') in CSFII, assuming that all foods potentially bearing the pesticide residue contain such residue at a value selected randomly from the exposure data sets. The exposure amounts for the thousands of person/days in the CSFII are then collected in a frequency distribution. EPA also uses DEEM–FCID to compute a distribution taking into account both the full range of data on consumption levels and the full range of data on potential residue levels in food. Combining consumption and residue levels into a distribution of potential exposures and risk requires use of probabilistic techniques.

The probabilistic technique that DEEM–FCID uses to combine differing levels of consumption and residues involves the following steps:

(1) Identification of any food(s) that could bear the residue in question for each person/day in the CSFII;

(2) Calculation of an exposure level for each of the thousands of person/days in the CSFII database, based on the foods identified in Step #1 by randomly selecting residue values for the foods from the residue database;

(3) Repetition of Step #2 one thousand times for each person/day; and

[1] Probabilistic analysis is used to predict the frequency with which variations of a given event will occur. By taking into account the actual distribution of possible consumption and pesticide residue values, probabilistic analysis for pesticide exposure assessments ''provides more accurate information on the range and probability of possible exposure and their associated risk values'' (Ref. 77). In capsule, a probabilistic pesticide exposure analysis constructs a distribution of potential exposures based on data on consumption patterns and residue levels and provides a ranking of the probability that each potential exposure will occur. People consume differing amounts of the same foods, including none at all, and a food will contain differing amounts of a pesticide residue, including none at all.

(4) Collection of all of the hundreds of thousands of potential exposures estimated in Steps ##2 and 3 in a frequency distribution.

The resulting probabilistic assessment presents a range of exposure/risk estimates.

2. Exposure from water. EPA may use field monitoring data and/or simulation water exposure models to generate pesticide concentration estimates in drinking water. Monitoring and modeling are both important tools for estimating pesticide concentrations in water and can provide different types of information. Monitoring data can provide estimates of pesticide concentrations in water that are representative of the specific agricultural or residential pesticide practices in specific locations, under the environmental conditions associated with a sampling design (*i.e.,* the locations of sampling, the times of the year samples were taken, and the frequency by which samples were collected). Although monitoring data can provide a direct measure of the concentration of a pesticide in water, it does not always provide a reliable basis for estimating spatial and temporal variability in exposures because sampling may not occur in areas with the highest pesticide use, and/or when the pesticides are being used and/or at an appropriate sampling frequency to detect high concentrations of a pesticide that occur over the period of a day to several days.

Because of the limitations in most monitoring studies, EPA's standard approach is to use simulation water exposure models as the primary means to estimate pesticide exposure levels in drinking water. Modeling is a useful tool for characterizing vulnerable sites, and can be used to estimate peak pesticide water concentrations from infrequent, large rain events. EPA's computer models use detailed information on soil properties, crop characteristics, and weather patterns to estimate water concentrations in vulnerable locations where the pesticide could be used according to its label (69 FR 30042, 30058–30065 (May 26, 2004)). These models calculate estimated water concentrations of pesticides using laboratory data that describe how fast the pesticide breaks down to other chemicals and how it moves in the environment at these vulnerable locations. The modeling provides an estimate of pesticide concentrations in ground and surface water. Depending on the modeling algorithm (*e.g.,* surface water modeling scenarios), daily concentrations can be estimated continuously over long periods of time, and for places that are of most interest for any particular pesticide.

EPA relies on models it has developed for estimating pesticide concentrations in both surface water and ground water. Typically EPA uses a two-tiered approach to modeling pesticide concentrations in surface and ground water. If the first tier model suggests that pesticide levels in water may be unacceptably high, a more refined model is used as a second tier assessment. The second tier model for surface water is actually a combination of two models: The Pesticide Root Zone Model (PRZM) and the Exposure Analysis Model System (EXAMS). The second tier model for ground water uses PRZM alone.

A detailed description of the models routinely used for exposure assessment is available from the EPA OPP Water Models Web site: *http://www.epa.gov/oppefed1/models/water/index.htm.* These models provide a means for EPA to estimate daily pesticide concentrations in surface water sources of drinking water (a reservoir) using local soil, site, hydrology, and weather characteristics along with pesticide application and agricultural management practices, and pesticide environmental fate and transport properties. Consistent with the recommendations of the FIFRA SAP, EPA also considers regional percent cropped area factors (PCA) which take into account the potential extent of cropped areas that could be treated with pesticides in a particular area. The PRZM and EXAMS models used by EPA were developed by EPA's Office of Research and Development (ORD), and are used by many international pesticide regulatory agencies to estimate pesticide exposure in surface water. EPA's use of the percent cropped area factors and the Index Reservoir scenario was reviewed and approved by the FIFRA SAP in 1999 and 1998, respectively (Refs. 30, 31).

In modeling potential surface water concentrations, EPA attempts to model areas of the country that are vulnerable to surface water contamination rather than simply model ''typical'' concentrations occurring across the nation. Consequently, EPA models exposures occurring in small, highly agricultural watersheds in different growing areas throughout the country, over a 30-year period. The scenarios are designed to capture residue levels in drinking water from reservoirs with small watersheds with a large percentage of land use in agricultural production. EPA's models take into account that pesticide residues in water fluctuate daily, seasonally, and yearly as a result of the timing of pesticide applications, the vulnerability of the water supply to pesticide loading through runoff, spray drift and/or leaching, and changes in the weather. Concentrations are also affected by the method of application, the location and characteristics of the sites where a pesticide is used, the climate, and the type and degree of pest pressure.

EPA uses the output of daily concentration values from tier two modeling as an input to DEEM–FCID, which combines water concentrations with drinking water consumption information in the daily diet to generate a distribution of exposures from consumption of drinking water contaminated with pesticides. These results are then used to calculate a probabilistic assessment of the aggregate human exposure and risk from residues in food and drinking water.

3. Aggregate Exposure Analyses. Using probabilistic analyses, EPA combines the national food exposures with the exposures derived for individual region and crop-specific drinking water scenarios to derive estimates of aggregate exposure. Although food is distributed nationally, and exposures to pesticide residues are therefore not expected to vary substantially throughout the country, drinking water is locally derived and consumed and there can be significant variations in pesticide levels in local watersheds due to geographic, climatic, and other factors. To be protective of all population subgroups, EPA uses modeled estimates from vulnerable watersheds in calculating aggregate exposure.

EPA's standard acute dietary exposure assessment calculates total dietary exposure over a 24-hour period; that is consumption over 24 hours is summed and no account is taken of the fact that eating and drinking occasions may spread out exposures over a day. This total daily exposure generally provides reasonable estimates of the risks from acute dietary exposures, given the nature of most chemical endpoints. Due to the rapid recovery associated with carbofuran toxicity (AChE inhibition), 24-hour exposure periods may or may not be appropriate. To the extent that a day's eating or drinking occasions leading to high total daily exposure might be found close together in time, or to occur from a single eating event, minimal AChE recovery would occur between eating occasions (*i.e.,* exposure events). In that case, the ''24-hour sum'' approach, which sums eating events over a 24-hour period, would provide reasonable estimates of risk from food

and drinking water. Conversely, to the extent that eating occasions leading to high total daily exposures are widely separated in time (within one day) such that substantial AChE recovery occurs between eating occasions, then the estimated risks under any 24-hour sum approach may be overstated. In that case, a more sophisticated approach—one that accounts for intra-day eating and drinking patterns and the recovery of AChE between exposure events—may be more appropriate. This approach is referred to as the ''Eating Occasions Analysis'' and it takes into account the fact that the toxicological effect of a first dose may be reduced or tempered prior to a second (or subsequent) dose.

Thus, rather than treating a full day's exposure as a one-time ''bolus'' dose, as is typically done in the Agency's assessments, the Eating Occasion analysis uses the actual time of eating or drinking occasion, and amounts consumed as reported by individuals to the USDA CSFII. The actual CSFII-recorded time of each eating event is used to ''separate out'' the exposures due to each eating occasion; in doing so, this ''separation'' allows the Agency to distinguish between each intake event and account for the fact that at least some partial recovery of AChE inhibition attributable to the first (earlier) exposure occurs before the second exposure event. For chemicals for which the toxic effect is rapidly reversible, the time between two (or more) exposure events permits partial to full recovery from the toxic effect from the first exposure and it is this ''partial recovery'' that is specifically accounted for by the Eating Occasion Analysis. More specifically, an estimated ''persisting dose'' from the first exposure event is added to the second exposure event to account for the partial recovery of AChE inhibition that occurs over the time between the first and second exposures. The 'persisting dose' terminology, and this general approach were originally suggested by the FIFRA SAP in the context of assessing AChE inhibition from cumulative exposures to OP pesticides (Ref. 33).

C. Selection of Acute Dietary Exposure Level of Concern

Because probabilistic assessments generally are based on a realistic range of residue values to which the population may be exposed, EPA's starting point for estimating exposure and risk for such aggregate assessments is the 99.9th percentile of the population under evaluation, which represents one person out of every 1000 persons. When using a probabilistic method of estimating acute dietary exposure, EPA typically assumes that, when the 99.9th percentile of acute exposure is equal to or less than the aPAD, the level of concern for acute risk has not been exceeded. By contrast, where the analysis indicates that estimated exposure at the 99.9th percentile exceeds the aPAD, EPA would generally conduct one or more sensitivity analyses to determine the extent to which the estimated exposures at the high-end percentiles may be affected by unusually high food consumption or residue values. To the extent that one or a few values seem to ''drive'' the exposure estimates at the high end of exposure, EPA would consider whether these values are reasonable and should be used as the primary basis for regulatory decision making (Ref. 77).

V. Carbofuran Background and Regulatory History

A. Tolerance Reassessment and Pesticide Reregistration

In July 2006, EPA completed a refined acute probabilistic dietary risk assessment for carbofuran as part of the tolerance reassessment program under section 408(q) of the FFDCA and pesticide reregistration under section 4 of FIFRA. The assessment was conducted using Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM–FCID™, Version 200–2.02), which incorporates consumption data from the United States Department of Agriculture's (USDA's) Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), 1994–1996 and 1998, as well as carbofuran monitoring data from USDA's Pesticide Data Program [2] (PDP), estimated percent crop treated information, and processing/cooking factors, where applicable. The assessment was conducted applying an additional 500-fold safety factor that included a 5X children's safety factor, pursuant to section 408(b)(2)(C). That refined assessment showed acute dietary risks from carbofuran residues in food significantly above EPA's level of concern (Ref. 14). Based in part on the results of that assessment, EPA concluded that carbofuran failed to meet the revised safety standard in FFDCA section 408(b) and the standard for FIFRA reregistration.[3]

The tolerance reassessment and FIFRA reregistration process for carbofuran contained numerous opportunities for public participation. These included public comment periods on the preliminary ecological risk assessment (June–August 2005), the preliminary human health risk assessment (September–November 2005), the revised combined risk assessment (March–May 2006), and the interim Registration Eligibility Document (RED) (August–November 2006). EPA received over 200 comments (plus a letter campaign supporting carbofuran with 2,896 signatories) to the 2006 RED. FMC submitted extensive comments throughout the process (including, but not limited to, a comment of 62 pages plus 13 attachments totaling over 900 pages on August 23, 2005, a letter with 20 attachments on November 11, 2005, 46 pages of comments on January 26, 2006, 78 pages of comments on February 17, 2006, a 15-page letter with 8 attachments on May 22, 2006, over 200 pages on May 24, 2006, and other submissions. Following issuance of the RED in August 2006, FMC stated that they would be submitting new data to refute EPA's ecological and human health risk concerns, as well as EPA's benefits assessments. Twenty-three submissions with studies and analyses were submitted in 2007, all of which EPA reviewed. FMC submitted 175 pages of comments to the proposed tolerance revocations jointly with the NPC, NCGA, NCC, and NSA on 9/29/09. The Agency has also met numerous times with FMC, growers, and other stakeholders regarding carbofuran.

One particular aspect of the risk assessment process that involved substantial public participation opportunities was EPA's review of the human toxicology studies performed with carbofuran. In making a determination on whether these studies met the standards of the Human Research rule, EPA, as required, sought the advice of the HSRB. The HSRB review process includes the opportunity for the public both to submit written comments and to make an oral presentation to the HSRB. FMC gave both written and oral comments at the HSRB meeting, which was held May 2–4, 2006. FMC also submitted written comments on the final HSRB report on the meeting.

[2] USDA's Pesticide Data Program monitors for pesticides in certain foods at the distribution points just before release to supermarkets and grocery stores.

[3] Although not relevant to this proceeding, in addition to determining that use of carbofuran resulted in unacceptable dietary risks, EPA concluded that use of carbofuran did not meet the standard for FIFRA registration based on unacceptable occupational and ecological risks.

B. Draft Notice of Intent to Cancel Carbofuran Registrations

In January 2008, EPA published a draft Notice of Intent to Cancel (NOIC) all carbofuran registrations, based in part on carbofuran's dietary risks. As mandated by FIFRA, EPA solicited comments from the FIFRA Scientific Advisory Panel (SAP) on its draft NOIC.[4] As part of that process, EPA presented its dietary risk assessment of carbofuran to the FIFRA SAP, and requested comment on key issues in the risk assessment: The Agency's approach to selecting the point of departure and the children's safety factor. FMC and the remaining Petitioners participated in this meeting, making substantial presentations to the SAP. As described in the proposal, the Agency believes that the Panel's responses unambiguously support the Agency's approach with regard to carbofuran's hazard identification and hazard characterization (73 FR 44875 (July 31, 2008)). In addition, EPA believes that, on balance, the application of a 4X children's safety factor is consistent with the SAP's advice. Additional detail on the SAP's advice and EPA's responses can be found at Ref. 83.

C. Proposed Revocation of Carbofuran Tolerances

Having considered the comments from the SAP, EPA initiated the process to revoke all carbofuran tolerances, publishing a proposed revocation on July 31, 2008 (73 FR 44,864 (July 31, 2008) (FRL–8378–8)). EPA proposed to revoke all of the existing tolerances for residues of carbofuran on the grounds that aggregate exposure from all uses of carbofuran fails to meet the FFDCA section 408 safety standard (Id). Based on the contribution from food alone, EPA calculated dietary exposures to carbofuran exceed EPA's level of concern for all of the more sensitive subpopulations of infants and children. At the 99.9th percentile, aggregate carbofuran dietary exposure from food and drinking water from contaminated ground water was estimated to range from 1100% of the aPAD for adults, to greater than 10,000% of the aPAD for infants, the population subgroup with the highest estimated dietary exposure (Ref. 12). Similarly, aggregate dietary exposures from food and drinking water from surface water, based on contamination from use on corn in Nebraska, ranged from 340% of the aPAD for adults, to 3,900% aPAD for infants. EPA also determined that, based on actual residue levels measured in food in commerce, individual children consuming typical amounts of a single food item received unsafe levels of carbofuran. For example, based on the level of residues detected on in the food supply, a child between 3–5 years, who consumed ½ cup of cantaloupe, would receive a dose ranging between 180% and 7,200% of the aPAD. Finally, the proposal discussed a number of sensitivity analyses the Agency had calculated in order to further characterize the potential risks to children. Every one of these sensitivity analyses determined that estimated exposures significantly exceeded EPA's level of concern for children.

EPA held a 60-day comment period on the proposed revocation rule. In the proposed rule, EPA made clear that if any person had concerns with EPA's proposed revocation, those concerns must be raised during the comment period to be preserved. Specifically, EPA stated:

> In addition to submitting comments in response to this proposal, you may also submit an objection at the time of the final rule. If you anticipate that you may wish to file objections to the final rule, you must raise those issues in your comments on this proposal. EPA will treat as waived, any issue not originally raised in comments on this proposal. Similarly, if you fail to file an objection to the final rule within the time period specified, you will have waived the right to raise any issues resolved in the final rule. After the specified time, issues resolved in the final rule cannot be raised again in any subsequent proceedings on this rule.

(73 FR at 44865).

D. Petitioners' Comments on the Proposed Rule

The comment period for the proposed rule closed on September 29, 2008. During the comment period, the Petitioners submitted comments challenging particular aspects of EPA's risk assessment. For example, the Petitioners challenged the basis for EPA's 4X children's safety factor, and the method and assumptions on which EPA relied to estimate drinking water concentrations. In addition, the registrant, FMC Corporation, requested that EPA cancel the use on 22 of the crops on which it was registered, including many of the foods posing the highest risks to children. FMC also requested that EPA modify its labels to include a number of additional restrictions intended to mitigate the risks identified in EPA's risk assessment. For example, use was prohibited on much of the Eastern US to protect vulnerable sources of groundwater; use restrictions were imposed in other areas of the country, preventing use within set distances to prevent runoff into sources of surface water drinking water supplies.

On November 7, 2008, the Petitioners submitted additional information as a supplement to their September comments. Specifically, they submitted carbofuran use data that the Petitioners used in preparing its surface water assessments. The information consisted of a spreadsheet that contained all of the data provided to the Water Panel by FMC, and a document that explained the materials, methods, and procedures employed by the Panel to utilize this data.

On December 24, 2008, FMC submitted a petition requesting that EPA stay the effective date of the tolerance revocations, and that EPA consider additional information, including further risk mitigation measure that the registrant intended to implement, as well as additional analyses that the Petitioners' experts were developing.

E. Final Rule Revoking Carbofuran Tolerances

On May 15, 2009, EPA published its final rule, based on a revised risk assessment that addressed the voluntary cancellations and label restrictions submitted by the close of the September 29 comment period. The only food uses that remained registered after the voluntary cancellations were sunflowers, corn, potatoes, and pumpkins. In response to the changes made on the labels, EPA revised its risk assessment to account for the reduced number of crops, the altered geographic restrictions, and the additional risk mitigation measures proposed as part of FMC's comments.

Having considered all comments received by the close of the comment period, and based on its revised analyses, EPA concluded that aggregate exposures from all remaining uses of carbofuran were still unsafe for infants and children, and that revocation of the remaining tolerances was warranted. The final rule explained that, although the recent cancellation of several registered uses reduced the dietary risks to children, EPA's analyses still showed that estimated exposures significantly exceed EPA's level of concern for children. For example, EPA determined that the estimated risks could be as high as 9,400% of the aPAD for infants. A detailed description of the risk assessment supporting the final rule follows.

[4] The draft NOIC was based on all of carbofuran's combined risks—dietary, occupational, and ecological. Because some non-food use registrations remain, EPA anticipates issuing the NOIC subsequent to undertaking the activities required to revoke the carbofuran tolerances to cancel these remaining uses.

1. Toxicity. AChE inhibition in brain and the PNS is the initial adverse biological event which results from exposure to carbofuran, and with sufficient levels of inhibition leads to other effects such as tremors, dizziness, as well as gastrointestinal and cardiovascular effects, including bradycardia (Ref. 15). Thus, AChE inhibition provides the most appropriate effect to use in risk extrapolation for derivation of RfDs and PADs. Protecting against AChE inhibition ensures that the other adverse effects associated with cholinergic toxicity, mentioned above, do not occur.

There are three studies available that compare the effects of carbofuran on eleven-day-old rats (*i.e.*, post-natal day 11 or PND11) rats with those in young adult rats (herein called comparative AChE studies) (Refs. 1, 2, 4, and 66). Two of these studies were submitted by FMC, the registrant, and one was performed by EPA–ORD. An additional study conducted by EPA–ORD involved PND17 rats (Ref. 63). Although it is not possible to directly correlate ages of juvenile rats to humans, PND11 rats are believed to be close in development to newborn humans. PND17 rats are believed to be closer developmentally to human toddlers (Refs. 10, 22, and 23). Other studies in adult rats used in the Agency's analysis included additional data from EPA–ORD (Refs. 54, 62, and 66).

The studies in juvenile rats show a consistent pattern that juvenile rats are more sensitive than adult rats to the effects of carbofuran. These effects include inhibition in AChE in addition to incidence of clinical signs of neurotoxicity such as tremors. This pattern has also been observed for other NMC pesticides, which exhibit the same mechanism of toxicity as carbofuran (Ref. 81). It is not unusual for juvenile rats, or indeed, for infants or young children, to be more sensitive to chemical exposures as metabolic detoxification processes in the young are still developing. Because juvenile rats, called 'pups' herein, are more sensitive than adult rats, data from pups provide the most relevant information for evaluating risk to infants and young children and are thus used to derive the PoD. In addition, typically (and this is the case for carbofuran) young children (ages 0–5 years) tend to be the age groups most exposed to carbofuran because they tend to ingest larger amounts of food and water per their body weight than do teenagers or adults. As such, the focus of EPA's analysis of carbofuran's dietary risk from residues in food and water is on young children (ages 0 to 5 years). Since these age groups experience the highest levels of dietary risk, protecting these groups against the effects of carbofuran will, in turn, also protect other age groups.

The Agency used a meta-analysis to calculate the BMD_{10} and $BMDL_{10}$ for pups and adults; this analysis includes brain data from studies where either adult or juvenile rats or both were exposed to a single oral dose of carbofuran. The Agency used a dose-time-response exponential model where benchmark dose and half-life to recovery can be estimated together. This model and the statistical approach to deriving the BMD_{10} s, $BMDL_{10}$ s, and half-life to recovery have been reviewed and supported by the FIFRA SAP (Refs. 34, 35, and 36). The meta-analysis approach offers the advantage over using single studies by combining information across multiple studies and thus provides a robust PoD.

For AChE-inhibiting pesticides, EPA generally evaluates the effects of the pesticide on both brain and RBC AChE. RBC AChE is used as a surrogate for effects on the PNS because data directly measuring effects on the PNS are difficult to obtain.

Using quality brain AChE data from the three studies (two FMC, one EPA–ORD) conducted with PND11 rats, in combination, provides data to describe both low and high doses. By combining the three studies in PND11 animals together in a meta-analysis, the entire dose-response range is covered. The results of the BMD analysis for PND11 pup brain AChE data provide a BMD_{10} of 0.04 mg/kg/day and $BMDL_{10}$ of 0.03 mg/kg/day—this $BMDL_{10}$ of 0.03 mg/kg/day provides the PoD (Ref. 70).

EPA, however, lacked adequate data on carbofuran's effects on RBC AChE. Two studies required from FMC were rejected as flawed. To account for the lack of data in the PNS and/or a surrogate (*i.e.*, RBC AChE inhibition data) in pups at the low end of the response curve, and for the fact that RBC AChE inhibition appears to be a more sensitive point of departure compared to brain AChE inhibition, EPA determined that, consistent with the statutory mandate, some portion of the statutory default 10X children's safety factor needed to be retained. Because there are some carbofuran data that characterize the toxicity in juveniles, EPA concluded that the weight-of-the-evidence supports reducing the statutory factor of 10X to a value lower than 10X. This results in a children's safety factor that is less than 10 but more than 1.

The modified children's safety factor takes into account the greater sensitivity of the RBC AChE. The preferred approach to comparing the relative sensitivity of brain and RBC AChE inhibition would be to compare the BMD_{10} estimates. However, BMD_{10} estimates from the available RBC AChE inhibition data are not reliable due to lack of data at the low end of the dose response curve. As an alternative approach, EPA used the ratio of brain to RBC AChE inhibition at the BMD_{50}, since there are quality data at or near the 50% response level such that a reliable estimate can be calculated. EPA estimated the RBC BMD_{50} to brain BMD_{50} potency ratio using EPA's data for RBC (the only reliable RBC data in PND11 animals for carbofuran) and all available data in PND11 animals for brain. There is, however, an assumption associated with using the 50% response level—namely that the magnitude of difference between RBC and brain AChE inhibition is constant across dose. In other words, EPA is assuming the RBC and brain AChE dose response curves are parallel. There are currently no data to test this assumption for carbofuran.

Comparing RBC BMD_{50} and brain BMD_{50} AChE inhibition, EPA calculated a BMD_{50} ratio of 4.1X. Accordingly, EPA concluded that a children's safety factor of 4X would be protective of infants and children.

Using the $BMDL_{10}$ of 0.03 mg/kg/day, combined with the default 10X interspecies and intraspecies factors, along with the 4X children's safety factor results in an aPAD = 0.000075 mg/kg/day for infants and children. The aPAD for youths and adults is calculated in the same manner, but EPA does not apply the 4X children's safety factor, resulting in an aPAD of 0.0002 mg/kg/day.

2. Acute Exposures from Food. The estimated acute dietary exposure from carbofuran residues in food alone (*i.e.,* assuming no additional carbofuran exposure from drinking water), is below EPA's level of concern for the U.S. Population and all population subgroups. Children 1 to 2 years of age (78% aPAD) were the most highly exposed population subgroup when food only was included. The major driver of the acute dietary exposure risk (food only) for Children 1 to 2 years is milk, at greater than 90% of the exposure.

3. Acute Exposures from Drinking Water. EPA's analyses show that those individuals-both adults as well as children—who receive their drinking water from vulnerable sources are exposed to levels that exceed EPA's level of concern—in some cases by orders of magnitude. This primarily includes those populations consuming drinking water from ground water from

shallow wells in acidic aquifers overlaid with sandy soils that have had crops treated with carbofuran. It could also include those populations that obtain their drinking water from reservoirs located in small agricultural watersheds, prone to runoff, and predominated by crops that are treated with carbofuran, although there is more uncertainty associated with these exposure estimates.

a. Ground Water. In EPA's revised assessment, ground water concentrations were estimated for all remaining crops on carbofuran labels, and used two new Tier 2 scenarios. Based on a new corn scenario, representative of potentially vulnerable areas in the upper Midwest, EPA estimated 1-in-10-year concentrations for ground water source drinking water of 16 to 1.6×10^{-3} µg/L, for pH 6.5 and 7, respectively. A potato scenario representing use in the Northwest estimated no measurable concentrations of carbofuran in ground water. Other remaining uses were modeled using a Tier 1 ground water model (Screening Concentration in Groundwater) with estimated peak 90-day concentrations of 48–178 µg/L, depending on application rate. Well setback prohibitions of 50 feet were proposed on the September 2008 label for the flowable and granular formulations in select counties in Kentucky (seven counties), Louisiana (one county), Minnesota (one county), and Tennessee (one county). Analysis of the impact of these setbacks for the use on corn indicated that the setbacks would not reduce concentrations significantly at locations where exposure to carbofuran in ground water is of concern because at acid pHs, carbofuran does not degrade sufficiently during the travel time from the application site to the well to substantially reduce the concentration.

Exposure estimates for this assessment are drawn primarily from EPA's modeling. To conduct its modeling, EPA examined readily available data with respect to ground water and soil pH to evaluate the spatial variability of pH. Ground water pH values can span a wide range; this is especially true for shallow ground water systems, where local conditions can greatly affect the quality and characteristics of the water (higher or lower pHs compared to average values). The ground water simulations reflect variability in pH by modeling carbofuran leaching in four different pH conditions (pH 5.25, 6.5, 7.0, and 8.7), representing the range in the Wisconsin aquifer system. The upper and lower bound of pH values that EPA chose for this assessment were measured values from the aquifer, and the remaining two values were chosen to reflect common pH values between the measured values. Based on EPA's assessment, the maximum 1-in-10-year peak carbofuran concentrations in vulnerable ground water for a single application on corn in Wisconsin, at a rate of 1 pound per acre were estimated to range from a low of less than 1 ppb based on a pH of 7 or higher, to a high of 16 ppb, based on a pH of 6.5.

The results of EPA's revised corn modeling, based on a scenario in Wisconsin, are consistent with the results of the PGW study developed by FMC in Maryland in the early 1980s. Using higher use rates than currently permitted, the peak concentration measured in the PGW study was 65 ppb; when scaled to current use rates, the estimated peak concentration was 11 ppb. EPA's modeling is also consistent with a number of other targeted ground water studies conducted in the 1980s showing that high concentrations of carbofuran can occur in vulnerable areas; the results of these studies as well as the PGW study are summarized in References 13 and 67.

While there have been additional ground water monitoring studies that included carbofuran as an analyte since that time, there has been no additional monitoring targeted to carbofuran use in areas where aquifers are vulnerable. However, data compiled in 2002 by EPA's Office of Water show that carbofuran was detected in treated drinking water at a few locations. Based on samples collected from 12,531 ground water supplies in 16 states, carbofuran was found at one public ground water system at a concentration of greater than 7 ppb and in two ground water systems at concentrations greater than 4 ppb (measurements below this limit were not reported). An infant receiving these concentrations would receive doses equivalent to 220% of the aPAD or 130% aPAD, respectively, based on a single 8 ounce serving of water. As this monitoring was not targeted to carbofuran, the likelihood is low that these samples capture peak concentrations. Given the lack of targeted monitoring, EPA has primarily relied on modeling to develop estimates of carbofuran residues in ground water sources of drinking water.

EPA compiled a distribution of estimated carbofuran concentrations in water based on these estimates, which was used to generate probabilistic assessments of the potential exposures from drinking water derived from vulnerable ground water sources. Based on these assessments, estimated exposures ranged between 770% aPAD for adults to 9400% aPAD for infants.

b. Surface Water. For the final rule, EPA conducted additional refined modeling based on the September 2008 label submitted by FMC. The modeling addressed all of the domestic uses that remain registered, and included certain refinements to better understand the impacts of varying pH. EPA also conducted modeling to assess the impact of the proposed spray drift buffer requirements and other spray drift measures included on the September label.

EPA estimated carbofuran concentrations resulting from the use on pumpkins by adjusting the estimated drinking water concentrations (EDWC) from a previous run simulating melons in Missouri; adjustments accounted for differences in application rate and row spacing. Two EDWCs were calculated for pumpkins: One based on a 36-inch row spacing, representing pumpkins for consumption (77.6 ppb); and a second based on a 60-inch row spacing, representing decorative pumpkins (46.6 ppb).

EPA had previously evaluated the corn rootworm rescue treatment at seven representative sites, representing use in states with extensive carbofuran usage at locations more vulnerable than most in each state in areas corn is grown. Using measured rainfall values, and assuming typical rather than maximum use rates, peak concentrations for the corn rescue treatments simulated for Illinois, Iowa, Indiana, Kansas, Minnesota, Nebraska, and Texas ranged from 16.6–36.7 ppb (Ref. 47). Under the revised assessment to account for the September 2008 use restrictions, concentrations for corn, calculated including the proposed spray drift buffers in Kansas and Texas, decreased 5.1% and 4.7%, respectively, from simulations with no buffer from the previous assessment (Ref. 47). In Kansas, the 1-in-10-year peak EDWCs decreased from 33.5 to 31.8 ppb when a 300-foot buffer was added, and in Texas, from 29.9 to 28.5 ppb with the addition of a 66-foot buffer.

For the sunflower use, 12 simulations were performed for sunflowers, 9 in Kansas, and 3 in North Dakota. The North Dakota scenario was used to represent locations where sunflowers are grown that are vulnerable to pesticide movement to surface water while the Kansas scenario represents places that are not particularly vulnerable, based on the limited rainfall and generally well-drained soils (hydrologic group B soils) that are found in that area. Estimated 1-in-10-year concentrations ranged from 11.6 to 32.7

µg/L. When simulating three applications, one at plant and two foliar with a 14-day interval between the two foliar applications and a 66-foot buffer, the 1-in-10-year peak EDWC for North Dakota was 22.4 µg/L. In contrast, the same three applications in Kansas with a 14-day interval between the foliar applications and a 300-foot buffer produced a 1-in-10-year peak EDWC of 20.5 µg/L. The 1-in-10-year peak EDWCs, assuming that carbofuran is applied only at plant, were 14.0 and 16.0 µg/L in Kansas and North Dakota respectively. EPA also evaluated the impact of pH on carbofuran concentrations for sunflowers, resulting in a 10% decrease in 1-in-10-year peak concentrations assuming high pH in the reservoir. Spray drift buffers of 66 and 300 feet decreased concentrations 4.7 and 5.1% for corn and 10.0% and 16.0% for sunflowers, respectively, in comparison to previous labels that had no spray drift buffer requirements. Additional details on these assessments can be found at Reference 84.

These predicted carbofuran water concentrations are similar or lower than the peak concentrations reported in the United States Geological Survey-National Ambient Water Quality Survey (USGS–NAWQA) monitoring data. In addition, these data, which represent concentrations in surface water prior to any treatment by a public drinking water system, are consistent with the results of the 2002 data on finished water compiled by EPA's Office of Water. Based on samples collected from 1,394 surface water source drinking water supplies in 16 states, carbofuran was found at no public drinking water supply systems at concentrations exceeding maximum contaminant level (MCL) of 40 ppb. However, carbofuran was found at one surface water public water system in finished (*i.e.,* post-treatment) water at concentrations greater than 4 ppb (measurements below this limit were not reported). Sampling is costly and is conducted typically four times a year or less at any single drinking water facility. The overall likelihood of collecting samples that capture peak exposure events is, therefore, low. For chemicals with acute risks of concern, such as carbofuran, higher concentrations and resulting risk is primarily associated with these peak events, which are not likely to be captured in monitoring unless the sampling rate is very high.

There are few surface water field-scale studies targeted to carbofuran use that could be compared with modeling results. Most of these studies were conducted in fields that contain tile drains, which is a common practice throughout midwestern states to increase drainage in agricultural fields (Ref. 13). Drains are common in the upper Mississippi river basin (Illinois, Iowa, and the southern part of Minnesota), and the northern part of the Ohio River Basin (Indiana, Ohio, and Michigan) (Ref. 58). Although it is not possible to directly correlate the concentrations found in most of the studies with drinking water concentrations, these studies confirm that carbofuran use under such circumstances can contaminate surface water, as tile drains have been identified as a conduit to transport water and contaminants from the field to surface waters.

EPA conducted dietary exposure analyses based on the modeling scenarios for the proposed September 2008 label. Exposures from all modeled scenarios substantially exceeded EPA's level of concern (Ref. 12). For example, a Kansas sunflower scenario, assuming two foliar applications at a typical 1 lb active ingredient (a.i.) per acre use rate, applied at 14-day intervals, estimated a 1-in-10-year peak carbofuran water concentration of 11.6 ppb. Exposures at the 99.9th percentile based on this modeled distribution ranged from 160% of the aPAD for youths 13 to 19 years, to greater than 2,000% of the aPAD for infants. This scenario is intended to be representative of sites that are less vulnerable than most on which sunflowers could be grown. By contrast, exposure estimates from a comparable North Dakota sunflower scenario, intended to represent more vulnerable sites, estimated a 1-in-10-year peak concentration of 22.4 ppb. These concentrations would result in estimated exposures ranging between 450% aPAD for youths 13 to 19 years, to 5,500% aPAD for infants. Similarly, exposures based on a Washington surface water potato scenario, and using a 3 lb a.i. acre rate, ranged from 230% of the aPAD for children 6 to 12 years to 890% of the aPAD for infants, with a 1-in-10-year peak carbofuran concentration of 7.2 ppb. Although other crop scenarios resulted in higher exposures, estimates for these two crops are presented here, as they are major crops on which a large percentage of carbofuran use occurs. For example, one of EPA's refined exposure analyses is based on a Nebraska corn rootworm ''rescue treatment'' scenario, and assumes a single aerial application at a typical rate of 1 lb a.i. per acre. The full distribution of daily concentrations over a 30-year period was used in the probabilistic dietary risk assessment. The 1-in-10-year peak concentration of the distribution of values for the Nebraska corn rescue treatment was 22.3 ppb. Estimated dietary exposures based on these concentrations ratned from 340% of the aPAD for adults to 3900% of the aPAD for infants. More details on these assessments, as well as the assessments EPA conducted for other crop scenarios, can be found in References 12, 47, and 67.

4. Aggregate (food and water) Exposures. EPA conducted a number of probabilistic analyses to combine the national food exposures with the exposures from the individual region and crop-specific drinking water scenarios. Although food is distributed nationally, and residue values are therefore not expected to vary substantially throughout the country, drinking water is locally derived and consumed and concentrations of pesticides in source water fluctuate over time and location for a variety of reasons. Consequently, EPA conducted several estimates of aggregate dietary risks by combining exposures from food and drinking water. These estimates showed that, because drinking water exposures from any of the crops on the label exceed safe levels, aggregate exposures from food and water are unsafe. Although EPA's assessments showed that, based on the Idaho potato scenarios, exposures from ground water from use on potatoes would be safe, surface water exposures from carbofuran use on potatoes far exceed the safety standard. More details on the individual aggregate assessments presented below, as well as the assessments EPA conducted for other regional and crop scenarios, can be found in References 12 and 13.

The results of aggregate exposures from food and from drinking water derived from ground water in extremely vulnerable areas (*i.e.,* from shallow wells associated with sandy soils and acidic aquifers, such as are found in Wisconsin), ranged from 780% of the aPAD for adults, to 9,400% of the aPAD for infants.

The results of aggregate exposure from food and water derived from one of the least conservative surface water scenarios—Kansas sunflower, with two foliar applications—ranged from 190% of the aPAD for adults to 2,100% aPAD for infants. These estimates reflect the risks only for those people in watersheds with characteristics similar to that used in the scenario, and assuming that water treatment does not remove carbofuran. The estimated water concentrations are comparable to the maximum peak concentrations reported in monitoring studies that were not designed to detect peak, daily

concentrations of carbofuran in vulnerable locations.

More details on this assessment, as well as the assessments EPA conducted for other crop scenarios, can be found in References 12, 47, and 67. For example, in the proposed rule, EPA presented the results from aggregate exposures resulting from a Nebraska surface water scenario based on a Nebraska corn rootworm ''rescue treatment.'' Estimated exposures from that scenario ranged from 330% of the aPAD for youths 13 to 19 years to 3,900% of the aPAD for infants.

As noted previously, EPA's food and water exposure assessments typically sum exposures over a 24-hour period, and EPA used this 24-hour total in developing its acute dietary risk assessment for carbofuran. Because of the rapid nature of carbofuran toxicity and recovery, EPA conducted an analysis using information about dietary exposure, timing of exposure within a day, and half-life of AChE inhibition from rats to estimate risk to carbofuran at durations less than 24 hours. Specifically, EPA has evaluated individual eating and drinking occasions and used the AChE half-life to recovery information (herein called half-life information) to estimate the residual effects from carbofuran from previous exposures within the day. The carbofuran analyses are described in the 2009 aggregate (dietary) memo (Ref. 55).

Using the two FMC time course studies in rat pups, EPA calculated half-lives for recovery of 186 and 426 minutes (Refs. 24 and 25). The two values provide an indication that half-lives to recovery can vary among juvenile rats. By extension, children are expected to vary in their ability to recover from AChE inhibition where longer recoveries would be associated with a potentially higher ''persisting dose'' (as described below).

This analysis had little impact on the exposures from food alone. However, accounting for drinking water consumption throughout the day and using the half-life to recovery information, risk is reduced by approximately 2–3X. Consequently, risk estimates for which food and drinking water are jointly considered and incorporated (*i.e.,* Food + Drinking Water) are also reduced considerably—by a factor of two or more in some cases—compared to baseline. But even though the risk estimates from aggregate exposure are reduced, they nonetheless still substantially exceed EPA's level of concern for infants and children. Using drinking water derived from the surface water from the Idaho potato surface water scenario, which estimated one of the lowest exposure distributions, aggregate exposures at the 99.9th percentile ranged from 328% of the aPAD under the scenario for which infants rapidly metabolize carbofuran (*e.g.,* 186 minute half-life), to a high of 473% of the aPAD under the scenario for which infants metabolize carbofuran more slowly, (*e.g.,* scenarios in which a 426 minute half life is assumed).

Moreover, even accounting for the estimated decreased risk from accounting for carbofuran's rapid reversibility, the Agency remains concerned about the risks from single eating or drinking events, as illustrated in the following example, based on an actual food consumption diary from the CSFII survey. A 4-month old male non-nursing infant weighing 10 kg is reported to have consumed a total of 1,070 milliters (ml) of indirect water over eight different occasions during the day. The first eating occasion occurred at 6:30 a.m., when this 4 month old consumed 8 fluid ounces of formula prepared from powder. The FCID food recipes indicate that this particular food item consists of approximately 87.7% water, and therefore, 8 ounces of formula contains approximately 214 ml (or grams) of indirect water; with the powder (various nutrients, dairy, soy, oils, etc.) accounting for the remaining 12.3%. This infant also reportedly consumed a full 8-ounce bottle of formula at 12 p.m., 4 p.m., and 8 p.m. that day. The food diary also indicates that the infant consumed about 1 tablespoon of water (14.8 ml) added to prepare rice cereal at 10 a.m., about 2 ounces of water (59.3 ml) added to pear juice at 11 a.m., another ½ tsp of water (2.5 ml) to prepare more rice cereal at 8:30 p.m.; and finally, he consumed another 4 ounces of formula (107 ml) at 9:30 p.m.

The infant's total daily water intake (1,070 ml, or approximately 107 ml/kg/day) is not overly conservative, and represents substantially less than the 90th percentile value from CSFII on a ml water/kg bodyweight (ml/kg/bw) basis. As noted, carbofuran has been detected in finished water at concentrations of 4 ppb. For this 10 kg body weight infant, an 8-ounce bottle of formula prepared from water containing carbofuran at 4 ppb leads to drinking water exposures of 0.0856 micrograms of active ingredient/kilogram of bodyweight (µg ai/kg bw), or 114% of the aPAD. Based on the total daily water intake of 1,070 ml/day (no reversibility), total daily exposures from water at 4 ppb concentration would amount to 0.4158 µg ai/kg bw, or 555% of the aPAD; this is the amount that would be used for this person-day in the Total Daily Approach.

Peak inhibition occurs following each occasion on which the infant consumed 8 fluid ounces of formula (6 a.m., 12 p.m., 4 p.m. and 8 p.m.); however, the maximum persisting dose occurs following the 9:30 p.m. eating occasion, based on a 186-minute half-life parameter. This produces a maximum persisting dose of 0.1457 µg ai/kg bw, or about 30% of the total daily exposure of 0.4158 µg ai/kg bw derived above, or expressed as a fraction of the level of concern, the maximum persisting dose amounts to about 194% of the aPAD (or 30% of 554%). Note that with drinking water concentration at 4 ppb, an infant consuming one 8 oz bottle of formula—prepared from powder and tap water containing carbofuran at 4 ppb will obtain exposures of approximately 114% of aPAD. Since many infants consume the equivalent of this amount on a single eating occasion, accounting for reversibility over multiple occasions is not essential to ascertain that infants quite likely have obtained drinking water exposures to carbofuran exceeding the level of concern based on drinking water concentrations found in public drinking water supplies.

In this regard, it is important to note EPA's Eating Occasion Analyses underestimate exposures to the extent that they do not take into account carry-over effects from previous days, and because drinking water pesticide concentrations are randomly picked from the entire 30-year distribution. As discussed previously, DEEM-FCID [FN(TM)] is a single day dietary exposure model, and the DEEM-based Eating Occasion Analysis accounts for reversibility within each simulated person-day. All of the empirical data regarding time and amounts consumed (and corresponding exposures based on the corresponding residues) from the CSFII survey are used, along with the half-life to assess an equivalent persisting dose that produced the peak inhibition expected over the course of that day. This is a reasonable assumption for food alone; since the time between exposure events across 2 days is relatively high (compared to the half-life)—most children (≤9 months) tend to sleep through the night—and the time between dinner and breakfast the following morning is long enough it is reasonable to ''ignore'' persisting effects from the previous day. A single day exposure model will underestimate the persisting effects from drinking water exposures (formula) among infants, and newborns in particular (<3 months), since newborns tend to wake up every 2 to 4 hours to feed. Any carry over

effects may be important, especially if exposures from the previous day are relatively high, since the time between the last feeding (formula) of the day and the first feeding of the subsequent day is short. A single day model also does not account for the effect of seasonal variations in drinking water concentrations, which will make this effect more pronounced during the high use season (*i.e.,* the time of year when drinking water concentrations are high). Based on these analyses, the Agency concludes that the current exposure assessment methods used in the carbofuran dietary assessment provide realistic and high confidence estimates of risk to carbofuran exposure through food and water.

F. Response to FMC Comments on the Final Rule

FMC's comments raised a range of issues. Those issues are not summarized here because FMC basically refilled many of its comments as objections without modifying them in response to EPA's decision in the final rule. In addition, FMA submitted a an alternate risk analysis purporting to show that aggregate carbofuran exposures to children would be safe. However, FMC failed to provide the data and details of that assessment to the Agency. They also failed to provide several critical components that served to support key inputs into that assessment; and for several of these, EPA was unable to replicate the claimed results based on the information contained in the comments. In the absence of such critical components, the Agency was unable to accept the validity or utility of the analyses, let alone rely on the results.

Nonetheless, based on the summary descriptions provided in the registrant's comments, EPA concluded that the risk analyses contained a critical flaw. The commenters' determination of safety rests on the presumption that under real world conditions, events will always occur exactly as hypothesized by the multiple assumptions in their assessment. For example, the comments assumed, despite all available evidence to the contrary, that children would not be appreciably more sensitive to carbofuran's effects than adults. They assumed that carbofuran's effects will be highly reversible, and that children will be uniformly sensitive, such that the effects will be adequately accounted for by the assumption of a 150-minute half-life, despite the fact that children are not uniformly sensitive. They further assumed that there would be no carry over effect from the preceding day's exposures for infants. They assumed that the cancellation of use on alfalfa would reduce carbofuran residues in milk by over 70%, even though many cows' diet consists primarily of corn. They assumed that residues would decrease between 19% and 23% as a result of the buffer requirements on the September 2008 label, even though the label does not require the use of all of the recommended ''best management practices'' (*e.g.,* no requirements regarding swath displacement), and applicators do not universally use such practices in the absence of any requirement. They assumed that average ground water pH adequately characterizes the temporal and spatial heterogeneity common in most areas, despite the available evidence to the contrary. Finally, they assumed that the percent of the crop treated in any watershed would never exceed 5%, despite varying pest pressures, consultant recommendations, and individual grower decisions. Leaving aside that EPA believes most, if not all of these assumptions are not supported by the available evidence described throughout the final rule, the probability of all these assumptions always simultaneously holding true under real world conditions is unreasonably low, and certainly does not approach the degree of certainty necessary for EPA to conclude that children's exposures will be safe.

Determining whether residues will be safe for U.S. children is not a theoretical paper exercise; it cannot suffice to hypothesize a unique set of circumstances that make residues ''fit in the box.'' There must be a reasonable certainty that under the variability that exists under real world conditions, exposures will be ''safe.'' EPA's assessments incorporate a certain degree of conservatism precisely to account for the fact that assumptions must be made that may not prove accurate. This consideration is highly relevant for carbofuran, because as refined as EPA's assessments are, areas of uncertainty remain with regard to carbofuran's risk potential. For example, a recent epidemiological study reported that 45% of maternal and cord blood samples in a cohort of New York City residents of Northern Manhattan and the South Bronx between 2000 and 2004, contained low, but measurable residues of carbofuran (Ref. 88). The Agency is currently unable to account for the source of such sustained exposures at this frequency.

A further consideration is that the risks of concern are acute risks to children. For acute risks, the higher values in a probabilistic risk assessment are often driven by relatively high values in a few exposures rather than relatively lower values in a greater number of exposures. This is due to the fact that an acute assessment looks at a narrow window of exposure where there are unlikely to be a great variety of consumption sources. Thus, to the extent that there is a high exposure it will be more likely due to a high residue value in a single consumption event. Additionally worrisome in this regard is that carbofuran is a highly potent (*i.e.,* has a very steep dose-response curve), acute toxicant, and therefore any aPAD exceedances are more likely to have greater significance in terms of the potential likelihood of actual harm. For all of these reasons, EPA determined that the existing carbofuran tolerances did not meet the FFDCA safety standard, and should therefore be revoked.

VI. Response to Objections and Requests for Hearing

A. Overview

Petitioners raised several objections that correspond to four basic categories of issues. The first category of objections and hearing requests relates to challenges to EPA's selection of the appropriate children's safety factor. In this category of issues, they raise primarily two claims: (1) That EPA's scientific basis for retaining a 4X safety factor is flawed, and (2) the statistical calculations supporting the 4X safety factor are flawed, and based on faulty assumptions. The second category of issues relate to the manner in which EPA conducted its assessment of the exposure from carbofuran through drinking water sources. In this regard, all of their objections fall within three basic categories of issues: (1) EPA should have accounted for a more realistic percent of the crop treated (PCT) in its surface water modeling; (2) EPA's ground water concentration estimates are not based on the best available data, but on obsolete data and overly conservative assumptions; and (3) FMC's new label restrictions and revised terms of registration will ensure that drinking water concentrations will not exceed 1.1 ppb. The third category of issues relates to the manner in which EPA conducted its dietary risk assessment. Under this category, the objections and hearing requests raise four primary issues: (1) Petitioners challenge the way in which EPA's risk assessments accounted for individuals to recover from the effects of carbofuran between exposures; (2) EPA should have relied on the carbofuran human study and therefore use of the default 10X interspecies factor is inconsistent with

the ''best available data; (3) the import tolerances by themselves are safe and EPA should have retained them even if EPA believed tolerances associated with the domestic uses were unsafe; and (4) Petitioners claim that the combined food and water exposures are safe, based on FMC's drinking water estimates of a 1.1 ppb maximum concentration, which are guaranteed by new label restrictions submitted as part of objections. Finally, Petitioners raise one legal objection unaccompanied by a hearing request. They argue that EPA lacks authority to limit issues and supporting information that can be raised in objections and hearing to those raised in earlier comments.

EPA denies each of the Petitioners' objections as well as their hearing requests. In the first instance, EPA denies Petitioners' objections and their hearing requests because the objections are inextricably intertwined with proposed changes to carbofuran's FIFRA registration that were not submitted until after publication of the final tolerance revocation rule. Objections to EPA's decision based on FIFRA registration amendments proposed after EPA's decision are irrelevant, and thus immaterial, to a challenge to EPA's decision (See Unit VI.C.). Secondly, an individual analysis of Petitioners' objections and hearing requests leads to the same conclusion for the reasons summarized below.

The Petitioners' hearing requests fail to meet the statutory and regulatory requirements for holding a hearing. In most cases, EPA has denied the request on the grounds that the objection is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation. In particular, many claims are immaterial because they largely restate the claims in their combined comments on EPA's proposed rule without challenging the substance or even responding to EPA's explanations for the reasons that EPA declined to adopt the approaches or otherwise make the revisions suggested by the Petitioners in their comments. These claims are irrelevant to the determinations reached in the final rule. In several instances, EPA concluded that Petitioners evidentiary proffer was inadequate, because the data and information submitted, even if accurate, would be insufficient to justify the factual determination urged, or to resolve one or more of the issues in their favor. Further, in many cases, the evidence submitted constituted mere allegations and general denials and contentions, which EPA regulations expressly provide to be insufficient to justify a hearing. In addition, many of Petitioners' claims do not present genuine and substantial issues of fact and/or are immaterial to the relief requested.

On the merits, the majority of Petitioners' objections are denied for substantially the same reasons given in EPA's final rule and response to comments. As noted, many of Petitioners' objections are simply their recycled comments which do not address the conclusions reached by EPA in the final rule. To the extent a response is even needed to such a stale claim, it is provided in the final rule and the response to comments.

The remainder of this Unit is organized in the following manner. Unit VI.B describes in greater detail the requirements pertaining to when it is appropriate to grant a hearing request. In Unit VI.C, EPA generally denies all of Petitioners' objections and hearing requests. Unit VI.D provides EPA's response to the Petitioners legal objection that EPA lacks the legal authority to limit the issues and supporting information that can be raised in an objection and hearing to those raised in comments on the proposed rule. Units VI. G and I provide Petitioners' claims regarding EPA's risk assessment. EPA's conclusions on the hearing requests and objections are summarized in Unit VI.K.

EPA has adopted a 4-part format in Units VI.E through I. for explaining its ruling on each of the subissues EPA identified in the objections. First, the Petitioners' claim and any arguments or evidence tendered to support that claim are described. Second, background information on the claim is provided including whether and how the claim was presented in Petitioners' comments and, if it was presented, EPA's reasons for denying the claim in its final rule and response to comments. Third, EPA explains its reasons for denying a hearing on that claim. Finally, EPA explains its reasons for denying the claim on the merits.

B. The Standard for Granting an Evidentiary Hearing

EPA has established regulations governing objections to tolerance rulemakings and tolerance petition denials and requests for hearings on those objections. (40 CFR Part 178; 55 FR 50291 (December 5, 1990)). Those regulations prescribe both the form and content of hearing requests and the standard under which EPA is to evaluate requests for an evidentiary hearing.

As to the form and content of a hearing request, the regulations specify that a hearing request must include: (1) A statement of the factual issues on which a hearing is requested and the requestor's contentions on those issues; (2) a copy of any report, article, or other written document ''upon which the objector relies to justify an evidentiary hearing;'' and (3) a summary of any other evidence relied upon to justify a hearing. (40 CFR 178.27).

The standard for granting a hearing request is set forth in section 178.32. That section provides that a hearing will be granted if EPA determines that the ''material submitted'' shows all of the following:

> (1) There is a genuine and substantial issue of fact for resolution at a hearing. An evidentiary hearing will not be granted on issues of policy or law.
>
> (2) There is a reasonable possibility that available evidence identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor, taking into account uncontested claims or facts to the contrary. An evidentiary hearing will not be granted on the basis of mere allegations, denials, or general descriptions of positions and contentions, nor if the Administrator concludes that the data and information submitted, even if accurate, would be insufficient to justify the factual determination urged.
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> (3) Resolution of the factual issue(s) in the manner sought by the person requesting the hearing would be adequate to justify the action requested. An evidentiary hearing will not be granted on factual issues that are not determinative with respect to the action requested. For example, a hearing will not be granted if the Administrator concludes that the action would be the same even if the factual issue were resolved in the manner sought.
>
> (40 CFR 178.32(b)).

This provision essentially imposes four requirements upon a hearing requestor. First, the requestor must show it is raising a question of fact, not one of law or policy. Hearings are for resolving factual issues, not for debating law or policy questions. Second, the requestor must demonstrate that there is a genuine dispute as to the issue of fact. If the facts are undisputed or the record is clear that no genuine dispute exists, there is no need for a hearing. Third, the requestor must show that the disputed factual question is material—*i.e.,* that it is outcome determinative with regard to the relief requested in the objections. Finally, the requestor must make a sufficient evidentiary proffer to demonstrate that there is a reasonable possibility that the issue could be resolved in favor of the requestor. Hearings are for the purpose of providing objectors with an opportunity to present evidence supporting their objections as the regulation states, hearings will not be granted on the basis of ''mere allegations, denials, or general

descriptions of positions or contentions.'' (40 CFR 178.32(b)(2)).

EPA's hearing request requirements are based heavily on FDA regulations establishing similar requirements for hearing requests filed under other provisions of the FFDCA (53 FR 41126, 41129 (October 19, 1988)). FDA pioneered the use of summary judgment-type procedures to limit hearings to disputed material factual issues and thereby conserve agency resources. FDA's use of such procedures was upheld by the Supreme Court in 1972, (*Weinberger* v. *Hynson, Westcott & Dunning, Inc.,* 412 U.S. 609 (1973)), and, in 1975, FDA promulgated generic regulations establishing the standard for evaluating hearing requests (40 FR 22950 (May 27, 1975)). It is these regulations upon which EPA relied in promulgating its hearing regulations in 1990.

Unlike EPA, FDA has had numerous occasions to apply its regulations on hearing requests. FDA's summary of the thrust of its regulations, which has been repeatedly published in the **Federal Register** in orders ruling on hearing requests over the last 24 years, is instructive on the proper interpretation of the regulatory requirements. That summary states:

> A party seeking a hearing is required to meet a threshold burden of tendering evidence suggesting the need for a hearing.' [] An allegation that a hearing is necessary to sharpen the issues' or fully develop the facts' does not meet this test. If a hearing request fails to identify any evidence that would be the subject of a hearing, there is no point in holding one.
>
> A hearing request must not only contain evidence, but that evidence should raise a material issue of fact concerning which a meaningful hearing might be held. [] FDA need not grant a hearing in each case where an objection submits additional information or posits a novel interpretation of existing information. [] Stated another way, a hearing is justified only if the objections are made in good faith and if they ''draw in question in a material way the underpinnings of the regulation at issue.'' Finally, courts have uniformly recognized that a hearing need not be held to resolve questions of law or policy

(49 FR 6672, 6673 (February 22, 1984); 72 FR 39557, 39558 (July 19, 2007) (citations omitted)).

EPA has been guided by FDA's application of its regulations in this proceeding. Congress confirmed EPA's authority to use summary judgment-type procedures with hearing requests when it amended FFDCA section 408 in 1996. Although the statute had been silent on this issue previously, the FQPA added language specifying that when a hearing is requested, EPA ''shall * * * hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections'' (21 U.S.C. 346a(g)(2)(B)). This language grants EPA broad discretion to determine whether a hearing is ''necessary to receive factual evidence'' to objections (H.R. Rep. No. 104–669, at 49 (1996)).

C. General Denial of Objections and Hearing Requests

Petitioners' objections and hearing requests are denied in their entirety as irrelevant, and therefore immaterial, to EPA's determination in the May 15, 2009 final rule that the carbofuran tolerances were unsafe and could not be sustained under FFDCA section 408. In that final rule, EPA assessed the risks from carbofuran based on existing uses of carbofuran, as modified by all use restrictions proposed by FMC. EPA concluded that the carbofuran tolerances substantially exceeded the FFDCA safety standard, particularly as to infants and children.

Petitioners' objections and hearing requests as to that final rule disclose on their face their irrelevance to the conclusions reached in the May 15, 2009 final rule. As Petitioners summarize their objections on the first page of their submission:

> Petitioners disagree that the carbofuran tolerances are unsafe and argue that the available scientific data show that there is a reasonable certainty of no harm to human health from the continued use of carbofuran for certain specific uses and related tolerances *under the terms for reregistration proposed by Petitioners.*

(Objections at 1) (footnote omitted) (emphasis added). As Petitioners' footnote to this sentence reveals, however, the proposed terms for FIFRA reregistration referenced by Petitioners include significant terms submitted to EPA on June 29, 2009, 44 days after publication of the final rule revoking carbofuran's FFDCA tolerances. In fact, the body of Petitioners' objections show that FMC's June 29, 2009 proposed FIFRA registration amendments are inextricably intertwined with the claims made in the objections. Thus, Petitioners are actually not objecting to the conclusions in EPA's final rule; rather, they are suggesting that EPA might reach a different result in a different factual scenario.

Objections, however, must be directed ''with particularity [at] the provisions of the regulation or order deemed objectionable.'' 21 U.S.C. 346a(g)(2). The key here is that a party must file particularized objections to—that is, identify some type of error in—a specific regulatory decision. In no sense, however, can it be claimed that EPA erred, or that there is something objectionable, in its May 15, 2009 file rule because EPA did not consider a proposed revision to the terms of the carbofuran registration that had not yet been made. EPA need not shoot at a moving target, much less a target that is not in existence. Therefore, Petitioners' objections are irrelevant, and thus immaterial, to the May 15, 2009 final rule; they are based on hypothetical terms of carbofuran use not before the Agency as it made its determination in that final rule.

Moreover, it is not as if Petitioners' proposed terms for carbofuran use are simple, straightforward use deletions that could be immediately effectuated. While such a proposal is still irrelevant as a challenge to a prior EPA determination, such a proposal might lead EPA to expeditiously modify its action. Rather, Petitioners have proposed an unprecedented scheme involving FMC playing a role as a middleman between EPA and growers to ensure that carbofuran use in no one area exceeds a certain percentage of the cropped area. FMC has properly filed proposed amendments to its FIFRA registration, which would incorporate these new restrictions on carbofuran use and EPA will review these proposals consistent with the substantive and procedural requirements of FIFRA. At such time as these new terms of registration are determined by EPA to meet the standard for registration, and not before, would it be appropriate for EPA to consider whether the tolerance revoked by the May 15, 2009 rule should be re-established.

Finally, Petitioners argue that it can raise its proposed terms of carbofuran use because EPA cannot limit them from putting forward new issues in a hearing. As explained below, EPA believes Petitioners have misconstrued the law on this point. However, even assuming for the sake of argument that Petitioners are correct that new issues can be raised at a hearing on objections, Petitioners admit that any newly raised issues must meet the standard of relevance. As explained above, however, objections based on terms or FIFRA registration proposed after EPA's final rule are irrelevant to the correctness of EPA's determination in that final rule.

EPA has nonetheless evaluated each of Petitioners' objections and hearing requests and determined that there are alternate grounds for denying them. (See Units VI.E through I). EPA has undertaken this analysis for all of the objections despite the fact that it is not at all clear that those of Petitioners'

claims which appear to be unrelated to FMC's recently proposed registration amendments would either individually or collectively change EPA's safety determination for the carbofuran tolerances given the relatively high level of risk estimated for the carbofuran tolerances in the final revocation rule. Petitioners have certainly not provided any road map as to how a safety finding could be made absent FMC's recently-proposed registration amendments. The failure to make such a showing is further justification for EPA's denial of Petitioners' objections and hearing requests.

D. Response to Petitioners' Objection That EPA Lacks the Authority To Limit the Issues That May Be Raised in Objections and Hearing Requests

1. Response to Legal Issue. Petitioners claim that EPA lacks the authority to restrict the issues that may be raised as part of their objections. Specifically, they challenge EPA's interpretation that the failure to raise issues or provide information during the comment period on the proposed rule bars consideration of such issues or evidence as part of submitted objections or hearings. Petitioners make two arguments in support of this contention: (1) That neither FFDCA section 408(g) on its face nor EPA's regulations implementing FFDCA section 408(g) limit the issues that can be raised in objections, or in any hearing; and (2) that even though the rulemaking phase is governed by 553 of the Administrative Procedure Act (APA), the hearing must be held in accordance with APA sections 556 and 557, which requires that the ''exclusive record for decision must consist of testimony and exhibits received at the hearing, as well as other papers filed in the hearing proceeding'' (Obj at 64). On this basis, the Petitioners conclude that all of the cases cited in the Final Rule requiring parties to raise all issues and information on which they intend to rely in subsequent proceedings are inapplicable.

These arguments are premised on several fundamental misconstructions of the FFDCA section 408 and the APA. None of the cases they cite address the specific question of whether and how the requirements of section 553 of the APA apply to FFDCA section 408. And for many of these cases, Petitioners misquote the cases, misinterpret the holdings, or misconstrue language taken out of context.

Petitioners' first argument, that neither section 408(g) nor EPA's regulations limit the issues that can be raised in objections or in any hearing, is incorrect and misses the point. As discussed at length in the Final Rule, the provisions of 408(g) are not to be viewed in isolation, but as part of a coherent statutory structure inextricably linked to the FFDCA's informal rulemaking procedures and section 553 of the APA. Petitioners concede that FFDCA section 408 establishes an informal rulemaking process (Obj at 62–63). As an informal rulemaking, the process is governed by section 553 of the APA and the case law interpreting these requirements, except to the extent that section 408 provides otherwise.[5] In this regard, it is well established that the failure to raise factual or legal issues during the comment period of a rulemaking constitutes waiver of the issues in further proceedings. *E.g., Forest Guardians* v. *U.S. Forest Service,* 495 F.3d 1162, 1170–1172 (10th Cir. 2007) (Claim held waived where commenters ''failed to present its claims in sufficient detail to allow the agency to rectify the alleged violation''); *Nuclear Energy Institute* v. *EPA,* 373 F.3d 1251, 1290–1291 (DC Cir. 2004) (''To preserve a legal or factual argument, we require its proponent to have given the agency a 'fair opportunity' to entertain it in the administrative forum before raising it in the judicial forum.'') *Native Ecosystems Council* v. *Dombeck,* 304 F.3d 886, 889–900 (9th Cir. 2002) (Purpose of requirement that issues not presented at administrative level are deemed waived is to avoid premature claims and ensure that agency be given a chance to bring its expertise to bear to resolve a claim); *Kleissler* v. *U.S. Forest Service,* 183 F.3d 196, 202 (3d Cir. 1999) (Policy underlying exhaustion requirement is that ''objections and issues should first be reviewed by those with expertise in the contested subject area''); *National Association of Manufacturers* v. *U.S. DOI,* 134 F.3d 1095, 1111 (DC Cir. 1998) (''We decline to find that scattered references to the services concept in a voluminous record addressing myriad complex technical and policy matters suffices to provide an agency like DOI with a 'fair opportunity' to pass on the issue''); *Linemaster Switch Corporation* v. *EPA,* 938 F.2d 1299, 1305–1306 (DC Cir. 1991) (declining to consider in challenge to final rule, data alluded to in comments but not submitted during the comment period, and information submitted to EPA office that was not developing the rule).

Moreover, EPA clearly stated in the proposed rule that the Agency considered that the usual requirements applicable to informal rulemakings would remain applicable in this informal rulemaking. The proposal explicitly noted that ''[i]f you anticipate that you may wish to file objections on the final rule, you must raise those issues in your comments on this proposal. EPA will treat as waived, any issue not originally raised in comments on this proposal'' (73 FR 44,865 (July 31, 2008)).

The fact that FFDCA section 408 in certain limited circumstances supplements the informal rulemaking with a hearing does not fundamentally alter the requirements applicable to informal rulemakings. Nor, as discussed below, does it convert this into a formal rulemaking, subject to the exception in section 553. The FFDCA section 408 establishes a unique statutory structure with multiple procedural stages, and delegates to EPA the discretion to determine the implementation that best achieves the statutory objectives. Accordingly, EPA interprets the notice and comment rulemaking portion of the FFDCA section 408 process as an integral part of the FFDCA process, inextricably linked to the administrative hearing. The point of the rulemaking is to resolve the issues that can be resolved, and to identify and narrow any remaining issues for adjudication. Consequently the administrative hearing does not represent an unlimited opportunity to supplement the record, particularly with information that was available during the comment period, but that commenters have chosen to withhold. For example, as discussed at greater length in Unit VI.E.2, both in their comments, and again in their objections, the Petitioners failed to provide the underlying mathematical modeling that supported their claim that the appropriate children's safety factor was 1X, rather than 4X. Instead, they presented only summary results. Similarly, although the Petitioners claimed in their comments to have conducted an alternate analysis showing that aggregate carbofuran exposures to children would be safe, they failed to provide the data and details of that assessment to the Agency. They also failed to provide several critical components that served to support key inputs into that assessment.

To read the statute otherwise would be to render the rulemaking portion of the process entirely duplicative of the hearing, and thus, ultimately meaningless. *See, e.g., FDA* v. *Brown & Williamson Tobacco,* 529 U.S. 120, 132–133 (2000) (Court must interpret statute as a symmetrical and coherent regulatory scheme, and fit, if possible,

[5] For example, section 408(d) allows the Agency to proceed to a final rule after publication of a submitted petition, rather than requiring publication of a proposal.

all parts into a harmonious whole.) *APW, AFL–CIO* v. *Potter,* 343 F.3d 619, 626 (2nd Cir. 2003) (''A basic tenet of statutory construction * * * [is] that a text should be construed so that effect is given to all its provisions, so that no part will be inoperative or superfluous, void or insignificant, and so that one section will not destroy another * * *''), *quoting Silverman* v. *Eastrich Mulitple Investor Fund,* 51 F.3d 28, 31 (3rd Cir. 1995). The equities of this construction are particularly strong, where, as here, the information was (or should have been) available during the comment period. *See, Kleissler,* 183 F.3d at 202 (''[A]dministrative proceedings should not be a game or a forum to engage in unjustified obstructionism by making cryptic and obscure reference to matters that 'ought to be' considered and then, after failing to do more to bring the matter to the agency's attention, seeking to have that agency determination vacated'') *citing Vermont Yankee Nuclear Power Corp.* v. *NRDC,* 435 U.S. 519, 553–54 (1978). For example, one of Petitioners' exhibits is the drinking water modeling that served as the basis for the comments submitted on the proposed rule. The documents are dated well before the close of the comment period, and were clearly available for submission along with the comments (Exhibit 15). Yet they were only provided to EPA as part of the Petitioners' objections.

Contrary to Petitioners' contention, EPA's interpretation is entirely consistent with the FFDCA's language and structure. The fact that the statute and regulations allow ''any person'' to file objections is immaterial. At issue is not ''who'' may raise objections, but what issues may be raised as part of the objections to justify a hearing. And on the relevant question, the statute is clear that only certain issues—those of material fact—may be raised in objections to justify a hearing (21 U.S.C. 346a(g)(2)(B)). EPA's regulations expand on this limitation, providing, among other requirements, that hearings will not be held on legal or policy issues, nor on the basis of mere allegations, nor where EPA concludes that the data and information submitted, even if accurate, would be insufficient to justify the factual determination urged (*See* 40 CFR 178.32). It is true that FFDCA section 408(g)(2)(A) provides little guidance on the objections that a party may raise, requiring only that parties identify the specific provisions challenged, and state ''reasonable grounds'' for their objection. But the relative silence of the statutory provision does not mean that EPA is required to allow parties to raise any and all objections; rather it means that Congress left the question of what constitutes ''reasonable grounds'' for EPA to resolve.

In construing that requirement, EPA gives weight to the fact that 408(g) is only one part of a larger, multi-stage, administrative process, and that the statute does not support an interpretation that this one phase be granted greater significance than the rest of the process. Also relevant is that Congress delegated broad discretion to the Agency to determine whether a hearing is ''necessary'' (21 U.S.C. 346a(g)(2)(B)). Accordingly, EPA believes that whether an objection states ''reasonable grounds'' is to be measured against the context of the rulemaking, and the provisions applicable to hearing requests.

Fundamentally, FFDCA section 408 delegates broad discretion to EPA, both to determine how best to harmonize the statutory process and to determine what constitutes ''reasonable grounds'' for objections. Consequently, the relevant question is whether EPA's exercise of discretion in requiring parties to present all available factual issues and evidence during the rulemaking is reasonable. It is undeniably a reasonable exercise of discretion to ensure that the rulemaking is not an opportunity for one party to waste the time and resources of all parties—both the government and other rulemaking participants—by failing to raise all of their issues or withholding information for the purpose of surprising the government at a later point during the proceeding. *See, e.g., Vt. Yankee,* 435 U.S. at 553–554; *United States* v. *L.A. Tucker Truck Lines,* 344 U.S. 33, 37 (1952) (''courts should not topple over administrative decisions unless the administrative body * * * has erred against objection made at the time appropriate under its practice'').

EPA has consistently interpreted section 408 in this fashion since the 1996 amendments. For example, EPA previously ruled that a petitioner could not raise new issues in filing objections to EPA's denial of its Original petition. *See* 72 FR 39318, 39324 (July 18, 2007) (''The FFDCA's tolerance revocation procedures are not some sort of 'game,' whereby a party may petition to revoke a tolerance on one ground, and then, after the petition is denied, file objections to the denial based on an entirely new ground not relied upon by EPA in denying the petition.''). EPA reasoned that new issues were not cognizable because they ''not an objection to the 'provisions of the * * * order [denying the petition]' '' (Id.). Similarly, in a recent decision EPA denied NRDC's request for a hearing because they had failed in their original petition to raise the claim asserted in their objection (73 FR 42683, 42696 (July 23, 2008)). EPA noted that although NRDC did argue in its petition that EPA cannot make a safety finding without completing the endocrine screening program under FFDCA section 408(p), it did not assert claims regarding the endocrine data and the children's safety factor. Citing its previous decision, EPA denied NRDC's objections and hearing requests as to the children's safety factor (Id.). In that same decision, EPA also denied a number of hearing requests on the ground that requestor failed to proffer supporting evidence; EPA opined that a failure to offer evidence at an earlier stage of the administrative proceeding could not be cured by suddenly submitting such evidence with a hearing request. (*See* 73 FR 42683, 42710 (July 23, 2008) (''Presumably Congress created a multi-stage administrative process for resolution of tolerance petitions to give EPA the opportunity in the first stage of the proceedings to resolve factual issues, where possible, through a notice-and-comment process, prior to requiring EPA to hold a full evidentiary hearing, which can involve a substantial investment of resources by all parties taking part * * * Accordingly, if a party were to withhold evidence from the first stage of a tolerance petition proceeding and only produce it as part of a request for a hearing on an objection, EPA might very likely determine that such an untimely submission of supporting evidence constituted an amendment to the Original petition requiring a return to the first stage of the administrative proceeding (if, consideration of information that was previously available is appropriate at all'').

The two cases Petitioners cite that are specific to section 408(d) do not alter this assessment. Neither of those cases addressed the scope of the evidence that could be properly raised as part of objections to justify a hearing. Nor were the courts examining the extent of EPA's authority to impose requirements on the filing of objections under 408(g). Rather these courts were evaluating the scope of the FFDCA's exclusive review provisions, and whether the plaintiffs could bring a challenge to EPA policies and individual tolerance decisions without first exhausting the FFDCA's petition process. *Geertson Farms* v. *Johanns,* 439 F.Supp.2d 1012, 1022–1023 (N.D. Ca 2006); *NY* v. *EPA,* 350 F.Supp.2d 429, 442–443 (S.D.N.Y. 2004). This issue is not identical to the questions at issue here: for example, the

court in *Geertson Farms* held that the plaintiffs' procedural and policy decisions were properly raised initially before the Agency through the petition process. 439 F.Supp2d at 442. Yet it is undeniable that EPA's regulations preclude the reliance on policy or legal issues as a justification for an Agency hearing.

Nor do the Petitioners' other cases compel a different result. The majority of the Petitioners' cases concern FFDCA section 701(e), which differs in several significant respects from FFDCA section 408. Section 701(e) imposes no requirements whatsoever on the party submitting the objection: ''any person may file objections * * * specifying the provisions of the order deemed objectionable, stating the grounds therefore * * *'' 21 U.S.C. 371(e)(2). This section also expressly provides that FDA must hold a hearing upon request: ''As soon as practicable after such request for a public hearing, the Secretary, after due notice, shall hold such a public hearing for the purpose of receiving evidence relevant and material to the issues raised by such objections.'' 21 U.S.C. 371(e)(3). In the face of this language, it is unsurprising that the courts held that FDA lacked discretion to deny a hearing. Further, under FFDCA section 701(e) the mere filing of an objection automatically stays the effectiveness of the challenged provisions. ''Until final action is taken upon such objections is taken by the Secretary under paragraph (3), the filing of such objections shall operate to stay the effectiveness of those provisions of the order to which the objections are made.'' 21 U.S.C. 371(e)(3). By contrast, section 408 grants the Administrator the discretion to stay the effectiveness of the regulation if objections are filed. 21 U.S.C. 346a(g)(1). Indeed, the Petitioners' own cases specifically distinguish between section 701(e) and other FFDCA provisions. See *Pactra Industries* v. *Consumer Product Safety Commission,* 555 F.2d 677, 685 (9th Cir. 1977) (rejecting FDA argument that FFDCA section 701 should be read consistently with FFDCA sections 505 and 507 to allow for summary judgment procedures).

Petitioners' second argument is equally incorrect.[6] As an initial matter, the parties agree that FFDCA 408 establishes a hybrid rulemaking procedure, with informal rulemaking initiating, and frequently ending, the process (74 FR 23070 (May 15, 2009)); Obj at 62). Hybrid rulemaking is not formal rulemaking, which is the only rulemaking to which APA sections 556 and 557 apply. Nevertheless, Petitioners contend that once objections are raised, ''Congress required the use of a formal rulemaking procedure involving an on-the-record hearing for resolving factual disputes.'' (Obj at 62) Nothing in the FFDCA section 408 or the APA supports this interpretation. And the cases cited in support of this argument are inapposite or misconstrued.

The APA section 553 on its face applies to all rulemakings except ''[w]hen rules are required by statute to be made on the record after opportunity for an agency hearing'' (5 U.S.C. 553(c)). Under this language, APA section 553 will apply unless two requirements are met: (1) The statute requires an opportunity for a hearing as part of the rulemaking, and (2) the hearing is required to be ''on the record.'' FFDCA section 408 hearings are neither ''required,'' nor mandated to be ''on the record.'' The case law is clear that statutes containing both characteristics are the hallmark of formal rulemaking, and that formal rulemaking is the rare exception. *AT&T* v. *FCC*, 572 F.2d 17, 21–23 (2d Cir. 1978) (''The APA requires trial-type hearings only '[w]hen rules (or adjudications) are required by statute to be made (or determined) on the record after opportunity for an agency hearing.' '') (citations omitted); *Minden Beef Co* v. *Cost of Living Council*, 362 F.Supp. 298 (D. Neb. 1973) (examining whether statutory provision that ''[t]o the maximum extent possible, the President or his delegate shall conduct formal hearings * * *'' makes hearings mandatory, in determinating whether formal rulemaking required). *See also*, *e.g., Girard* v. *Klopfenstien*, 930 F.2d 738, 741 (9th Cir. 1991) (''The APA does not apply because a debarment hearing is not required by statute. The fact that the hearing is 'on the record' does not trigger an application of the formal adjudication provisions of section 554 of the APA''); *Smedberg Machine & Tool* v. *Donovan*, 730 F.2d 1089, 1092–93 (7th Cir. 1984) (holding section 554 inapplicable to a proceeding that ''gives the adminsitrative law judge the discretion, rather than the obligation to conduct a review hearing.''). As discussed below, in contrast to other sections of the FFDCA, such as section 701(e), FFDCA section 408 makes clear that a hearing is not mandatory upon request, but that EPA has broad discretion to determine whether a public hearing is necessary to receive factual evidence. *See*, 21 U.S.C. 346a(g)(2)(B), 346a(g)(2)(C). *See also*, H.R. Rep. No. 104–669, at 49 (1996).

The Supreme Court made clear in *Florida East Coast Railway* v. *FLRA*, that the circumstances under which rules are ''required to be made on the record after opportunity for an agency hearing'' are limited to those where Congress clearly indicates the intent to do so. 410 US 224, 241 (1973). The mere fact that statute offers an *opportunity* for an agency hearing is not sufficient to bring rulemaking under scope of this exemption. Id. *See also*, *U.S.* v. *Allegheny-Ludlum Steel*, 406 U.S. 742 (1972); *NRA* v. *Brady*, 914 F.2d 475, 485 (9th Cir. 1990) (No oral hearing required where statute required Secretary to ''afford interested parties opportunity for hearing'' and Agency regulations reserved right to determine whether oral hearing warranted); *Wisconsin Gas Co* v. *FERC*, 770 F.2d 1144, 1165–1168 (DC Cir. 1985) (APA 556 hearing not required when statute only contained provisions requiring decision ''after a hearing'' and ''substantial evidence'' standard of judicial review); *AT&T* v. *FCC*, 572 F.2d 17, 21–23 (2d Cir. 1978) (APA 556 hearing not required when statute only contained provisions requiring decision ''after a hearing'' and ''substantial evidence'' standard of judicial review) *Philips Petroleum Co* v. *FPC*, 475 F.2d 842, 851–852 (10th Cir. 1973) (formal rulemaking not required even though statute required ''full hearing'' and Agency traditionally conducted trial-type adjudicative hearing).

Unless the statute providing for agency action prescribes ''hearings on the record,'' either in those exact words or by using similar words to indicate that Congress specifically intended to impose the full trial-type requirements of sections 556 and 557, the statute does not fall within section 553's exception. *FL East Coast Railway*, 410 US at 241. While the absence of those words is not dispositive, ''in the absence of these magic words, Congress must clearly indicate its intent to trigger the formal, on the record hearing provisions of the APA.'' *City of West Chicago, Illinois* v. *NRC*. 701 F.2d 632, 641 (7th Cir. 1983) (citations omitted). *See also*, *e.g.*, *National Classification Committee* v. *ICC*. 765 F.2d 1146, 1150–1151 (DC Cir. 1985) (''Thus under *Florida East Coast*, there is a strong presumption that the procedural guarantees of section 553 of the APA are sufficient unless Congress specifically indicates to the contrary'' *citing Vermont Yankee Nuclear Power Corp* v. *NRC*, 435 U.S. 519 (1978)); *AT & T* v. *FCC*, 572 F.2d at 21–23 (''The words, 'on the record' have become, as the District of Columbia Circuit has

[6] As discussed below, it is not clear that a determination that a hearing, if held, must be held in accordance with APA sections 556 and 557 precludes EPA from exercising its discretion to restrict the issues and evidence that may be raised at this final stage of the administrative process.

observed, a 'touchstone test' for the applicability of the APA's trial-type procedures''); *Philips Petroleum Co*, 475 F.2d at 851–852 (''The fact, as previously noted, that the Gas Act does not contain the words 'on the record' furnishes a strong argument in support of the Commission's contention that informal rulemaking satisfies the requirements of the APA''); *Minden Beef Co*, 362 F.Supp. at 306–307 (''Requiring 'formal hearings' is not identical with requiring that rules be made on the record after opportunity for agency hearing.'') What is notable is that, in all cases, the court required clear expression that Congress specifically intended to impose full trial-type requirements.

Thus the question is whether Congress indicated any intent to entirely remove the FFDCA section 408 process from the requirements of 553. The mere fact that FFDCA section 408 requires some (or even many) of the procedures applicable under section 556 and 557 does not resolve the question. *See*, *e.g.*, *National Classification Committee* v. *U.S.*, 765 F.2d 1146, 1150–1151 (DC Cir. 1985) (Rejecting argument that formal rulemaking required on grounds that ''[u]nder *Florida East Coast* there is a strong presumption that the procedural guarantees of section 553 of the APA are sufficient unless Congress specifically indicates to the contrary''); *Association of National Advertisers* v. *FTC*, 627 F.2d 1151, 1165–1168 (DC Cir. 1979) (formal rulemaking not required, even though statute ''did order use of procedures not required in informal rulemaking'' such as rights to rebuttal and cross-examination at public hearing.); *American Public Gas Association* v. *FPC*, 567 F.2d 1016, 1065–1067 (DC Cir. 1977) (Formal rulemaking not required by statutory provisions requiring ''full hearing'' and ''substantial evidence'' standard of judicial review).

In fact, the language and legislative history of section 408 provide clear indication of Congressional intent not to subject proceedings under these sections to APA sections 556 and 557. FFDCA section 408 does not reference APA sections 556 or 557 (see, *e.g.*, 7 U.S.C. 136d(c)(2)). By contrast, the previous version of section 408 did reference APA section 556, and the deletion of this requirement provides clear evidence of Congressional intent not to exempt FFDCA from APA 553. Prior to the 1996 amendments, section 408(d)(5) of the original act, which governed the conduct of hearings, specifically referenced APA 556. (''Any report, recommendations, underlying data, and reasons certified to the Secretary by an advisory committee shall be made part of the record of the hearing, if relevant and material, subject to the provisions of section [556] of the APA.''). 21 U.S.C. 346(d)(5). Moreover, the previous version of the statute contained additional language consistent with the requirement of hearings subject to APA sections 556 and 557; for example, the previous version of section 408(d)(5) repeatedly makes reference to ''testifying at such hearing.'' A further consideration is that several other provisions of the FFDCA do explicitly reference APA sections 554 or 556. *Compare*, 21 U.S.C. 333(g)(3) (''A civil penalty * * * shall be assessed by the Secretary by an order made on the record after opportunity for a hearing provided in accordance with this subparagraph and section 554 of title 5''); 21 U.S.C. 342(f)(1)(C) (requiring the Secretary, upon any declaration of imminent hazard under this section to ''initiate a proceeding in accordance with sections 554 and 556 of title 5''). The fact that Congress chose not to explicitly reference APA sections 556 or 557 provides a strong indication that they did not intend to impose such a requirement on section 408 proceedings. *See*, *e.g.*, *St Louis Fuel and Supply Co* v. *FERC*, 890 F.2d 446, 449 (DC Cir. 1989) (holding that formal hearing under APA 554 not required on that grounds that ''[w]e consider it significant that, unlike section 7193(c), other prescriptions in the DOE Organization Act expressly invoke the APA'') (citations omitted).

Nor does any provision of FFDCA section 408 include the requirement that the hearing be ''on the record.'' By contrast, several other provisions of the FFDCA include that exact phrase. *Compare*, 21 U.S.C. 335a(i) (''The Secretary may not take action * * * unless the Secretary has issued an order for such action made on the record after opportunity for an agency hearing on disputed issues of material fact.''); 21 U.S.C. 335b(b)(1)(A) (''A civil penalty shall be assessed * * * by an order made on the record after an opportunity for an agency hearing * * *''); 21 U.S.C. 335(c)(b) (''The Secretary may not take action * * * unless the Secretary has issued an order for such action made on the record after opportunity for an agency hearing on disputed issues of material fact.'') Under all rules of statutory construction, those differences are presumed to be intentional. *Russello* v. *United States*, 464 U.S. 16, 23 (1983) (''[W]here Congress includes particular language in one section of a statute and omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion'').

Equally significant is that the language of section 408 explicitly grants EPA broad discretion to deny a hearing. Section 408(g)(2)(B) provides that EPA shall ''hold a public evidentiary hearing, *if and to the extent* the Administrator *determines that such a public hearing is necessary* to receive factual evidence relevant to material issues of fact raised by the objections'' (21 U.S.C. 346a(g)(2)(B)) (emphasis added). This language grants EPA the discretion to determine whether the issues raised in objections are ''material'' issues of fact. Further, even where evidence relevant to an issue of material fact is proffered (essentially the standard set forth in 40 CFR 178.32), EPA construes the statutory language as requiring it to hold a hearing only where it determines it is necessary to receive proffered evidence. In other words, the statute grants EPA the discretion to determine that the issues could be resolved entirely on the basis of the existing written record. *See Philips Petroleum*, 475 F.2d at 848–849 (Formal rulemaking under APA 556 not required even though statute required that hearing be held, but ''Commission has a very broad discretion in determining the form of its proceedings'').

EPA's construction is confirmed by the House Commerce Committee Report accompanying the final bill, which states:

> New subparagraph (g)(2)(B) allows an objector to request a public evidentiary hearing. *The Administrator would decide whether [a] hearing were necessary* to receive factual evidence relevant to material issues of fact raised by the objections. *The Committee expects EPA to use this discretion fairly* and to grant hearings to responsible parties on all sides.

H.R. Rep. No. 104–669, at 49 (1996) (emphasis added). Notably, in an earlier version of the 1996 amendments, the House bill provided for a mandatory hearing during the notice-and-comment rulemaking stage of an EPA-initiated proceeding. [H.R. 1627, 104th Cong. Section 405 (new FFDCA section 408(e)(2)) (''EPA *shall provide* an opportunity for a public hearing * * *'') (emphasis added). This requirement was dropped prior to enactment but the contrast with section 408(g)(2)(B) confirms the discretionary character of the latter.

If this were not sufficient indication of Congressional intent, further evidence is provided by the fact that in amending section 408, Congress chose not to adopt the provisions of section 701(e) that Petitioners cite in their objections. Clearly, Congress could have

adopted the same provisions found in FFDCA 701(e), or in any of the other comparable FFDCA provisions discussed above, but chose not to do so.

EPA agrees that, when a hearing is warranted, the FFDCA requires an evidentiary hearing that comports with the procedures contemplated by 408(g)(2)(B). But that is not the same as a requirement that section 553 be inapplicable to the proceedings, or that any hearing be held in accordance with APA sections 556 and 557.[7] Rather, section 408's provisions are consistent with APA sections 553 (b) and (c), which recognize the potential for hearings as part of informal rulemaking: ''Except when notice or hearing is required by statute, * * * the agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments, *with or without the opportunity for oral presentation.''* 5 U.S.C. § 553(b)(c) (emphasis added).

Finally, Petitioners' citation to case law interpreting FFDCA section 701(e) does not compel a different result. Petitioners claim that the provisions of FFDCA 701(e) are ''near identical'' to those under section 408, and on this basis, argue that, ''by analogy'' these decisions compel an identical interpretation of the requirements of FFDCA section 408 (Obj at 65). Petitioners are correct that section 701(e) of the FFDCA has been held to be ''one of those statutes, few in number, that does require rule-making hearings to be on the record in accordance with APA sections 556.'' *Pactra, supra*, 555 F.2d 677, 685 (9th Cir. 1977), *citing Florida East Coast Railway*, 410 U.S. at 237–38, (*dictum*). But in all other regards, Petitioners are incorrect.

As previously discussed, there are several significant differences between the statutory language of FFDCA sections 701 and 408 that render Petitioners' citation to these cases inapposite. Hearings are mandatory upon request under section 701, and the filing of objections operates to automatically stay the provisions of the rule. Section 701(e)(2) requires only that the objection ''state the grounds therefore,'' rather than requiring the a statement of ''reasonable grounds.'' *See Pactra* at 684 (distinguishing FFDCA section 701(e) from 507(f) because the latter requires hearing applicants to show 'reasonable grounds'). Further, although section 701 does not itself contain the requirement that the hearing be ''on the record,'' the legislative history of this provision indicates that Congress intended such hearings to be ''on the record.'' *Pactra*, 555 F.2d at 682–684 (detailing FFDCA section 701 legislative history). These characteristics played a significant role in the court's decision that FDA lacked the authority to deny hearings under section 701(e) on the basis of summary judgment proceedings.[8] However, as shown above, the legislative history of section 408 provides a clear indication of a contrary Congressional intent with respect to hearings under this section.

Petitioner's reliance on the ''substantial evidence'' standard in FFDCA section 408(i) is equally misplaced. Incorporation of that standard into judicial review provisions alone has been consistently held to be insufficient to indicate Congressional intent to impose the full requirements of APA sections 556 and 557 to a rulemaking. *Wisconsin Gas Co* v. *FERC*, 770 F.2d at 1167 (''The procedures required to develop this 'substantial evidence' are not necessarily the strict adversary procedures of sections 556 and 557 of the Administrative Procedures Act''); *Public Systems* v. *FERC*, 606 F.2d 973, 979, n. 32 (DC Cir. 1979) (substantial evidence requirement in Natural Gas Act ''carries no implications for procedures to be followed by the Commission in compiling the record''); *American Public Gas Association* v. *FPC*, 567 F.2d 1016, 1065–1067 (DC Cir. 1977) (''In our view, however, this requirement [of the substantial evidence standard] in the judicial review provision of the Act does not dictate the procedure to be followed, or the nature of the hearing to be held).

The specific language of 408(i) defines the standard for the reviewing court; it does not describe the process by which the agency hearing is to be conducted. This is quite different from the language under 501(c) of the CWA, on which the DC Circuit relied in holding that hearings pursuant to APA section 554 were required. *Marathon Oil* v. *EPA*, 564 F.2d 1253, 1262–1265 (DC Cir. 1977). The CWA section 501(c) states ''[i]n any judicial proceeding * * * in which review is sought of *a determination under this chapter required to be made on the record after notice and opportunity for a hearing * * *''* 33 U.S.C. 1369(c) (emphasis added).[9] By contrast, FFDCA section 408(i) merely provides that ''[a]s to orders issued following a public evidentiary hearing, the findings of the Administrator with respect to questions of fact *shall be sustained if supported by substantial evidence when considered on the record as a whole''* (21 U.S.C. 346a(i)) (emphasis added). It is also worth noting that the court expressly distinguished this case, which dealt exclusively with an adjudicatory proceeding, from those circumstances in which an agency proceeds through rulemaking. 564 F.2d at 1262, n. 30.

In any event, even if section 556 did apply to hearings under section 408, Petitioners cannot avoid the case law under section 553 and EPA's interpretation of the interrelationship between any hearing granted under section 408(g)(2) and the rulemaking preceding it. Petitioners cite to the general evidentiary provision in section 556(d) that provides that only irrelevant or immaterial evidence may be excluded and argue that this generic standard necessarily defines the scope of a hearing regardless of the statutory scheme in which it is embedded. However, context matters. As the DC Circuit noted, ''the informal procedures of section 553 of the APA and the more formal requirements of sections 556 and 557 are not mutually exclusive.'' *American Public Gas Association*, 567 F.2d at 1067. Even the caselaw relied upon by Petitioners does not suggest that section 556(d)'s evidentiary provision trumps all other considerations. Petitioners cite primarily to *Catholic Medical Center, Inc.* v. *NLRB*, 589 F.2d 1166, 1170 (2d Cir. 1978). In that case, the Second Circuit interpreted section 556(d) as specifying that ''an agency thus may not provide for the exclusion of evidence *not protected by a privilege or countervailing policy* . * * *'' Id. (emphasis added). Here, EPA has interpreted its authority to impose such a countervailing policy. Moreover, EPA's interpretation is clearly within the broad discretion granted it by the statute and the policy underlying the interpretation is a reasonable adaptation of judicial practice with regard to issues not presented in notice and comment rulemaking proceedings. Thus, Petitioners' technical and formalistic argument concerning section 556(d), which ignores the context of the section 408(g)(2) hearing provision, must be rejected.

Similarly unavailing is Petitioners' argument concerning section 556(e)'s

[7] EPA's regulations currently provide for a trial-type adjudicatory hearing. These regulations were adopted under the preceding statutory provision, and EPA has not yet undertaken any effort to revise the regulations to take into account the revised provisions of section 408.

[8] Contrary to Petitioners' allegation, the DC Circuit has not ''arrived at the same conclusion'' (Obj at 65). All of the discussion from *Independent Cosmetic Manufacturers and Distributors* v. *U.S. Dept of Health, Education, and Welfare* presented in their objections is dicta from a dissenting opinion. 574 F.2d 553, 572 (DC Cir. 1978).

specification that the ''exclusive record for decision'' after a hearing is material or testimony submitted in the hearing or hearing proceeding. Petitioners assert that this provision somehow removes any limitations on what can be submitted at the hearing because ''that 'exclusive record' is independent of whatever record may exist in the prior informal rulemaking * * *.'' (Obj at 64). Yet the hearing record is not ''independent'' of the rulemaking record in that EPA regulations require that the rulemaking record be included in the record of the hearing (40 CFR 179.179.83(a)(1)). Once again, Petitioners' argument fails because it considers section 556 in isolation rather than taking into account the context of the entire administrative proceeding in which the hearing is embedded.

Finally, Petitioners complain that EPA ''raised a host of new issues and assertions for the first time in the Final [rule],'' and it would be inequitable for EPA to prevent them from raising objections on these new assessments. Petitioners identify ten categories of ''new computations and contentions'' that they claim raise issues that go beyond those addressed in their prior comments. With one exception, all of these ''new computations and contentions'' were revisions to analyses conducted in response to Petitioners' comments. Indeed, some of these were revisions undertaken in response to Petitioners' specific request; for example, the ''new'' BMD analyses they identify were: (1) Corrections made in response to an EPA error identified in their comments; (2) an extrapolation of BMD_{50} s, using the dose-time-response model, to develop a common point of comparison between all studies, which they had claimed was the appropriate approach; and (3) a calculation generating a new dose-response model in order to calculate the BMD_{50} s for brain and RBC AChE inhibition, in response to Petitioners' claim that failure to do so was inappropriate (Refs. 24, 25, 85). Since these analyses were done at their behest, they can hardly complain that they present new issues on which they had no opportunity to comment. The Agency's underlying methodologies were the same as those used for the proposed rule; the analyses were based on information provided by the Petitioners and/or to address the revisions requested as part of the Petitioners' comments.

Regarding the remaining analyses: The ''new exposure estimates for ground and surface water,'' as well as the ''revised dietary risk and drinking water assessments'' and ''new assessment of the impact of buffers and setbacks'' were conducted to accurately reflect the use under the registration, as modified by FMC's cancellation of uses and additional mitigation measures. The same is true for the ''new analysis of the various carbofuran labels;'' the analysis related to the labels submitted as part of the September 2008 comments. The chlopyrifos studies were raised in response to the Petitioners' citation to a subset of chlorpyrifos data. They acknowledge that the ''new literature citations'' were provided to address one of their contentions (Obj at 56). The sole exception relates to EPA's calculation of carbofuran-specific half-lives for use in the dietary risk assessment. As discussed in Unit VI.G.2, EPA does not reject Petitioners' challenge to EPA's calculation of the 186-minute half-life on the basis that it is untimely.[10]

A fair indication that EPA has not raised a host of new issues in the final rule is that, with the exception of the revised half-lives, Petitioners do not challenge the substance of any of the allegedly ''new'' information. Indeed, as discussed in the sections below, Petitioners have in many instances failed to address any of the explanations or revised analyses EPA presented in the final rule.

Ultimately, Petitioners' complaint misses the point. EPA does not interpret the statute and regulations to preclude the submission of any new information as part of the objections phase. Such a position would in fact be inconsistent with EPA's own regulations and past practice, which require that in order to support a hearing request, a party submit more than ''mere allegations or denials'' (40 CFR 178.32(b)(2)). Rather, EPA's interpretation in this regard is analogous to the determination of whether a final rule is the logical outgrowth of the proposal and the comments. For example, EPA does not reject Petitioners' citation to new studies in support of the contention that RBC AChE data are generally more sensitive than PNS tissues on the grounds that they are untimely. This is because these studies are simply more evidence supplementing the issue they fairly raised in their comments, and are intended to rebut EPA's response in the final rule. Similarly, the submission of new analyses relating to the ground water pH in Exhibit 14 is not considered untimely, as the issues they raise relating to ground water pH were fairly raised in comments and discussed throughout the rulemaking. Ultimately, EPA's policy is merely that the objections phase does not present an opportunity for parties to begin the process entirely anew, by raising issues or information that could have been fairly presented as comments on the proposed rule. Nor is the statute's additional procedural step an excuse to withhold information that was clearly available at the time of the rulemaking.

2. Implications for FMC's Submission of New Registration Amendments as Part of their Objections. On June 29, 2009, in conjunction with their objections on the final rule, FMC Corporation submitted a request for EPA to amend its registration in several regards. Some of the requested amendments were further mitigation measures intended to address carbofuran's dietary risks. The most significant of these was a proposal intended to ensure that only 2% of any watershed would be treated with carbofuran. The proposal would require that, within five days of applying the product, all applicators report to FMC the following information: The location that the product will be used, crop, use rate, application method, acreage, and quantity applied. Based on this information, FMC would track the percentage in each watershed. ''Whenever it appears that carbofuran has been applied to 1.75% of any watershed,'' the registrant would report that information immediately to EPA, ''cease further sales in any county that overlaps with such a watershed for that use season, and shall attempt to recall all unused carbofuran within such counties by offering to repurchase such unused product'' (Exhibit 2). Additionally, FMC requested that its registration be amended to require that ''based on watershed boundaries, FMC * * * prior to each use season, allocate to its distributors in a manner which will attempt to ensure that no distributor receives more carbofuran for sale than can be accommodated by the 2% watershed area cap in any watershed supplied by that distributor.''

In addition, FMC proposed to add geographic restrictions that would prohibit use in certain parts of the country. Specifically, they proposed to restrict the use of carbofuran on potatoes to the three states: Idaho, Oregon, and to select counties in Washington. They proposed to restrict use on Sunflowers to only Colorado, Kansas, Nebraska, and South Dakota, as well as limited portions of North Dakota and Oklahoma. Under this proposal, use on corn would be restricted to Colorado, Iowa, Illinois, Indiana, Kansas, Missouri, Nebraska, and limited counties in Wisconsin. Further, they

[10] The Petitioners' claim that ''EPA provided new information concerning the raw data collected and records maintained by ORD in relation to its toxicology studies'' is inaccurate. EPA provided no new information on this topic in the final rule.

proposed to add set-backs (*i.e.*, areas where carbofuran could not be applied) ranging between 100 and 1,000 feet from drinking water wells, depending on the geographic area. Finally, as part of these amendments, FMC also requested that EPA revise its registration to permit use of carbofuran on pumpkins in Ohio, Illinois, and Indiana, and to cancel the use on pumpkins in the southeastern United States.

As made clear in Unit VI.C., FMC's newly-proposed registration amendments are irrelevant to the prior determinations made in the final tolerance revocation rule. Further, as discussed in Unit VI.D., as a consequence of the failure to raise these amendments measures as part of their comments on the proposal, EPA considers that all issues arising exclusively as a result of these proposed amendments have been waived. There is no evident reason that FMC could not have offered these amendments as part of its September 2008 proposals. All of the information on which they rely was available in September of 2008. All of the risk concerns that the amendments were intended to address were discussed at length in EPA's proposed rule. Since 2006, EPA has clearly stated its determination that carbofuran's potential to leach into ground water and to runoff into surface water caused unacceptable dietary risks. EPA's methodologies for evaluating these risks have not changed since 2006. Indeed, EPA deferred regulatory action for several months, subsequent to the Agency's determination in 2006 that carbofuran did not meet either the FIFRA or FFDCA standard, to allow the Petitioners time to generate data to address the exact same issues these proposals are intended to address. In their comments on the proposed rule, Petitioners provided some mitigation measures intended to address issues relating to the carbofuran's leaching and runoff potential: Well set-backs, buffers, geographic use restrictions, and aerial application recommendations.

As previously discussed, EPA provided clear notice in the proposed rule that issues that that were not raised during the comment period would be considered waived in subsequent stages of the administrative process (73 FR 44,865). Petitioners were well aware of this, as they commented that ''EPA's requirement to raise all issues in the comments does not appear to be legally binding'' (Ref. 18 at 118). Indeed they acknowledged that they ''agree that identifying disputed issues in the comments is efficient and desirable, and may help to narrow the issues arising in subsequent objections and an administrative hearing. Therefore, the commenters have made a good faith attempt to raise in these comments the principal issues of which they are aware'' (Id.).

At this stage of the process, the statute requires the Petitioners to object to the conclusions and provisions in EPA's final rule, not to propose some new alternate license that they claim would meet the statutory standards (21 U.S.C. 346a(g)(2)(A) (''any person may file objections * * * specifying with particularity the provisions of the regulation * * * deemed objectionable''). In fact, one might fairly read their proposal as an admission that the existing license fails to meet the statutory standards.

A further consideration is that the question of whether these amendments can be approved depends on whether the Agency eventually determines the amended registration meets the standards of FIFRA, which include considerations beyond the dietary risks evaluated under the FFDCA. Under FIFRA, the Agency's review of the amendments is also subject to a statutorily mandated schedule (established as part of the Pesticide Regulatory Improvement Act (PRIA)). These are no small matters. In terms of timing, FMC explicitly acknowledged in its letter submitting the proposed amendments that the amendments were subject to the PRIA review process, requesting that the actions be subject to the PRIA 8-month statutory deadline (which would establish a statutory deadline of February 2010 for Agency consideration of FMC's application). It is not clear whether FMC is arguing that its application be accorded a higher priority than other applications and be taken out of turn, or whether FMC is arguing that the consideration of the objections and request for hearing must be delayed until the FIFRA review process is completed. EPA rejects either position; Petitioners cannot use this tolerance proceeding to evade FIFRA's statutory review scheme, or use that scheme to delay this tolerance proceeding.

As noted, although FIFRA incorporates the FFDCA dietary risk standard, FIFRA also requires the Agency to evaluate a much wider scope of issues in determining whether to grant new license requirements. For example, EPA must evaluate the impact this proposal would have on worker and ecological risks. In addition, EPA must carefully evaluate the policy implications involved in authorizing Petitioners' scheme. In this regard, it is worth noting that FMC's scheme is a novel one that raises significant policy questions that are specific to FIFRA, such as whether the steps proposed could be adequately enforced, which could affect the confidence that everybody would, in fact, comply with all the steps, (*e.g.,* who would investigate whether users have properly notified FMC of use of the product; would users have to keep records to demonstrate to inspectors that they had appropriately reported use; how would further sales in a county be prohibited); and whether the steps themselves are appropriate tools from a policy perspective for dealing with risks associated with the use of a pesticide (*e.g.,* is it appropriate to require users to report use to a pesticide manufacturer; is such reporting subject to approval under the Paperwork Reduction Act; is it appropriate public policy to limit sales in a watershed so that some growers may have preferential access to a product; would the scheme encourage early and potentially unnecessary purchase of product by users; under what circumstances, if any, should EPA approve label and license conditions that require the extra vigilance that would be required here of users, distributors, and state and federal regulators). Even if this scheme were determined independently to meet the FFDCA safety standard, if ultimately EPA were unable to grant the amendment based on the other considerations that it must evaluate under FIFRA, the unacceptable dietary risks would still remain. Thus, whether this scheme could result in a determination that the dietary risks are acceptable is not ultimately severable from the larger FIFRA process. Nor would it be appropriate to attempt to resolve FIFRA issues in a hearing under the FFDCA.

Indeed it is questionable whether consideration of the proposed amendments would be appropriate even under Petitioners' position that all objections made in good faith may be presented at this stage of the proceeding (Obj at 61). For example, less than six months prior to their recent submission, the Petitioners proposed voluntarily cancellation of all use on pumpkins except in the Southeastern United States, alleging that sales data demonstrated that carbofuran was needed in the Southeastern U.S. In response to this amendment, which was submitted as part of their comments on the proposed rule, EPA analyzed the dietary risks based on this proposed use pattern for the final rule. A request, mere months later, for additional use on pumpkins in states with different geographic and weather conditions and

cancellation of the use in the Southeastern U.S., may fairly be considered suspect—an action intended to delay the revocation process by forcing the Agency to conduct yet additional analyses, rather than a good-faith objection.

For all of these reasons, EPA has determined that reliance on these proposed amendments as a basis for raising objections to the final rule, or for requesting a hearing is not appropriate. Nevertheless, EPA evaluated the individual objections premised on the newly requested terms and conditions of registration. And in each case, the submitted materials relating to these objections and hearing requests independently failed to meet the statutory and regulatory requirements to justify a hearing, as discussed in the Units below.

E. Response to Specific Issues Raised in Objections and Hearing Requests Relating to EPA's Children's Safety Factor

To more fully understand Petitioners' objection and hearing request with regard to EPA's choice of a 4X children's safety factor and EPA's responses, a little background is helpful. Section 408 of the FFDCA imposes a default additional safety factor for the protection of infants and children, to take into account the fact that children are frequently more sensitive to a pesticide's effects than adults. This default 10X safety factor can only be revised if the Agency has ''reliable data'' to demonstrate that the alternative safety factor—or no safety factor—''will be safe for infants and children'' (21 U.S.C. 346a(b)(2)(C)). In determining whether a different factor is safe for children, EPA focuses on the three factors listed in section 408(b)(2)(C)—the completeness of the toxicity database, the completeness of the exposure database, and potential pre- and post-natal toxicity. In examining these factors, EPA strives to make sure that its choice of a safety factor, based on a weight-of-the-evidence evaluation, does not understate the risk to children. (Ref. 79). The Agency's approach to evaluating whether sufficient ''reliable'' data exist to support the reduction or removal of the statutory default 10X is described below in Figure 1.

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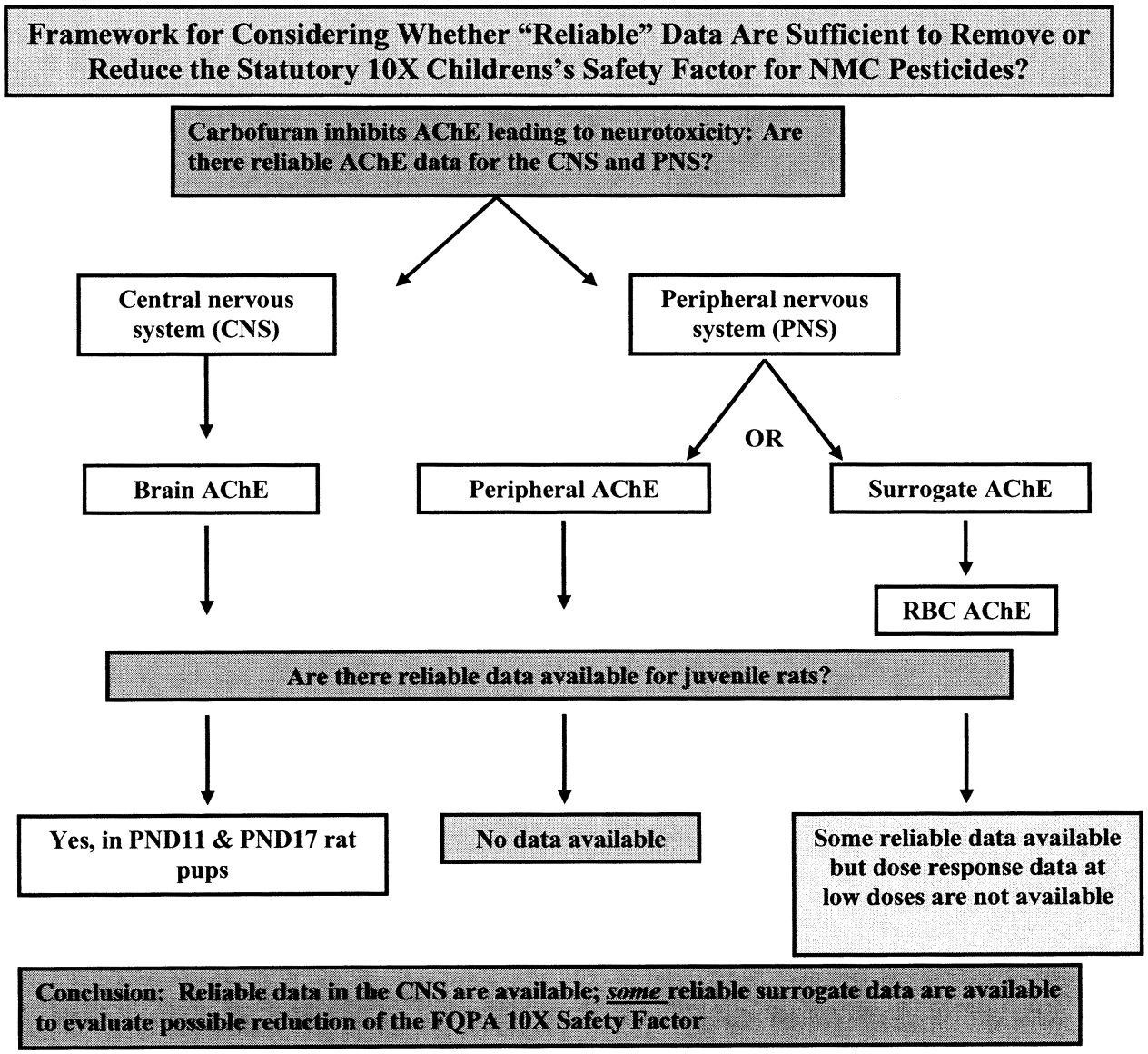

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EPA has consistently required that data comparing the AChE inhibition in young rat pups (typically PND11) and adult rats be submitted on AChE-inhibiting pesticides, such as carbofuran, to determine the extent of children's potential sensitivity. The study measures the levels of AChE inhibition in both potentially relevant target tissues: The brain and either the PNS or red blood cell (RBC), which serves as a surrogate for the PNS. EPA required these data from FMC for carbofuran, and FMC on two occasions submitted the studies. Both sets of data, however, were rejected by EPA as scientifically flawed because they inaccurately measured the levels of RBC AChE.

Despite the invalidity of the two FMC studies as to RBC AChE, EPA still has certain, limited RBC AChE data and other PNS-related data on carbofuran from other studies. These other carbofuran data indicate the following: (1) PNS-related effects (tremors) occur in pups as a result of exposure to carbofuran at low doses; (2) juveniles are more sensitive than adults to carbofuran based on brain measures; (3) juveniles are more sensitive than adults to carbofuran based on RBC AChE measures; and (4) the relative sensitivity of juveniles compared to adults as to RBC AChE is significantly greater the relative sensitivity of juveniles compared to adults as to brain AChE. It is also noteworthy that the data in adult rats showed RBC AChE was generally more sensitive to carbofuran's effects than brain AChE (RBC AChE inhibition was higher than brain at every dose except the lowest), although these data are of limited relevance, because they were conducted on adult animals rather than pups, and adult responses are frequently not predictive of children's responses. However, because the available pup RBC AChE data from EPA–ORD did not involve testing at doses that produced a sufficiently low level of inhibition, the data were not sufficient to develop a PoD for juveniles based on RBC AChE.

Accordingly, in making its children's safety factor determination for carbofuran, EPA was faced with three significant issues: (1) Sufficient data on carbofuran that are routinely-required for AChE-inhibiting pesticides to measure PNS effects was not available; (2) available data measuring the levels of AChE inhibition in brain and RBC indicated that juveniles were more sensitive than adults to carbofuran and other carbofuran data indicated that PNS-related effects could occur in pups at low dose levels; and (3) although the evidence on carbofuran as to RBC AChE inhibition in juveniles indicated that effects on juveniles' PNS might be the most sensitive endpoint, there was not sufficient data to calculate a PoD (for use in determining the safe dose or PAD) on these effects. Despite the incompleteness of the toxicity database and the evidence indicating the potential for pre- and post-natal toxicity at a very sensitive level, which indicate the need to retain a children's safety factor, EPA nonetheless determined that, because there was limited reliable data in juveniles, a full statutory default 10X was not necessary to ensure that children's exposures would be ''safe.'' EPA undertook a complex comparison of the brain and RBC AChE data in juveniles and determined that the likely increased level of sensitivity for RBC AChE inhibition is 4X. EPA thus concluded that using an additional children's safety factor of 4X applied to the PoD from data on brain AChE inhibition in juveniles would protect infants and children.

1. Challenge to EPA's Scientific Basis for Retention of a 4X Children's Safety Factor. Petitioners object to EPA's conclusion that the lack of peripheral tissue data justifies retention of any portion of the children's safety factor. Petitioners raise two claims in this regard. First, they allege that a carbofuran PoD based on brain AChE is adequately protective of PNS effects. Second, they claim that RBC AChE inhibition data are not the best surrogate for PNS effects when brain data are available, and therefore, these data are not an ''appropriate surrogate for PNS effects'' and should not have been relied upon as the basis for retaining any portion of the safety factor. In support of these points, Petitioners submit summaries of the testimony they intend to offer at a hearing, along with copies of published studies that they allege provide evidence of the points raised in the testimony.

In essence, these two main issues overlap, particularly with respect to the evidence submitted. Petitioners rely on the same studies to support both points. However, they are presented below separately as discrete issues in the interest of clarity. Supplemental to these two main points, EPA has identified three separate allegations made by Petitioners in support of this objection, which are also analyzed individually in this section.

a. *Objection/hearing request subissue: Whether a carbofuran PoD based on pup brain AChE inhibition data alone is adequately protective of PNS effects.* Petitioners argue that by establishing the PoD on pup brain AChE inhibition data, EPA has adequately accounted for all PNS effects in pups without the need for an additional children's safety factor. They argue that brain data will adequately protect against PNS effects, based on the claim that the available data show that the brain is equally sensitive or more sensitive than PNS tissue. In support of this objection, Petitioners' submit the evidence contained in Exhibits 4 and 6. Exhibit 4 consists of a report by Kendall Wallace, PhD, entitled ''Expert Report: Carbofuran FQPA Safety Factor,'' along with published studies conducted with OP chemicals, and other NMC chemicals (Ref. 17, 51, 53, 54, 59, 61, 62, 72). Exhibit 6 consists of a report by Lucio Costa, PhD, entitled, ''Expert Report: Carbofuran's FQPA Safety Factor and Interspecies Uncertainty Factor,'' as well as published literature studies conducted with chlorpyrifos and disulfoton, both OP pesticides, and a single study with propoxur, an NMC pesticide.

i. Background. In the proposed tolerance revocation, EPA presented its rationale for retention of a children's safety factor.

As explained in Unit IV.A, EPA uses a weight of evidence approach to determine the toxic effect that will serve as the appropriate PoD (or regulatory endpoint) for a risk assessment for AChE inhibiting pesticides, such as carbofuran (Ref. 78). Neurotoxicity resulting from carbofuran exposures can occur in both the central (brain) and peripheral nervous systems (PNS). In its weight of the evidence analysis, EPA reviews data, such as AChE inhibition data from the brain, peripheral tissues and blood (*e.g.*, RBC or plasma), in addition to data on clinical signs and other functional effects related to AChE inhibition. Based on these data, EPA selects the most appropriate effect on which to regulate; such effects can include clinical signs of AChE inhibition, central or peripheral nervous tissue measurements of AChE inhibition or RBC AChE measures (Id). Due to the rapid nature of NMC pesticide toxicity it is difficult to document effects in the PNS or even AChE inhibition in the PNS and thus studies measuring AChE inhibition in the PNS are very rare for NMC pesticides. Although RBC AChE inhibition is not adverse in itself, EPA's policy is to use it as a surrogate for inhibition in peripheral tissues when peripheral data are not available. As such, RBC AChE inhibition provides an indirect indication of adverse effects on the nervous system (Id.).

There are laboratory data on carbofuran for cholinesterase activity in plasma, RBC, and brain from studies in

multiple laboratory animals (rat, mouse, dog, and rabbits). Among these are three studies that compare the effects of carbofuran on PND11 rats with those in young adult rats (*i.e.*, 'comparative AChE studies') (Refs. 1, 2, 66). Two of these studies were submitted by FMC and one was performed by EPA–ORD. An additional study conducted by EPA–ORD involved PND17 rats (Ref. 63).

The studies in juvenile rats show a consistent pattern that juvenile rats are more sensitive than adult rats to the effects of carbofuran. These effects include inhibition of brain AChE in addition to the incidence of clinical signs of PNS neurotoxicity, such as tremors, at lower doses in the young rats. This pattern has also been observed for other NMC pesticides, which exhibit the same mechanism of toxicity as carbofuran (Ref. 81). The 2008 SAP, in its review of the carbofuran draft NOIC, concurred with EPA that the brain AChE data clearly indicate that the juvenile rat is more sensitive than the adult rat (Ref. 36).

The Agency does not have any AChE inhibition data for carbofuran in the PNS tissue of adult or juvenile animals. There is data on RBC AChE inhibition, which is a surrogate for PNS tissue AChE inhibition, in adult animals at both high and low doses, and RBC data in pups, but only at doses causing greater than 50% AChE inhibition (a very high level of inhibition). In adults, the data show that RBC is generally more sensitive to the effects of carbofuran than the brain, but that at the lowest dose tested, brain and RBC have similar sensitivity. In pups, the available data at higher doses show that, like adults, RBC is more sensitive than brain. For example, the EPA–ORD studies showed that RBC AChE inhibition is more sensitive than brain AChE inhibition in both PND11 and PND17 pups at the lowest dose tested. However, the lowest dose (0.1 mg/kg) in both studies missed the lower portion of the RBC AChE inhibition dose-response curve for pups. At the lowest dose, PND 11 pups had approximately 40% brain and 53% RBC AChE inhibition while PND17 pups had approximately 25% brain and 50% RBC AChE inhibition. Consequently, the Agency does not have RBC AChE inhibition data in pups at the low doses (*i.e.*, those that cause only 10% inhibition) that are relevant to risk assessment to serve as a surrogate for PNS tissue data.

EPA explained that additional evidence for the sensitivity of the PNS to carbofuran's effects comes from data in pregnant rats exposed to carbofuran that showed clinical signs that may be indicative of peripheral toxicity. Finally, EPA explained that data from other AChE inhibiting pesticides show that direct measures of peripheral nervous system (*e.g.*, lung, heart, and liver AChE) can be more sensitive than brain AChE inhibition. To help illustrate, EPA gave an example of another chemical for which brain inhibition alone was not at all predictive of toxicity, to help explain why the lack of carbofuran data was so significant. The example given was fenamiphos (an OP pesticide), where cholinergic toxicity (*e.g.*, tremors, miosis, salivation) was observed following inhibition of RBC, but not brain, even up to maximally tolerated doses (McDaniel and Moser, Ref. 53).

Normally, EPA would regulate based on the most sensitive endpoint, which in this case would appear to be the effects on children's PNS. However, as discussed above, EPA lacked the information that would allow it to establish a PoD (or regulatory endpoint) based on the effects on children's PNS. EPA therefore established its PoD based on the AChE inhibition in pup brain. Generally, by regulating based on pup data, EPA would directly account for any additional sensitivity that children might have, because the safe levels estimated from these data would be the levels at which infants and children would be affected. In such circumstances, EPA could reduce the children's safety factor.

But because EPA lacked the data on the PNS effects in pups at low doses of carbofuran, which are most analogous to the exposures that infants and children will receive from eating food with carbofuran residues, the Agency could not be confident that assessing risk using brain AChE inhibition would be protective of potential effects in the PNS for infants and children. Accordingly, EPA determined that, even though the Agency was relying on pup data, consistent with the statutory mandate that an additional safety factor be applied to account for children's increased sensitivity in the absence of information affirmatively demonstrating that no such safety factor is necessary, the Agency could not conclude that removal of the statutory default 10X would be ''safe for infants and children.'' As some information was available to characterize the effects on infants and children, EPA concluded that the full default 10X was unnecessary, and that it could safely reduce the factor to 4X.

Petitioners raised many of the same assertions in their comments on EPA's proposed rule that they raise in their objections. For example, the Petitioners claimed that because EPA relied on pup brain data, no additional safety factor would be necessary to account for children's increased sensitivity, because ''brain data are a better surrogate for the PNS than RBC data.'' The comments also contended that RBC data are problematic in a number of regards, *e.g.,* they are more variable. They also argued that EPA had generally relied exclusively on brain data for other NMC pesticides, and that to require an additional safety factor for carbofuran based on the lack of RBC AChE data was inconsistent with those other decisions.

In the final rule and response to comments EPA responded to all of the Petitioners' claims, and comprehensively restated its reasoning that the lack of PNS inhibition data warranted retention of some portion of the children's safety factor for carbofuran (74 FR 68694–68695 (May 15, 2009)). In essence, EPA explained that Petitioners had not presented any information that fundamentally altered the available risk information before the Agency. Specifically, EPA concluded that, given that (1) the EPA–ORD data clearly show that a surrogate measure of the peripheral nervous system (RBC AChE) in juvenile rats is more sensitive to the effects of carbofuran than brain AChE inhibition; (2) clinical signs consistent with toxicity to the peripheral nervous system were seen at very low doses of carbofuran; and (3) data from other AChE inhibiting pesticides show that direct measures of peripheral nervous system (*e.g.,* lung, heart, and liver AChE) can be more sensitive than brain AChE inhibition, the Agency could not be confident that assessing risk using brain AChE inhibition would be protective of potential effects in the peripheral nervous system for infants and children.

ii. Denial of hearing request. EPA is denying Petitioners' hearing request on this subissue because the evidence proffered, even if established, is insufficient to justify the factual determination urged (40 CFR 178.32(b)(2)). The totality of the evidence submitted fails to demonstrate a reasonable possibility that exclusive reliance on *carbofuran* brain data will be protective, largely because they have failed to proffer any evidence on several points that are critical to their argument. As such, the objection rests on speculation and mere allegation, and a hearing will not be granted on this basis (Id. *See, e.g.,* 73 FR 42708 (July 23, 2008); 57 FR 6667, 6671 (February 27, 1991)).

It is important to remember that to obtain a hearing on EPA's children's safety factor decision, Petitioners must proffer more than evidence on whether

EPA erred, Petitioners must proffer evidence showing there is ''reliable data'' supporting the children's safety factor they urge. Without the latter, their objection is immaterial because the default position is retention of an additional 10X safety factor. Accordingly, EPA has evaluated Petitioners' proffers on its children's safety factor claims in terms of whether they are sufficient to provide the ''reliable data'' needed to justify the 1X safety factor that Petitioners propose.

For purposes of resolving whether the statute requires the retention of a children's safety factor, the critical issue is whether sufficient data exists to determine the effects on children's peripheral nervous systems from low doses of carbofuran. None of the evidence submitted affirmatively addresses this question. As discussed in more detail below, the only evidence proffered in support of this objection was: (1) A subset of the available carbofuran data from adult animals; and (2) data, primarily in adult animals, from other chemicals to demonstrate that generally, reliance on brain data will be protective of PNS effects, and therefore EPA can assume that the same will hold true for carbofuran. However, the Petitioners have failed to submit any data to demonstrate that the effects seen in adults will be predictive of the effects in juveniles. They have also submitted no evidence specific to carbofuran that demonstrates the effects of low doses on children's peripheral nervous systems. This is critical because the evidence they do proffer on other chemicals fails to establish that as a general matter, reliance on brain data will always be protective of the effects on the PNS. The majority of the evidence in other chemicals actually proves that reliance on brain data is frequently not protective of the effects on the PNS. And the remainder of the evidence on this point, taken in the light most favorable to the Petitioners, provides only equivocal support for Petitioners. Such evidence, by itself, is insufficient to relieve the uncertainty that remains with respect to carbofuran, based on the affirmative evidence in carbofuran-specific data, showing that reliance on brain data may not be protective. And such evidence, that entirely fail to address the points that the statute makes central to a determination of the appropriate children's safety factor, cannot justify a hearing.

When examined more closely, their overall evidentiary proffer is even less impressive. As discussed, much of the evidence was conducted in adult rats. Indeed the only evidence Petitioners submitted in support of this objection that was specific to carbofuran's effects on the PNS was data in adult rats. No evidence was submitted to demonstrate that adult data are generally predictive of responses in pups. Nor was any evidence submitted to support the assumption that pups will respond to low doses of carbofuran in the same way as adults. Thus their evidentiary proffer is effectively based on mere speculation that adult data will be predictive of pup responses, which cannot justify a hearing (40 CFR 178.32(b)(2)). As EPA previously explained in the proposed and final rules, responses in adult rats are not necessarily predictive of, or relevant to, responses in juveniles since the metabolic capacity of juveniles is less than that of adults (73 FR 44864, 74 FR 23046). As such, juvenile rats can be more sensitive to some toxic agents. Simply put, studies that only involve adult animals, therefore, do not provide information on effects on the young, which is the focus of the children's safety factor. No matter how much evidence Petitioners can amass showing that brain AChE is protective of RBC AChE in adult animals, that does not relieve the uncertainty concerning potential sensitivity of PNS tissues in juvenile animals, particularly when all of the existing carbofuran data shows that pups are more sensitive than adults to the effects of carbofuran, and that clinical signs consistent with toxicity to the PNS were seen in pups at very low doses of carbofuran. Accordingly, in the absence of carbofuran data in pup PNS tissues or a surrogate such as RBC data, the Petitioners' evidentiary proffer fails to establish a reasonable possibility that this issue could be resolved in their favor. A hearing is not appropriate in such cases (40 CFR 178.32(b)(2)).

The central tenet of this objection is that regulating based on the effects in the CNS will ensure that the PNS is protected. In this regard, Petitioners do cite to studies in juvenile animals, but all of them are conducted with chemicals other than carbofuran.[11] Moreover, the Petitioners' evidence fails to demonstrate that the PNS can never be more sensitive than the CNS, or even that the PNS is typically less sensitive than the CNS. Rather, the evidence shows only that the CNS (brain) is sometimes more sensitive, and sometimes less sensitive than the PNS, depending on the chemical involved. Because the data do not show a consistent pattern, it indicates only that the relative sensitivity between the central and peripheral nervous systems varies depending on the chemical involved, which cannot establish that exclusive reliance on brain data as a general proposition will always be protective of PNS effects in pups. Nor can it establish that reliance on the brain data will be protective of the PNS effects in the case of carbofuran.

When data are not available for a specific chemical, conclusions based on other chemicals can only be scientifically supported if it has been demonstrated that the conclusion is always true. If, ''in some cases,'' the conclusion is not true, then in the absence of data on the specific chemical, the conclusion cannot be made for that chemical, and uncertainty exists regarding the effects of the individual chemical. Since there are no data on the effects of carbofuran in PNS tissues or RBC data at low doses in pups, even assuming that they were able to prove that for the specific chemicals identified, the CNS is sometimes more sensitive than the PNS, significant uncertainty would remain regarding carbofuran's effects on the PNS. This is because the only evidence specific to the effects of carbofuran on the PNS at low dose levels that can be used as a comparison with the brain AChE levels is the adult RBC data.

This also affects the materiality of this objection. If the adult RBC AChE data are not considered, as Petitioners suggest, no carbofuran-specific data exists to demonstrate the level of AChE inhibition in the PNS of either adults or pups at the low dose levels relevant to risk assessment. Thus, even assuming Petitioners could successfully establish every point they raise in this regard, the fact still remains that a decision maker would have no data that provides any information relating to the potential effects of carbofuran on a child's PNS. Given that FFDCA section 408(b)(2)(C) compels the application of a 10X safety factor in the absence of information to account for the presumptive sensitivity of children, the lack of any data bearing on carbofuran's PNS effects would require the Agency to apply a 10X safety factor, rather than the 4X factor applied in the final rule.

A further flaw in the Petitioners' evidence is that it is internally inconsistent. Notwithstanding their allegations (discussed in subissue b below) that RBC data are inherently unreliable and should be discounted in favor of brain data, the carbofuran adult RBC data are one of the primary pieces of evidence proffered to support the claim that reliance on the carbofuran pup brain data will protect against all

[11] Most of the studies were conducted on OP chemicals, and expressly caution against extending the results to NMC chemicals such as carbofuran; a point also raised by Petitioners' own experts (Ex 4, 6).

potential PNS effects (Exhibit 4). As discussed in more detail below, the Report cites to the carbofuran data with adult rats to conclude that brain AChE inhibition correlated closely with RBC AChE inhibition. ''This was further substantiated by the study published by McDaniel *et al.* (Ref. 54), where they report that the 'lowest dose of carbofuran (0.10 mg/kg) significantly decreased brain ChE activity but not RBC ChE or motor activity' * * *'' (Id. at 4, 6). Yet having granted scientific validity to the adult RBC data, they must also concede the relevance of the EPA–ORD carbofuran pup RBC data, which clearly demonstrate that at every dose tested, RBC AChE, and therefore the PNS for which it is a surrogate, is more sensitive than the brain in juvenile rats exposed to carbofuran. They raise no challenge specific to the scientific validity of the EPA–ORD data, but rely only on their generic challenge that RBC data are inherently less reliable than brain data. No hearing is warranted based on such evidence. See 49 FR 6672 (February 22, 1984) (challenge to one of five related studies; in the absence of any additional data bearing on the clinical study, the objection constitutes nothing more than an allegation); 68 FR 46403 (August 5, 2003) (hearing denied because cited studies only contained equivocal statements supporting objector's position).

Accordingly, the sum of their evidence is no more than mere speculation that the effects of carbofuran exposure in the CNS will be protective of effects in the PNS. This falls far short of the ''reliable data'' on the safety of infants and children needed to justify the entire removal of the 10X children's safety factor and thus cannot justify a hearing (40 CFR 178.21(b)(2)). *See, e.g.,* 73 FR 42697 (July 23, 2008) (denying hearing where the only evidence submitted was NRDC's claim that if the DDVP two-generation rat reproduction study had been conducted pursuant to the 1998 guidelines it might have shown endocrine effects at lower doses than the doses at which DDVP's cholinesterase effects were seen on grounds that this was mere speculation); 57 FR 6667 (February 27, 1992) (hearing denied to an objector who challenged FDA's rejection of a study for only containing partial histopathological data on the grounds that ''[s]peculation regarding data that do not exist cannot serve as the basis for a hearing'').

A detailed examination of Petitioners' evidence follows below.

(a) Testimony intended to show that brain is the appropriate endpoint. Petitioners allege that the ''critical effect of concern due to carbofuran is nervous system AChE. Brain is a direct measure of such toxic effects, while RBC not linked to any biological function.'' On this basis, they conclude that brain represents the most appropriate endpoint for risk assessment.

Essentially this testimony fails to prove any dispute of material fact. EPA relied on the carbofuran pup brain AChE inhibition data to establish carbofuran's PoD. The Petitioners have not argued that PNS effects are irrelevant. Indeed, their submissions make clear that effects on the PNS are appropriate considerations in a risk assessment; the only point they dispute is whether brain or RBC data best account for those effects (Exhibits 4, 6).

Alternatively, if they intend to argue that RBC data entirely lacks any scientific validity, this is contradicted in several places by their other objections and their own submissions. As discussed above, the commenters rely on the adult carbofuran RBC data to support their claim that reliance on the pup brain data is adequately protective of PNS effects. Moreover, they explicitly acknowledge that reliance on RBC data is scientifically valid in the context of the human data (Obj at 13). Consequently, the submitted materials are insufficient to justify the factual determinations urged, and therefore fail to support a determination that an evidentiary hearing is warranted (40 CFR 178.32(b)(2)).

(b) Testimony purporting to show that reliance on brain data is sufficiently protective of the PNS. The Petitioners raise several arguments in this regard. First, they allege that, ''brain responds rapidly to carbofuran, which readily passes blood/brain barrier'' (Obj at 12–13). Petitioners' primary point, however, is that ''the extent of brain inhibition by carbofuran more accurately compares with the extent of PNS inhibition, and therefore brain data are adequately protective'' (Id.). In support of this claim, Petitioners cite to Exhibits 4 and 6, containing a mixture of ''expert testimony'' and published studies. None of the information contained in these exhibits is sufficient to establish a reasonable possibility that this issue could be resolved in their favor.

Petitioners' first claim simply reiterates points made in their comments on the proposed rule. As explained in the final rule, EPA agrees that the data show that the brain responds rapidly to carbofuran, and that it readily passes the blood/brain barrier. However, evidence regarding the speed with which the brain reacts proves nothing with regard to the relative sensitivity of PNS tissues (Ref. 85 at 46). Petitioners have presented nothing that challenges the substance of EPA's response. Consequently, these claims do not present a live controversy as to a material issue of disputed fact; both parties agree on the facts at issue, which is that the brain responds rapidly to carbofuran. Moreover, a simple repetition of comments made on the proposal without more is insufficient to warrant a hearing. *See, e.g.,* 73 FR at 42698–42699 (July 23, 2008) (denying several NRDC hearing requests because the objections were based on EPA's preliminary DDVP risk assessment, rather than the revised risk assessment published with the final order); 53 FR 53176 (December 30, 1988) (where FDA responds to a comment in final rule, repetition of comment in objections does not present a live controversy unless objector proffers some evidence calling FDA's conclusion into question); 62 FR 64102, 64105 (December 3, 1997) (objector claimed that addition of ethoxyquin invalidated studies; hearing denied because objector did ''not dispute FDA's explanation in the final rule as to why addition of ethoxyquin did not compromise the CIVO studies, and provided no information that would have altered the agency's conclusion on this issue'').

Petitioners' second point—that brain AChE inhibition correlates closely with PNS inhibition, and demonstrates that reliance on brain data will be protective of the PNS—is a disputed material issue of fact that could warrant a hearing, except that none of the evidence submitted in support of this point presents a reasonable possibility that the Petitioners could establish the points alleged. Consequently, they have failed to demonstrate that a hearing is warranted on this objection (40 CFR 178.32(b)(2)).

(c) Exhibit 4. This exhibit consists of a report by Kendall Wallace, PhD, entitled ''Expert Report: Carbofuran FQPA Safety Factor,'' along with published studies (Ref. 17, 51, 53, 54, 59, 61, 62, 72). The report argues that, ''it is my opinion that for carbofuran, the evidence indicates that inhibition of brain AChE is an appropriate surrogate for PNS AChE inhibition and that there is reasonable certainty that a PoD for carbofuran based on brain AChE inhibition is protective of any adverse CNS and PNS effects.'' The only carbofuran evidence directly cited in support of this allegation is data conducted on adult animals, using RBC AChE data, which they elsewhere try to discount. This assumes that adults and pups are similarly sensitive despite the carbofuran-specific evidence to the contrary. No evidence is discussed or

submitted to support this assumption. This therefore constitutes a mere allegation, which does not justify a hearing.

None of the published studies conducted with other chemicals cited in the Report provide more than equivocal support for the points above; in fact, in several instances, the study results support EPA rather than the Petitioners.[12] The studies contained in this exhibit fall into two general categories. The first group of studies consists of a subset of the chlorpyrifos literature—which is generally more relevant to the subissue discussed in the next objection, arguing that RBC data are not a good surrogate for the PNS—rather than demonstrating affirmatively that brain is a protective surrogate for the PNS. The second category of studies is one paper on physostigmine, a carbamate, that is discussed in the body of the report. All but one of these studies was conducted using adult rats.

Marable, *et al.* (Ref. 51) and Nostrandt *et al.* (Ref. 59) are two of the chlorpyrifos studies Petitioners submitted as part of the comments on the proposed rule, and they contain little evidence to demonstrate that brain data correlate well with the PNS, and thus are generally protective of the PNS. Marable *et al.* involved chronic exposures to adult dogs; in addition to the fact that adult animals were used, and therefore provide evidence of little relevance to the question at issue, there are significant differences between the results of chronic and acute exposures. As a result of the repeated exposures, blood, brain and peripheral tissues were at steady state, which cannot occur from an acute exposure, and therefore this study can provide no information on the effects from acute exposures. Nostrandt *et al.* actually reported that, following a single low dose of chlorpyrifos, brain inhibition was less (not greater) than the inhibition obtained in heart which is part of the PNS (although higher inhibition was not seen in the diaphragm or retina, other parts of the PNS). At higher doses, the inhibition in brain and peripheral tissues were more similar. Thus, this study contradicts the Petitioners' claim that brain data will be protective of all PNS effects. Petitioners offer no explanation of how the resubmission of these studies addressed EPA's conclusion in the final rule that the chlorpyrifos data failed to prove their claim.

Chen, *et al.* (Ref. 17), another study of chlorpyrifos, discussed whether plasma or RBC AChE should be used to establish a regulatory endpoint in humans and compared data from several animal studies, some of which were conducted with adults and some with pups. This is the only study in Exhibit 4 that contains data on pups. The results of one of the studies reported in Chen, *et al.* shows that at the lowest doses, inhibition was greater in the heart, which is part of the PNS, than in the brain (56% and 41% respectively); note that these are the data in adult rats reported in Nostrandt *et al.* (described above). Based on data from a developmental study of chlorpyrifos by Hoberman (Ref. 37), Chen *et al.* reported that the doses estimated to produce 50% inhibition in heart and brain actually show that in 5-day old pups (both males and females), the heart is 2–3 times more sensitive than brain. Thus, this study contradicts Petitioners' claim that brain data will be protective of PNS effects, since the PNS inhibition was greater than brain at the lowest doses in both adults and pups. And in fact, it supports EPA's concern that the absence of data at low doses is significant because the effects at low doses can differ significantly from those at higher doses. The data from Hoberman showed that at higher doses, ranging from 30–100 mg/kg, the levels of inhibition in the brain were higher than the levels in the PNS (Ref. 37 at 16)—the exact opposite of what occurred at the lowest doses.

The second group of studies consists of data on NMC chemicals. McDaniel *et al.* (Ref. 53) and Padilla *et al.* (Ref. 62) were cited in support of the claim that the difference in sensitivity between the brain and RBC is generally less for NMC chemicals. These studies were conducted with adult animals, and so do nothing to address the question before the Agency with respect to pups. These studies merely confirm the existing carbofuran data in adults, which shows that at the lowest dose tested, brain and RBC are essentially the same.

Somani *et al.* (Ref. 72) is a study on another NMC chemical, physostigmine, in adult animals, cited to support the claim that ''in adult rats, brain AChE is somewhat more sensitive than RBC or peripheral AChE to inhibition by acute doses of physostigmine.'' As an initial matter, it is unclear that this study provides more than equivocal support for their claim; the study authors claim only that the brain ''appears'' to have the lowest values. However, even conceding that this study shows that the CNS tissues in adult rats are more sensitive to the effects of physostigmine than the PNS tissues, the data in this study is of limited relevance to the issue at hand, which is the effects in juveniles. Thus it is ultimately insufficient to affirmatively support the Petitioners' claim.

In sum, based on the evidence contained in this exhibit, EPA concludes that there is not a reasonable probability that the proffered evidence would resolve the issue in Petitioners' favor, and that consequently no hearing is warranted on this basis. First, all but one of the studies discussed in this exhibit were conducted with adult animals, rather than pups. As such, they provide evidence of little relevance to the question of whether pups' PNS are more sensitive than the CNS. In the absence of carbofuran PNS data, or pup RBC data, much of this evidence is effectively mere speculation about whether adult data will be predictive of pup responses, which cannot justify a hearing (40 CFR 178.32(b)(1)).

(d) Exhibit 6. This exhibit consists of a report by Lucio Costa, PhD, entitled, ''Expert Report: Carbofuran's FQPA Safety Factor and Interspecies Uncertainty Factor,'' as well as published literature studies conducted with chlorpyrifos and disulfoton, both OP pesticides, and a single study with propoxur, an NMC pesticide (Refs. 71, 19, 20, 21, 61, 52, 41, 64, 16). According to Costa, these studies generally show that there was similar or greater AChE inhibition in brain than in the PNS tissues of heart, ileum, or the diaphragm, which Petitioners claim proves that reliance on carbofuran pup brain AChE inhibition data will necessarily be protective of all effects in the PNS (Exhibit 6 at 3). The exhibit also references a human incident study (Ref. 50) of carbamate poisoning in early childhood and in adults, claiming that, ''Lifshitz * * * showed that signs of adverse effects in the CNS, rather than PNS, prevailed in young children at the low dose levels covered by the paper.''

EPA concludes that there is not a reasonable probability that the evidence contained in this exhibit would resolve the issue in Petitioners' favor. The results of these studies fail to demonstrate the point for which Petitioners cite them—that brain AChE is always equally or more sensitive than PNS AChE, and therefore exclusive reliance on brain data can be assumed to be protective. Consequently, the fact that Petitioners can identify examples of other chemicals, whether OPs or NMCs, that sometimes affect the brain more severely than the PNS does not prove

[12] It is interesting to note that, in Exhibit 4, the expert actually faults EPA for comparing OP and NMC pesticides, saying ''Although OP pesticides inhibit AChE, they are completely different from carbofuran and other *N*-methylcarbamates * * *:'' (Exhibit 4 at 4). Yet the Exhibit includes papers on effects of chlorpyrifos, an OP, and these papers are not discussed in the text of the Exhibit.

that this will be the case with carbofuran. Furthermore, in several of the cited examples the Petitioners misinterpret the findings, which actually support EPA's position.

As explained in EPA's final rule, Petitioners are relying on only a subset of the chlorpyrifos data. The data, when examined in total, do not support a conclusion that brain data will always be protective of PNS effects (74 FR 23054–23055 (May 15, 2009)). But even relying solely on the studies Petitioners reference in this exhibit, it is clear that brain is not always inhibited to the same degree as peripheral tissues, nor is it always protective of peripheral tissues. The data in Padilla *et al.* (Ref. 61) are the only chlorpyrifos data that support a conclusion that reliance on the CNS data will be protective of the PNS. However, the Padilla study involved chronic dosing of rats via the feed, and as such, cholinesterase measurements reflected steady-state conditions. This study cannot provide information relevant to acute exposure. None of the other chlorpyrifos studies referenced in this exhibit support this conclusion. In Mattson *et al.* (Ref. 52), and Hunter *et al.* (Ref. 41), following a single dose to pregnant dams, heart and liver tissues were more inhibited than brain tissues. Similarly, in Richardson and Chambers (Ref. 64), where repeated doses were administered to pregnant dams, at both the low and high doses, the lung tissue was more inhibited than the brain tissue in the one-day old pups. In Carr *et al.* (Ref. 16), the results were more equivocal; in a repeated dosing study using pups of varying ages, whether brain or peripheral tissues were most inhibited depended on the age of the pups and the dose. Nevertheless, Carr (2001) showed that brain inhibition decreased as the age of the pups increased, even though inhibition in the heart tissues did not. In other words, the submitted material only supports a conclusion that brain is sometimes inhibited by chlorpyrifos to the same degree as the peripheral tissues, and in reality, the studies show that brain is often inhibited to a lesser extent than peripheral tissues. This cannot support a conclusion that reliance exclusively on brain data will necessarily be protective in the absence of some additional carbofuran-specific evidence.

The results are similar for the disulfoton studies. Schwab *et al.* (Ref. 71) shows that after both a single dose and repeated doses, the brain and peripheral tissues were equally inhibited. However, these results are contradicted by Costa *et al.* (Ref. 19) and Costa and Murphy (1983), where the results varied depending on the dosing and the brain area examined. In Costa and Murphy (Ref. 21), diaphragm tissues were more inhibited than brain tissues after a single dose of disulfoton, while after repeated doses, brain and diaphragm tissues were similarly inhibited. Thus, the relative sensitivity between CNS and PNS changes with repeated dosing, and these studies provide no information on RBC inhibition with which to compare the other tissues.

Finally, the Lifshitz study does not support the claim for which it was cited. The study presents no data on the dose levels associated with the poisoning incidents, and in fact concludes that there was ''insufficient information to compare the doses ingested by [adults and children].'' However, based on the symptomology reported (comas, stupor, and severe hypotoxicity) it is likely that the doses were high, not low, as the Report claims. Also, this study cannot be used to discount PNS effects in children; a large percentage of the children clearly showed PNS effects (myosis, diarrhea). In addition, because this was a retrospective study of patients admitted to a hospital intensive care unit, given the severity of some of the CNS symptoms, such as comas, it is not unlikely that even if the subjects also showed PNS symptoms, they were not reported. Finally, the study authors' conclusion was that in children, the ''clinical presentation [of carbamate poisoning] differs from adult poisoning manifestations'' (Ref. 50). Or in other words, that the effects in adults from exposure to carbamates such as carbofuran are not necessarily predictive of the effects in children. It is difficult to see how this study could be fairly argued to support Petitioners' allegations.

In conclusion, the totality of the evidence in Exhibits 4 and 6 fail to support Petitioners' contention. As shown in Table 1 below, the majority of the study results demonstrate that the PNS is frequently more sensitive than the CNS. The remainder, taken in the light most favorable to the Petitioners, provide merely equivocal support.

TABLE 1—SUMMARY OF PETITIONERS' STUDIES

	Study design	Relative inhibition	Is CNS protective of PNS?
Chlorpyrifos Studies			
Padilla *et al.* 2005	Single dose, adults	RBC > brain ≈ diaphragm	Yes (same sensitivity).
Mattsson *et al.* 2000	Single dose, pregnant dams	RBC > heart > brain	No.
Hunter *et al.* 1999	Single dose, pregnant dams	Liver > brain Blood not measured.	No.
Richardson and Chambers 2003	Repeated doses to pregnant dams, measured pups at 1 day old (not direct dose).	Low dose, lung > serum ≈ brain > heart. High dose, lung > brain ≈ heart > serum. Note, serum has only ≈ 50% AChE, not true measure of AChE.	No.
Carr *et al.* 2001	Repeated doses to pups	PND6: brain ≈ diaphragm > heart ≈ lung > skeletal muscle ≈ serum. PND10: heart ≈ hindbrain ≈ diaphragm ≈ lung > skeletal muscle > forebrain ≈ serum. PND16: heart ≈ lung > brain. PND20: heart > lung > brain. PND25: brain > PNS. Brain inhibition decreased with age, heart did not.	Not always, depending on age, dose, and brain region.

TABLE 1—SUMMARY OF PETITIONERS' STUDIES—Continued

	Study design	Relative inhibition	Is CNS protective of PNS?
Nostrandt *et al.* 1997 (also cited in Chen *et al.* 1999).	Acute dose, adults	RBC > heart > brain > diaphragm	No.
Hoberman 1998 as cited in Chen *et al.* 1999.	Repeated doses to pregnant dams, measured in pups at 5 days old (not direct dose).	RBC > heart > brain	No.
Disulfoton Studies			
Schwab *et al.* 1981	Single dose	heart ≈ ileum ≈ brain	Yes, similar sensitivity.
	Repeated doses	brain ≈ ileum > heart No blood measured	
Costa *et al.* 1981	Single dose	Brain > ileum	Not always, depends on dosing paradigm and brain region.
	Repeated doses	Forebrain > ileum > hindbrain	
		Brain ≈ ileum	Not consistent within same study.
	Repeated doses	No blood measured.	
Costa and Murphy 1983	Single dose	Diaphragm > brain	Not always, depends on dosing paradigm.
	Repeated doses	Brain ≈ diaphragm ≈ plasma. Note, plasma has only ≈ 50% AChE, not true measure of AChE.	

Accordingly, Petitioners' proffer is facially insufficient because there is no reasonable possibility that it can establish a necessary element of Petitioners' objection—that there are ''reliable data'' that show it would be safe for infants and children to remove entirely the 10X children's safety factor.

iii. *Denial of objection.* The objections do not address the fundamental issue that EPA is required by the statute to resolve: Are there 'reliable' data to support reduction or removal of the statutory 10X for protection of infants and children? The statute compels that EPA may only revise the 10X default safety factor if, ''on the basis of reliable data'' EPA can conclude that the alternative safety factor will be ''safe'' (21 U.S.C. 346a(b)(2)(C)). The statute also requires EPA to account for the ''completeness of the toxicity data'' in making this determination (Id). In this case, the Agency concluded that there are sufficient data to reduce the 10X safety factor but there is insufficient information to justify removing the factor entirely.

Similar to other AChE inhibiting pesticides, carbofuran can affect both the central and peripheral nervous system. Because the relative sensitivity of the central and peripheral nervous system varies among pesticides and the children's safety factor should account for the most sensitive toxicity endpoint, the Agency considers the availability of data in both the central and peripheral nervous systems important in its safety factor evaluation.

As shown in Figure 1, above, there are several datasets that evaluate the effects of carbofuran on the central nervous system (*e.g.,* brain AChE inhibition) in juvenile rats. There are no AChE data from peripheral tissues. Lack of peripheral AChE data is typical of NMCs due to the rapid reactivation of AChE. As a matter of science policy, the Agency typically uses AChE data from blood, particularly RBCs, as a surrogate measure for the peripheral nervous system (Refs. 76, 87). In the case of carbofuran, RBC AChE data from two separate studies submitted by FMC are considered unreliable and unusable in human health risk assessment (Ref. 83). Data from EPA's ORD includes high quality RBC AChE data, but only high doses were used in the ORD studies. Data at the low end of the dose response curve are not available for assessing the effects in juvenile rats, which are the doses relevant for human health risk assessment. Thus, because reliable data are available to assess affects on the CNS and some surrogate data are available to assess the PNS, the Agency believes that the children's safety factor can be reduced. However, this factor cannot be completely removed since the available carbofuran data show that RBC AChE inhibition in pups is more sensitive than brain AChE inhibition.

Given that (1) data from other AChE inhibiting pesticides show that direct measures of peripheral nervous system (*e.g.,* lung, heart, and liver AChE) can be more sensitive than brain AChE inhibition; (2) a surrogate measure of the peripheral nervous system (RBC AChE) is more sensitive in juvenile rats to carbofuran; and (3) clinical signs consistent with toxicity to the peripheral nervous system were seen at very low doses, the Agency can not be confident that assessing risk using brain AChE inhibition is protective of potential effects in the peripheral nervous system for infants and children. For example, in the first FMC-sponsored comparative ChE studies (Ref. 4) every pup at the 0.3 mg/kg dose group exhibited tremors. The range-finding portion of the second FMC-sponsored comparative ChE study (Ref. 1) resulted in tremors in rats exposed to 0.3 mg/kg carbofuran (2/5 males and 2/5 females) within 15 minutes post-dosing.

Additional evidence for sensitivity of the PNS comes from carbofuran data in pregnant rats that showed clinical signs that may be indicative of peripheral toxicity. The California Department of Pesticide Regulation (CDPR) has calculated a BMD_{10} and $BMDL_{10}$ of 0.04 and 0.03 mg/kg/day, respectively, for mouth smacking and chewing in pregnant rats exposed to carbofuran. These signs are early indicators of toxicity from some cholinesterase inhibitors (Ref. 56). This is notable for two reasons. First, cholinergic toxicity (*e.g.,* tremors, miosis, salivation) may be observed following inhibition of blood, but not brain, cholinesterase. This was the case with fenamiphos (an OP pesticide), even up to maximally tolerated doses (Ref. 53). Second, the $BMDL_{10}$ from the mouth smacking and chewing in pregnant rats is similar to that being used by EPA for brain AChE in juveniles. The similarity of the CDPR BMD in adults and EPA's BMD in juveniles is striking because all of the available data show that pups are more sensitive than adults to carbofuran toxicity. This therefore suggests that behavioral effects and/or clinical signs may be occurring in juvenile animals at lower doses, but which cannot be detected, in part due to the challenges

with assessing clinical signs in juvenile rats. As noted by the SAP, this ''limitation reflects the limited range of toxic signs detectable in very young pups (p. 54).'' This provides further support that the lack of pup data at lower doses is significant, because the Agency cannot fully evaluate the behavioral effects on juvenile animals.

Further support for the Agency's concern comes from other clinical reports of the effects of carbamate poisoning in children. For example, Lifshitz reported that all children presented with CNS symptoms (coma, stupor), but CNS symptoms were observed in only 54% and 23% of children as reported by Zweiner and Ginsburg (1988) and El-Naggar *et al.* 2009 (Refs. 91, 26). Peripheral muscarinic symptoms were the most commonly reported (73% and 100%) signs of toxicity in these latter two reports. These markedly different findings emphasize that conclusions cannot be unequivocally drawn from only one study.

In addition, Petitioners' own data show that effects can differ significantly between high and low doses. In Chen, for example, the data from Hoberman showed that at the lowest doses the levels of inhibition were higher in the PNS than in the brain, but at higher doses, the levels were higher in the brain.

Thus, for a number of reasons, the Agency has concerns that children's PNS may be more sensitive to the effects of carbofuran than the CNS. This concern is the basis for retention of a portion of the children's safety factor.

The carbofuran RBC data in adult animals does not resolve this question. There can be substantial differences in response between pups and adults, and, as noted, the data show clearly that pups are more sensitive to the effects of carbofuran. It is not unusual for juvenile rats, or indeed, for infants or young children, to be more sensitive to chemical exposures as metabolic detoxification processes in the young are still developing. Because pups are more sensitive than adult rats, data from pups provide the most relevant information for evaluating risk to infants and young children and are thus used to derive the PoD. In addition, typically (and this is the case for carbofuran) young children (ages 0–5) tend to be the most exposed age groups because they tend to eat larger amounts of food per their body weight than do teenagers or adults.

b. Objection/hearing request subissue: Reliance on RBC AChE inhibition data as a surrogate for PNS effects. This objection also challenges EPA's decision to retain some portion of the presumptive 10X children's safety factor, rather than remove it entirely. As explained above, EPA retained a portion of the presumptive 10X children's safety factor because of the absence of sufficient data on PNS effects in juveniles and the uncertainty created by the limited data relevant to the PNS that showed greater sensitivity in juveniles. In the previous subissue, Petitioners argued that in fact there is no uncertainty created by the lack of low dose RBC data and the finding of sensitivity in the RBC AChE data because brain AChE data is protective of PNS effects. In this subissue, Petitioners attempt to buttress their first argument by claiming that RBC AChE data are not an ''appropriate surrogate'' for PNS effects, and should not have formed the basis for retention of any portion of the children's safety factor.

Petitioners do not argue that RBC data are entirely irrelevant, but rather that brain data are ''preferred.'' They raise several points in support of this contention; first, that ''RBC AChE inhibition data are only preferred for risk assessment purposes in two circumstances: (1) Where the PoD is set using data from human studies where only RBC data are available or (2) where data from the relevant target tissues are unavailable.'' They allege that, despite the absence of carbofuran data in the PNS tissues, brain is preferred in this case because the brain is ''target tissue'' from the nervous system, and because brain data are a ''better predictor'' of PNS effects than RBC. As further evidentiary support, they cite to evidence from OP studies that RBC AChE can ''in some cases'' be inhibited to a greater degree than either PNS or brain AChE, and therefore reliance on RBC AChE data can overstate potential PNS effects. They also argue that RBC AChE is more variable and less reliably measured at low response levels, such as 10% AChE inhibition. The evidence in Exhibits 4 and 6 is also proffered in support of this objection.

i. Background. EPA's well-established policy when evaluating cholinesterase-inhibiting compounds is to rely on data in the target tissue where it is available (Ref. 76). As noted in the preceding section, measures of AChE inhibition in the PNS are rarely collected for NMC pesticides. And in fact, there are no carbofuran data measuring effects in PNS tissues. But in the absence of target tissue data, as a matter of science policy, EPA typically uses RBC AChE inhibition data as an indicator of possible effects on AChE in the PNS for number of reasons. (Ref. 76 at 32). Although RBC AChE inhibition is not adverse in itself, it is a surrogate for inhibition in peripheral tissues. As such, RBC AChE inhibition provides an indirect indication of adverse effects on the nervous system (Id.).

Petitioners raised many of the same issues raised in the objections in their comments on the proposed rule. For example, they argued that, ''as a matter of science policy, brain AChE inhibition is the preferred endpoint over RBC AChE inhibition.'' They also argued that no physiological function has been demonstrated for RBC, and RBC AChE inhibition is not itself an adverse effect.

In the final rule, EPA responded to each of their comments, but concluded that no information had been submitted to justify altering the Agency's general policy that reliance on RBC is appropriate as a surrogate for PNS effects in the absence of direct measurements in PNS tissues.

ii. Denial of hearing request. This subissue does not raise a dispute of material fact. There is no dispute regarding many of the facts raised in this objection: When data in the target tissue are available, it is preferred over a surrogate. RBC AChE can be more variable and less reliably measured at low response levels than brain AChE. RBC AChE inhibition can, in some cases, be more extensive than PNS AChE inhibition. Equally, there is no dispute that no physiological function has been demonstrated for RBC, and RBC AChE inhibition is not itself an adverse effect. All of these points are explicitly recognized in EPA's Cholinesterase policy and in the tolerance revocation rulemaking record, and relate purely to the ease or wisdom of relying on these measures rather than others, as opposed to the scientific invalidity of such data. The only point on which there is a dispute is, given that there is no data in the target tissues of the PNS, which data—brain or RBC—is ''preferred.'' The Petitioners expressly acknowledge this to be the issue: ''There are other surrogate measures of PNS AChE that could have been selected by OPP, such as brain AChE'' (Exhibit 4 at 5). This is clearly a question of scientific policy, since both EPA and the Petitioners agree on the scientific validity and relevance of RBC AChE inhibition data. As they expressly acknowledged in their comments, the choice of which surrogate to use is a matter of ''science policy'' (Ref. 18). Indeed, Petitioners explicitly concede the propriety of relying on RBC data ''where data from the relevant target tissues are unavailable, or when relying on human data, where RBC AChE inhibition data are the only data available (Obj at 13). Hearings are not

appropriate for debating questions of policy (40 CFR 178.32(b)(1)).

Nor does the proffered evidence present any other issue that would warrant a hearing. The evidence submitted in Exhibits 4 and 6 on this point only relates to the question of whether brain data can sometimes correspond more closely with PNS effects than RBC AChE data, rather than the question of whether the RBC data are scientifically invalid. Or in other words, the submitted materials relate only to the point that reliance on RBC data is unnecessarily conservative, because sometimes it overestimates the potential PNS effects, rather than to the factual question of whether RBC data bears no relation whatsoever to PNS effects. Unless Petitioners can show that RBC AChE is not related to CNS effects generally or specifically for carbofuran, or that brain AChE is protective of CNS effects generally or specifically for carbofuran, then the mere fact that RBC AChE may be a conservative, or even very conservative, indicator of PNS effects is simply immaterial to the question of whether there are ''reliable data'' to justify removing the presumptive 10X children's safety factor in the absence of sufficient RBC AChE data. As shown in the discussion of subissue 1, the Petitioners' evidence does not demonstrate that reliance on juvenile brain data as a surrogate for effects in the juvenile PNS will guarantee that the levels chosen on that basis will be predictive of all PNS effects from carbofuran, because the PNS effects occur only at the same or higher doses than those that produce effects on the brain AChE—*i.e.,* that the brain data ''bound'' all potential PNS effects. Nor, as discussed below, does any of Petitioners' evidence support a conclusion that RBC AChE is unrelated to PNS effects.

Indeed, much of the evidence in the Exhibit 4 and 6 Reports is ultimately an irrelevance, and thus fails to present a material factual dispute. Instead of focusing the stated objection—RBC AChE is inappropriate marker for CNS effects—the Reports attempt to link EPA's children's safety factor decision to findings concerning chlorpyrifos (Exhibit 4 at 4). In fact, a fair portion of the Report in Exhibit 6 is dedicated to a rebuttal of EPA's conclusion that the majority of the more recent and more relevant chlorpyrifos evidence did not support Petitioners' contention. EPA, however, has been clear throughout the rulemaking that the basis for retention of a children's safety factor has been the absence of carbofuran data to determine the levels of exposure that will be protective of children's PNS, in the context of a statutory provision that expressly requires EPA to account for missing data. EPA's point in discussing the chlorpyrifos data—which Petitioners initially raised as relevant—was simply that it showed that because peripheral tissues can be more sensitive than central nervous system tissues, the absence of data addressing carbofuran's effects on the PNS is highly relevant. Whatever the chlorpyrifos data show cannot resolve the extent of carbofuran's risks. As the Petitioners' experts themselves point out, ''Even conceding that [EPA's conclusion in the final rule that peripheral tissues are often shown to be more sensitive than brain tissue following exposure to chlorpyrifos] may be true, it is still unclear how this would be relevant to carbofuran * * *'' (Exhibit 6 at 3). Accordingly, this evidentiary submission fails to demonstrate that a dispute exists on a question of material fact.

Finally, their submission provides an inadequate basis on which to grant a hearing; because evidence is not proffered on critical points, the objection ultimately rests on allegation, speculation, and general denials (40 CFR 178.32(b)(2)). As discussed in preceding section, the majority of the evidence comes from adult data, which are of limited relevance. Further, and more significantly, the evidence fails to demonstrate that brain data always—or even more frequently than not—correlates more closely with PNS effects than RBC AChE data. Instead, the proffered evidence only demonstrates that whether brain or RBC data correlate better with actual PNS effects can vary depending on the chemical. This, therefore, cannot resolve the question as to whether, in the case of carbofuran, brain AChE data will necessarily correspond more closely with the PNS. Finally, as also discussed in the preceding section, Petitioners' argument is internally inconsistent, because they rely on carbofuran adult RBC AChE data to support their argument that exclusive reliance on the brain data will be protective of potential PNS effects in pups. No hearing is appropriate where the proffered evidence fails to prove the points for which it is offered, or offers merely equivocal support (See, 73 FR 42705 (July 23, 2008) (hearing denied because published articles focus on an issue not applicable to the facts of the case at hand); 68 FR 46405–46406 (August 5, 2003) (a hearing was denied because the cited studies only contained equivocal statements)).

A detailed examination of Petitioners' evidence follows below:

(a) Exhibit 4. As discussed in the previous objection, this exhibit consists of a report, along with published studies. The Report criticizes EPA for assuming that RBC AChE inhibition provides ''a stronger and more quantitative concordance with the sensitivity of AChE of the PNS to inhibition by carbofuran,'' on the ground that EPA failed to cite to evidence to support this inference (Exhibit 4 at 5). In the absence of such evidence, the report concludes that, ''one cannot discount the plausibility that brain AChE may be a more quantitative and representative surrogate measure of PNS sensitivity'' (Id). To support this allegation, the report argues that the cited NMC data show that the difference in sensitivity between brain and RBC shown with NMC chemicals is less than the differences seen with OP chemicals, citing studies by Padilla *et al.* (Ref. 62) and McDaniel *et al.* (Ref. 54). In this regard, the Report actually misquotes McDaniel *et al.* The Report claims that the paper concluded that there was a stronger correlation between brain AChE inhibition and motor activity. The study actually concluded that there was little difference between brain AChE inhibition and RBC AChE inhibitions (''higher correlation for brain and motor activity compared to RBC were not significantly different.'') (Ref. 54). In any event, the Report's equivocal conclusion that ''one cannot discount the plausibility'' that brain AChE might be the most representative measure of PNS effect is, on its face, insufficient grounds to overcome the statutory presumption for retention of the additional 10X children's safety factor in the face of the evidence of children's additional sensitivity to carbofuran, and the lack of carbofuran data in PNS tissues or in a surrogate for such tissues, RBC AChE.

Chen *et al.* (Ref. 17), which was discussed at length in the earlier objection, evaluated whether plasma or RBC AChE should be used to establish a regulatory endpoint; it did not evaluate whether brain AChE would be an appropriate surrogate for PNS effects. It is true that the authors conclude that ''[i]nhibition of RBC AChE activity is consistently exhibited at lower dosages of chlorpyrifos than those required to result in clinical symptoms of OP toxicity, or alterations in cognitive functional responses.'' However, since the study authors ultimately concluded that, ''inhibition of RBC AChE activity is an appropriate surrogate for measurement of chlorpyrifos exposure and provides a conservative endpoint for establishing appropriate margins of

safety for both adults and infants,'' it is difficult to see how this could be argued to provide unequivocal support for Petitioners' objections.

Exhibit 6. This exhibit consists of a report by Lucio Costa, PhD, entitled, ''Expert Report: Carbofuran's FQPA Safety Factor and Interspecies Uncertainty Factor,'' as well as published literature studies. The report discussed the results of several published studies that they claim demonstrate that ''where available, brain AChE inhibition data provide a superior surrogate'' to RBC data because ''in some cases RBC AChE may overestimate PNS AChE inhibition, while in other cases * * * RBC AChE inhibition may underestimate actual AChE inhibition in the PNS.'' In support of this allegation, the report references data from several studies conducted with chlorpyrifos and disulfoton, both OP pesticides, and a single study with propoxur, an NMC pesticide (Refs. 16, 19, 20, 21, 41, 52, 61, 64, and 71). According to the Report, these studies generally show that there was similar or greater AChE inhibition in brain than in the PNS tissues of heart, ileum, or the diaphragm, which Petitioners claim proves that reliance on carbofuran pup brain AChE inhibition data is more predictive of all effects in the PNS. The exhibit also references a human incident study (Ref. 50) of carbamate poisoning in early childhood and in adults, claiming that, ''Lifshitz * * * showed that signs of adverse effects in the CNS, rather than PNS, prevailed in young children at the low dose levels covered by the paper.''

In its denial of the hearing request on the previous issue, EPA examined the results of the studies in this exhibit at length, and demonstrated that the results of the studies failed to support a conclusion that brain data correlate more closely to PNS effects than RBC data. Indeed, in most of these studies, brain AChE inhibition poorly reflected the AChE inhibition in PNS tissues. For example, the Carr *et al.* study results, reproduced in Table 1 of Exhibit 6, showed that for PND 10, 16, and 20 rat pups, the heart tissue had the greatest levels of inhibition, and that PND 16 and 20 rat pups had greater levels of inhibition in lung tissue than in the brain (Ref. 16 at 3). Further, since the study was conducted with serum, which contains no RBC, it is unclear how this study could prove that brain data are a better indicator of PNS effects than RBC data.

The remainder of the report consists of criticisms of EPA's conclusions, and contentions that EPA was inconsistent, without citation to biological evidence to support these claims. For example, the Report addresses EPA's rejection of the Bretaud study in goldfish on the grounds that the ''distribution of carbofuran across fish and mammalian tissues may be quite different,'' by criticizing EPA for failing to provide ''evidence or a citation to support this point'' (Exhibit 6 at 1). But they cite to nothing demonstrating the similarity of fish and mammalian tissues or otherwise supporting their proposed extrapolation across taxa; at this stage of the administrative process the obligation is on the Petitioners to come forward with evidence to call EPA's conclusions into question. *See,* 73 FR 42683, 42706, July 23, 2008 (''NRDC does no more than state 'we are aware of no statistical test' which would support EPA's use of the Gledhill data. As EPA's regulations make clear, a mere 'denial' of an EPA position is not enough to satisfy the standard for granting a hearing.''); 53 FR 53176, 53199, December 10, 1982 (''Rather than presenting evidence, [the objector] asserts that FDA did not adequately justify its conclusions. Such an assertion will not justify a hearing.''). The report also attempts to dismiss EPA's conclusions by complaining that EPA's assessment fails to include ''any analysis of the relationship between RBC AChE and PNS AChE.'' This also, cannot justify a hearing. As has been previously noted, FMC, who bears the statutory burden for producing such data, has failed to provide data in the PNS that would allow EPA to make the suggested comparison (*See,* 73 FR 42683, 42699, July 23, 2008 (hearing denied where NRDC made no evidentiary proffer supporting its claim that each of the factors cited in EPA's risk assessment ''poses a serious risk of understating the risks''); 70 FR 21619, April 27, 2005 (objector questioned exposure assessment and studies relied on for assessment; hearing denied because no information presented); 72 FR 39557, 39560, July 19, 2007 (''Although Public Citizen alleged that the studies that FDA evaluated do not support the safety of x-rays of 10 MeV or lower used for inspection of cargo containers that may contain food, Public Citizen did not present any evidence that would have led to a different conclusion concerning the safety of the subject additive.'').

iii. Denial of Objection. EPA's well-established policy when evaluating blood cholinesterase inhibition is to use RBC AChE data as an indicator of possible effects on AChE in the PNS; EPA adopted this policy for a number of reasons (Ref. 76 at 32). EPA's reasoning here is straightforward. As a biomarker of exposure, blood AChE inhibition can be correlated with the extent of exposure. There is often a direct relationship between a greater magnitude of exposure and an increase in incidence and severity of clinical signs and symptoms as well as blood AChE inhibition. In other words, the greater the exposure, the greater the amount of AChE inhibition that will be present in the blood and the greater the potential for an adverse effect to occur. RBC measures of AChE inhibition also provide: (1) Pharmacokinetic evidence of absorption of the pesticide and/or its active metabolite(s) into the bloodstream and systemic circulation; and (2) pharmacodynamic evidence of binding to AChE, the neural form of the target enzyme. Because the interaction with AChE is widely accepted as a key event of the mechanism of toxicity for anticholinesterase pesticides, inhibition of this AChE in the blood creates the presumption that a chemical also is causing inhibition of neural AChE. Chemicals are absorbed into the blood and transported to the PNS. Pharmacokinetically, the blood compartment and the PNS are ''outside of'' the central nervous system, *i.e.,* separated from the CNS by the blood-brain barrier. Thus, RBC measures of AChE activity are viewed as a better surrogate for the effects on AChE in the peripheral nervous system than are enzyme changes in the CNS. Because data on AChE inhibition in the PNS have rarely been gathered in animals, blood AChE inhibition measures are generally the only information available to assess the potential of chemicals to inhibit AChE in the peripheral nervous system.

Finally, based on the record, FMC seemingly intended in the past for RBC AChE to be used as a surrogate for peripheral AChE inhibition. In 2005, FMC submitted a time course study with plasma and RBC AChE inhibition following acute exposure to carbofuran in adult rats. The title of this study is ''The toxicokinetics of peripheral cholinesterase inhibition from orally administered carbofuran in adult male and female CD rats (Ref. 5).'' Although this study is entitled ''peripheral cholinesterase inhibition,'' there are no actual measures of peripheral toxicity (*e.g.,* liver, lung, heart). Instead, RBC and plasma ChEs are the only measures included. That report states that ''carbofuran reversibly inhibits cholinesterase activity by binding to acetycholinesterase in red blood cells * * * Carbamylation of cholinesterase after the association of carbofuran leads

to an accumulation of acetylcholine and inhibition of nerve function at the neuronal and neuromuscular synapse.'' Based on this statement, FMC assumed at the time of conducting and submitting this study that measures of RBC AChE were relevant for predicting neurotoxicity and for use in risk assessment. For all of these reasons, the Petitioners' objection is denied.

c. *Objection/hearing request subissue: ''Lip-smacking'' as CNS effect.* Petitioners object that EPA's evidence of ''lip smacking'' in a carbofuran adult developmental rat study does not support concern for potential PNS effects because lip smacking is more properly correlated to CNS, rather than PNS inhibition. In support, the Petitioners proffer testimony that relies on four published studies, none of which was conducted with carbofuran. The papers describe pharmacological and physiological analyses of the bases of ''purposeless chewing movements'', ''chewing jaw movements'', ''chewing motions and tongue protrusions'', and ''tongue protrusion and gaping'' seen in rats dosed with either cholinergic or dopaminergic drugs.

i. Background. In the proposed rule, in addition to the data in pups showing frank PNS effects (tremors), EPA discussed the results of another carbofuran study that appeared to be a possible consequence of PNS inhibition, to provide further explanation of the basis for EPA's concern that carbofuran could cause adverse PNS effects. The proposed rule stated that ''[t]here is indication in a toxicity study where pregnant rats were exposed to carbofuran that effects on the PNS are of concern; specifically, chewing motions or mouth smacking was observed in a clear dose-response pattern immediately following dosing each day'' (73 FR 44873, July 31, 2008). EPA explained that the California Department of Pesticide Regulation calculated a BMD_{05} and $BMDL_{05}$ of 0.02 and 0.01 mg/kg/day, and established the acute PoD based on this study. The Agency also explained that ''[t]hese BMD estimates are notable as they are close to the values EPA has calculated for brain AChE inhibition and being used as the PoD for extrapolating risk to children'' (73 FR 44873, July 31, 2008). The similarities of the BMDs in adult and juvenile rats suggests that toxicity may be occurring in juvenile animals which cannot be detected due to the challenges with assessing clinical signs in juvenile rats.

The Petitioners did not raise the allegation contained in their objections as part of the Petitioners' comments. The context in which ''lip smacking'' was addressed was a sentence that states, ''One issue raised at the FIFRA SAP meeting was whether 'lip smacking' observed in the adult females in the developmental toxicity study were the result of PNS or CNS AChE inhibition'' (Ref. 18 at 82). In a footnote to this allegation, the Petitioners stated ''Moreover, it is impossible to tell from the study data whether this ''lip smacking'' was a PNS or a CNS effect.'' (Ref. 18 at 82). The Petitioners' comments focused instead on the contention that the study was irrelevant because the dose levels in the study were higher than the dose levels at which EPA was regulating for AChE inhibition (Ref. 18 at 82).

EPA did not respond to the Petitioners' description of the discussion at the SAP, since it correctly characterized the discussion. However EPA responded fully to the Petitioners' comment regarding the dose levels in the final rule and response to comments.

ii. Denial of hearing request. There can be no legitimate argument that this comment raised the issue in sufficient detail to allow Petitioners to object that ''lip smacking'' is more properly correlated with CNS inhibition, and to supplement the objection with the published literature studies they cite here. *See, e.g., Forest Guardians v. US Forest Service,* 495 F.3d 1162, 1170–1172 (10th Cir. 2007) (Claim held waived where comments ''failed to present its claims in sufficient detail to allow the agency to rectify the alleged violation''); *National Association of Manufacturers v. US DOI,* 134 F.3d 1095, 1111 (DC Cir. 1998) (''We decline to find that scattered references to the services concept in a voluminous record addressing myriad complex technical and policy matters suffices to provide an agency like DOI with a 'fair opportunity' to pass on the issue.'') For the reasons discussed in Unit VI.C, EPA considers the objection and evidence untimely, and therefore waived. As such, this objection does not warrant a hearing.

But in any event, this issue is not material. EPA's decision to retain a 4X children's safety factor did not rest exclusively, or even significantly—on the effects observed in this developmental study. Rather, EPA retained the children's safety factor based on the lack of data in the PNS and/or a surrogate at the low end of the response curve, and the fact that the available pup RBC data at higher doses affirmatively indicate that the PNS appears to be significantly more sensitive than the CNS (73 FR 44871–44872; 74 FR 23073–23075). Indeed, it is clear from both the proposed and final rules that the results of this study merely supplemented the Agency's bases for concern (73 FR 44871–44872; 74 FR 23073–23075). The Petitioners' complaint that the effects occurred at dose levels three times higher than PoD and therefore do not quantitatively support the 4X children's safety factor is equally immaterial. The record is clear that EPA relied on comparisons between the BMD_{50} estimated for pup brain and RBC AChE inhibition to derive the 4X (73 FR 44871–44872; 74 FR 23073–23075). A hearing can only be based on a genuine issue of disputed fact. Where a party's factual allegations are contradicted by the record, there is no genuine dispute (40 CFR 178.32(b)(1)) (*See,* 73 FR 42683, 42701 July 23, 2008; 57 FR 6667, 6672, February 27, 1992) (''A hearing must be based on reliable evidence, not on mere allegations or on information that is inaccurate and contradicted by the record.'').

iii. Denial of objection. The carbofuran developmental study does not definitively resolve whether the effects described were the product of PNS or CNS AChE inhibition; because only RBC AChE inhibition data were collected it is not possible to determine the degree of CNS inhibition. However, as the Petitioners acknowledge, chewing or oral fasciculations, which are the movements EPA described at the SAP meeting and in the proposed and final rules, have often been reported as an early sign of toxicity produced by carbamates and OPs in rats (Exhibit 5 at 2). Petitioners also acknowledge that ''oral fasciculations'' are indeed a peripheral neuromotor response (Id.) (''some of the toxicity is peripherally mediated or an effect on the PNS (for example, muscle fasiculations and tremors are due to inhibition of AChE at the motor endplate of the muscle)''). Nevertheless, Petitioners attempt to confuse the issue by providing several different descriptions of oral movements, from lip-smacking to mouth smacking to mouth movements to chewing movements, and claiming that it is clear that these are all CNS effects. As an initial matter, it is unclear whether all of the study authors in Petitioners' cited literature are referring to the same phenomenon. It is therefore unclear whether the oral movements from the carbofuran developmental study (which EPA described as ''lip-smacking'' and ''fasiculations'') are the same responses described as ''tongue protrusion,'' ''gaping,'' ''yawning,'' and ''chewing movements'' in the pharmacology papers Petitioners reference. It is not unlikely that all of

the different papers refer to somewhat different actions; Rupniak *et al.* (Ref. 68) were able to produce ''chewing jaw movements'' by chronic treatment with haloperidol, a dopaminergic receptor antagonist, which suggests that the movements studied in that paper are not purely cholinergic. The fact that anticholinergics could block the haloperidol-induced dopaminergic movements shows that this is not a straightforward physiological response dealing only with the cholinergic system. For the same reason, this calls into question the contention that the effects are exclusively CNS-related.

Similarly, the claim that the ''the masticatory response'' is clearly a CNS effect is equally misleading and inaccurate. The report in Exhbit 5 claims that ''[t]he masticatory response is considered a preliminary index of convulsive activity and convulsions have been demonstrated to be caused by changes in brain chemistry.'' None of the papers the Petitioners cited describe this ''masticatory response'' in that way. Instead, those papers all state that this response is seen at relatively low doses of these anticholinesterases. By way of contrast, convulsions are seen at high doses. The Exhibit also implies that the ''masticatory'' response and convulsions are a continuum of the same phenomemon; however EPA is aware of no scientific support for this claim, and Petitioners have provided none.

Petitioners' objection on this issue is therefore denied.

The Exhibit also implies that the ''masticatory'' response and convulsions are a continuum of the same phenomemon; however EPA is aware of no scientific support for this claim, and Petitioners have provided none.

d. *Objection/hearing request subissue: EPA's analysis does not rely on Good Laboratory Practice (GLP)-compliant studies.* Petitioners object that EPA's reliance on the ORD data is problematic because the data were not conducted in accordance with EPA's GLP regulations at 40 CFR part 160.

i. Background. The only data available on the effects of carbofuran on the pup PNS are RBC AChE inhibition data from two studies conducted by EPA–ORD. These data unequivocally show that pup RBC AChE is more sensitive than pup brain AChE. EPA also used these data in its calculations supporting the 4X children's safety factor. In their comments on the proposed rule, Petitioners alleged that, ''the Moser study may not meet minimum criteria for scientific acceptability.'' They based this on a claim that critical data were unavailable for this study, including: A complete protocol, analysis of dosing solutions, clinical observations, standardization of brain and RBC AChE results in terms of amount per unit of protein, and quality assurance records of inspections for the carbofuran portion of the study. However, no more specific explanation was provided as how this purportedly missing data rendered the data scientifically deficient. EPA responded in full to these allegations in the final rule and response to comments document.

EPA's regulations at 40 CFR part 160 establish a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. GLP helps assure EPA that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments. The regulations are applicable only to studies that support, or are intended to support applications for ''research or marketing permits'' for pesticides regulated under FIFRA (40 CFR 160.1(a)).

ii. Denial of hearing request. On several grounds, a hearing on this subissue is not warranted. First, this objection fails to identify a dispute of material fact. There is no dispute that the EPA–ORD studies were not conducted in strict accordance with EPA's GLP regulations. Nor have Petitioners identified a substantive flaw in those studies that they believe resulted from the lack of compliance with the regulations, or otherwise challenged the scientific validity of those studies. Thus, the only issue presented is whether EPA should rely on otherwise scientifically valid studies that were not conducted in accordance with its GLP regulations. This is clearly a legal or policy issue. Hearings are not appropriate on such issues; issues of fact, not of law or policy are required to justify a hearing (40 CFR 178.32(b)(1)).

A further defect is that Petitioners have submitted no evidence on this point. In fact, this claim consists of nothing more than the bare statement that EPA's analysis does not rely on GLP-compliant studies. A hearing will not be granted on ''mere allegations'' or ''general contentions'' (40 CFR 178.32(b)(2)). To the extent the Petitioners are relying on the information submitted as part of their comments on the proposed rule, this does not cure the defect, since no substantiating information or other evidence was presented in support of their comments. Nor can simple reiteration of a comment made on the proposed rule justify a hearing. EPA responded to these comments in the final rule, and by ignoring the EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Both EPA and FDA precedent make clear that when the agency substantively responds to comments on the proposal, the commenter may only keep that issue alive in its objections by addressing the agency's substantive response. *See, e.g.,* 73 FR 42701 (denying hearing because NRDC merely repeated its assertion that the study was not representative from its petition, rather than objecting to the basis EPA asserted in its petition denial for concluding that the study was representative).

Indeed, this entire objection is not material. The EPA–ORD data are the only valid pup RBC data using carbofuran; in the absence of these data, EPA would have no data that would provide relevant information on carbofuran's effects on children's PNS. Under such circumstances, EPA would be required to retain the statutory default 10X, because there would be no ''reliable data'' on which to base any other factor.

iii. Denial of objection. The mere fact that a study is not conducted in accordance with EPA's GLP regulations does not mean that the study is scientifically invalid, or that EPA is prohibited from considering the study. The GLP regulations do not apply to EPA–ORD generated data, but rather to studies conducted to ''support applications for research or marketing permits for pesticide products'' (40 CFR 160.1(a)). Moreover, the regulations establish general practices; they do not identify the only good laboratory practices that will result in scientifically valid data. Other laboratory protocols, such as that used by EPA–ORD are equally valid. In recognition of this fact the regulations do not prohibit EPA from considering studies that were not conducted in accordance with EPA's GLP regulations, but merely provide that EPA may refuse to consider such studies to be ''reliable'' (40 CFR 160.17(a)).

Nor does compliance with EPA's GLP regulations guarantee the validity of the study's results. The RBC data from FMC's carbofuran CCA studies, which were conducted in accordance with EPA's GLP regulations, were unanimously determined to be scientifically invalid by the FIFRA SAP (Ref. 36).

Any claim that the conduct of the EPA–ORD studies raised questions as to their scientific validity is equally baseless. EPA's ORD data were reviewed by the FIFRA SAP, which concluded that, ''EPA–ORD has provided excellent

data regarding RBC AChE inhibition by carbofuran'' (Ref. 36 at 55).

As EPA explained in response to the Petitioners' comments, all of the information the Petitioners claimed was missing had been previously made publically available as part of the SAP review of the carbofuran NOIC, and was provided again in response to FMC's FOIA request. A complete study protocol, as well as a report of the quality assurance (QA), technical, and data reviews of the study, were available, which demonstrated that the procedures and documentation are in accordance with the National Health and Environmental Effects Laboratory (NHEERL)/ORD Quality Assurance Management Plan. Concerning standardization of brain and RBC AChE in terms of protein concentration, the Agency notes that this analysis has not been performed or provided in all the studies on the record, including those sponsored by FMC. However, in the Moser study (Ref. 56), the AChE activity was standardized in terms of tissue weight per ml, so the amount of protein was consistent across samples, which is an acceptable and widely used practice. Further, abnormal (or ''clinical'') observations were recorded when they occurred, although the animals could not be watched while they were in the motor activity chambers. Finally, the registrant is correct that the dosing solutions for the comparative ChE study were not analyzed, but ORD performed this analysis for the adult studies in McDaniel *et al.* (Ref. 54), and the preparation and stability of the carbofuran samples were confirmed therein. For these reasons, this objection is denied.

e. Objection/hearing request subissue: Consistency of EPA's approach to deriving the carbofuran children's safety factor—i. Background. The Petitioners argue that EPA's approach to deriving carbofuran's children's safety factor is inconsistent with that Agency's approach in deriving the safety factors for other NMC chemicals. Specifically, they point to carbaryl, which had a safety factor of 1X.

Petitioners raised this issue in their comments on the proposed rule. In the final rule, EPA explained at length, the basis for its conclusion that the available data using carbaryl, provided by the carbaryl registrant, supported a finding that a 1X children's safety factor would be ''safe'' (74 FR 23058 and Ref. 85). EPA explained that the different safety factors established for carbaryl and carbofuran resulted from differences in the chemicals themselves, as reflected by the available data (Id).

ii. Denial of hearing request. A hearing is not appropriate on this objection because it raises a legal or policy claim, rather than a dispute as to a material issue of fact. The claim that EPA acted inconsistently in assessing different pesticide chemicals is purely a legal issue. There is no factual dispute that EPA established a children's safety factor of 1X for carbaryl, and a safety factor of 4X for carbofuran. The only dispute concerns whether EPA's basis for distinguishing between the two is reasonable, and this is a legal claim, on which a hearing is not appropriate (40 CFR 178.32(b)(1)).

In addition, the Petitioners make no claim other than to reiterate the allegation made in their comments on the proposed rule, that EPA's assessment of carbofuran is inconsistent with its assessment of carbaryl. Consequently, Petitioners' objection on this subissue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation because Petitioners ignored EPA's extensive analysis of this issue in the final rule and refiled their comments on the proposal as if EPA's determination in the final rule did not exist. By ignoring the EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Nor have they proffered any evidence in support of this claim. When EPA responds to a comment in the final rule, mere reiteration of the comment in objections does not present a live controversy unless the objector proffers some evidence calling EPA's objection into question (*See, e.g.*, 73 FR 42700–42701).

iii. Denial of objection. Carbaryl was evaluated no differently than carbofuran. The different children's safety factors applied to each chemical reflects the differences in the chemicals themselves, as reflected by the data.

It is typical EPA practice to use the central estimate on the BMD as an appropriate measure for comparing chemical potency and the lower limit on the central estimate (*i.e.*, BMDL) as an appropriate measure for extrapolating risk. In the case of carbaryl, the Petitioners inappropriately focused on the $BMDL_{10}$, instead of the BMD_{10}. The more appropriate comparison is between the BMD_{10}; the carbaryl brain BMD_{10} is 1.46 mg/kg compared with the RBC BMD_{10} of 1.11 mg/kg. As such, the brain to RBC ratio is 1.3X. Therefore, for carbaryl, the brain and RBC AChE data are similarly sensitive. When the tissues are similarly sensitive, the Agency prefers to use data from the target tissue (*i.e.*, central or peripheral nervous system) rather than data from a surrogate tissue (*i.e.*, RBC). EPA's hazard identification for carbaryl states:

> ''Although the RBC $BMDL_{10}$ for the more sensitive PND 11 rat is numerically the lowest (0.8 mg/kg) of the two compartments, biologically the RBC $BMDL_{10}$ is similar to the brain $BMDL_{10}$ (1.1 mg/kg). Since the brain is the target tissue for the NMCs, and the brain $BMDL_{10}$ 1.1 mg/kg is also protective of the surrogate and often more variable RBC ChE measurements ($BMDL_{10}$ 0.8 mg/kg), then the brain $BMDL_{10}$ of 1.1 mg/kg is the appropriate PoD for both children and adults in the carbaryl risk assessment (Ref. 82).''

Thus, for carbaryl, biologically the RBC and brain AChE inhibition were basically equivalent where brain AChE inhibition is a direct measure in a target tissue and RBC AChE inhibition is used as a surrogate for the peripheral nervous system. This is quite different from the situation with carbofuran where a significant difference was noted between RBC and brain AChE inhibition, showing that RBC AChE inhibition (used as a surrogate for the PNS) is more sensitive.

The approach used for carbaryl—*i.e.*, relying on the central estimate for purposes of comparison across age groups, and using biological compartments and the lower limits for use as PoDs—is being used by EPA in its carbofuran risk assessment. In addition, this approach was used in the NMC cumulative risk assessments (CRA) and single chemical risk assessments for multiple OPs. Thus, the Agency is, in fact, being consistent in its hazard identifications among the AChE-inhibiting pesticides.

With regard to the carbaryl children's safety factor, the available brain and RBC dose-response data in PND11 pups include data from the lower end of the dose-response curves. ORD's comparative ChE data with carbaryl show that at the lowest dose at or near 20% inhibition in brain and RBC AChE were observed. Although not ideal, the carbaryl data provide information closer to the benchmark response of 10%, and therefore allow for a reasonable estimation of the BMD_{10} and $BMDL_{10}$. This is distinctly different from ORD's data with carbofuran in PND11 and PND17 pups where the 50% or greater RBC AChE inhibition was observed at the lowest dose. Accordingly, the objection is denied.

2. EPA's Mathematical Modeling Underlying the Calculation of a 4X Children's Safety Factor. Petitioners argue that EPA committed numerous errors in calculating the 4X children's safety factor. First, Petitioners allege that, even assuming that RBC values are relevant, EPA's conclusion that the RBC-related effects in the relevant

studies were four times more sensitive than brain effects is not mathematically supportable. Referencing statistical analyses performed by a contractor, they claim that ''[a]t most, the data support a 2X safety factor, based on actual difference between brain and RBC (ranging between 1 and 1.9).''

Second, the Petitioners claim that there are several technical errors in the way EPA conducted the statistical modeling that formed the quantitative support for the 4X children's safety factor. They also object that the mathematical assumptions underlying EPA's modeling are not justified and fail to support the 4X children's safety factor. In this regard, they allege that EPA's children's safety factor was based on calculations that (i) are not based on ''within animal comparisons;'' (ii) have been applied incorrectly and inconsistently to the data, which exaggerated the difference; (iii) overstate the evidence for higher relative RBC sensitivity; and (iv) treated carbofuran inconsistently as compared to other NMCs. They claim that by removing the inconsistencies from EPA's data, the data yield a brain/RBC ratio of 1.3, which confirms Petitioners' approach. These five allegations are addressed separately below.

In support of these claims, the Petitioners offer allegations on the points above, referencing two memoranda from Drs. R. Sielken and C. Valdez-Flores (Exhibits 7, 8, 9) that generally describe and summarize the analyses and modeling they conducted. The full analyses underlying these memoranda were not included with the objections.

a. Objection/Hearing Request Subissue: Use of Within-Animal Brain to RBC Inhibition Comparisons To Derive the Children's Safety Factor

i. Background. In the proposed rule, EPA explained its approach to deriving an alternate to the default 10X children's safety factor. This safety factor was calculated using the ratio of RBC and brain AChE inhibition, using the data on administered dose for the PND11 animals from the EPA–ORD studies and the FMC studies combined. In other words, EPA estimated the BMD_{50} for PND11 animals for RBC and brain from each quality study and used the ratio from the combined analysis, resulting in a BMD_{50} ratio of 4.1X. EPA estimated the RBC to brain potency ratio using EPA's data for RBC (the only reliable RBC data in PND11 animals for carbofuran) and all available data in PND11 animals for brain. EPA's approach yields a ratio of about 4 fold.

EPA also compared the BMD_{50} ratios for PND17 pups (who are slightly less sensitive than 11-day olds) in the EPA–ORD study, to confirm that the observed differences in sensitivity between RBC and brain were not unique to the PND11 data. The result of EPA's modeling showed a BMD_{50} ratio of 3.3 [13] between brain and RBC in the PND17 pups.

In their comments on the proposed rule, Petitioners presented essentially the same arguments raised in this objection. They argued that a more plausible and straightforward approach would be to compare the RBC and brain AChE levels at the same time in the same rat when these rats are exposed to carbofuran. The comments claimed that a statistical evaluation of the experimental data on AChE inhibitions in RBC and brain in rats due to carbofuran exposure had been performed by Sielken & Associates, which showed that the percentage inhibition of RBC AChE in a rat is almost the same as the percentage inhibition of brain AChE in the rat. Although the results of the statistical analyses were summarized in the comments, the underlying analyses were not submitted.

In the final rule, EPA provided a detailed explanation of its rationale for rejecting the Petitioners' approach (74 FR 23055; Ref. 85).

ii. Denial of hearing request. EPA is denying Petitioners' request for a hearing on this objection for two reasons. First, as in its comments, Petitioners failed to submit the underlying modeling conducted in support of its assertions. Petitioners' consultant merely asserts that the results are as presented in his summarized testimony. In the absence of the underlying scientific analyses, these are effectively no more than mere allegations or general contentions. Hearings will not be granted on this basis alone. (40 CFR 178.32(b)(2); see also 73 FR 42702 (July 23, 2008)(denying NRDC's hearing request on objection that EPA's risk assessment was inadequate because EPA lacked data on how pest strips were used in their homes, because ''NRDC provided no factual information to support its claim''); 68 FR 46403, 46406–46407 (August 5, 2003) (FDA denied a hearing involving a challenge to FDA's reliance on consumption pattern data because the objector ''did not present any specific information to dispute P & G's consumption pattern data; instead, [objector] simply asserted that other consumption patterns were likely.''); *accord Community Nutrition Institute* v. *Novitch*, 773 F.2d 1356, 1363 (DC Cir. 1985) (''Mere differences in the weight or credence given to particular scientific studies * * * are insufficient [to show a material issue of fact for a hearing].'')).

Second, Petitioners' hearing request is inadequate because they do not object to the basis EPA asserted in the final rule for rejecting this approach. Specifically, Petitioners do not challenge EPA's conclusion that their suggested approach is fundamentally flawed in several regards, nor proffer evidence in support of that challenge. Petitioners also do not challenge EPA's analyses, showing that the results of their suggested approach are in fact consistent with EPA's conclusions. As a consequence, Petitioners' objections are irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation. The statute, however, requires that objections be filed on the final rule not the proposal. By ignoring the EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Prior FDA decisions under its regulations are instructive here. Objections and hearing requests were filed in response to a food additive regulation covering the irradiation of poultry. (62 FR 64102 (December 3, 1997)). The objector argued that the addition of an anti-oxidant (ethoxyquin) to irradiated chicken prior to the chicken's use in animal feeding studies compromised the studies because the ethoxyquin would have decreased the level of lipid peroxides in the chicken to levels found in chicken that had not been irradiated. The FDA noted, however, that it had considered the question of ethoxyquin's effect on lipid peroxide levels in the final rule and determined that while ethoxyquin can retard the normal oxidation of chicken fat to peroxides, ethoxyquin cannot reverse oxidation that has already occurred. FDA denied the hearing request reasoning that because the objector did ''not dispute FDA's explanation in the final rule as to why addition of ethoxyquin did not compromise the CIVO studies, and provided no information that would have altered the agency's conclusion on this issue * * * there is no factual issue that can be resolved by available and specifically identified reliable evidence'' (62 FR 64105). *See also* 53 FR 53176, 53191 (December 30, 1988) (FDA denied a hearing request noting that given FDA's prior conclusion that the studies relied upon by the objector were unreliable, the ''burden shifted to [the objector] to maintain the viability of its

[13] EPA corrected a technical error identified in Petitioners' comments, which resulted in a revised ratio of 2.6X, for the final rule.

objection by proffering some information that called into question the agency's conclusion on this matter.'')). Similarly, here, Petitioners have not challenged the basis EPA asserted for rejecting their suggested within-animal analyses, nor have they proffered any information calling into question EPA's conclusion.

iii. Denial of objection. EPA notes that the Petitioners recommended this approach of comparing the degree of inhibition for each animal as part of their presentation to the carbofuran SAP. EPA also addressed this approach, comparing RBC to brain in the same animals, at the SAP and in the responses to the SAP report (Ref. 83). It is notable that the SAP did not endorse this approach (Id.).

EPA's analyses of the Petitioners' approach identified several significant deficiencies. First, the comparison suggested by the Petitioners would require that EPA ignore existing data. This is because only EPA's study of PND 11 animals contains both brain and RBC data, so the comparisons suggested by the commenter can only be made using that dataset. However, the dose levels in that study were so high that the lower portion of the dose-response curve was missed. At these higher doses, there is little difference between the levels of brain and RBC inhibition. This phenomenon—*i.e.*, that the relative sensitivity of RBC compared to brain appears smaller at higher doses—is also shown in multiple chlorpyrifos studies where blood or peripheral measures of AChE inhibition are more sensitive than brain at low to mid doses, but the tissues appear to be similar at higher doses.

Second, the Petitioners' approach is fundamentally flawed. The Petitioners' suggested alternative relies exclusively on comparisons between the degree of inhibition in the treated animals without any regard to the doses at which the effects occurred. For example, one animal may have shown, on average, 10% inhibition in the brain, when it demonstrated 20% RBC inhibition. Under this approach, what would be relevant would simply be the ratio of 1:2. But the Agency believes it is critical to focus on the ratios of potency, which is the ratio of the doses in the data that cause the same level of AChE inhibition. The Agency's approach of comparing potencies is more directly relevant for regulatory purposes than comparisons of average inhibition. This is because dose corresponds more directly to potential exposures, which is what EPA regulates (*i.e.*, how much pesticide residue does a child ingest). By comparison, the Petitioners' suggested reliance purely on the average degree of inhibition provides no information that corresponds to a practical basis for regulation.

Finally, the range of ratios of effects that the Petitioners propose as an alternative is consistent with range of potencies that EPA has calculated *at these higher doses*, so the Petitioners' results do not ultimately contradict EPA's assessment, which is intended to account for the effects at lower doses. Briefly, if the dose-responses for RBC and brain inhibition were linear, ratios of inhibition would equal ratios of BMDs. However, these dose-responses are not at all linear; rather the available data demonstrate that brain and blood dose-responses have somewhat different shapes. Thus, estimates of relative effects at particular, relatively high, doses will not determine the estimated ratios at lower doses. This is because the dose-response curves begin to level off as they reach maximal inhibition (*i.e.*, no more inhibition is possible), so, at high doses, there is almost no difference between the ratio of brain and RBC inhibitions. Except at the lowest dose, which produced 50% AChE inhibition, where the ratio is slightly greater than 2, the remaining ratios are only slightly greater than 1. Given the inevitable statistical noise in these measures, it is clear that the ratios expected from EPA's modeling are substantially similar to the results the Petitioner finds in its comparison between individuals. Accordingly, the Petitioners' suggested comparisons at higher doses provide no evidence of what occurs at lower doses; and thus provides no evidence that demonstrates that EPA's modeling results at lower doses is inaccurate.

b. Objection/hearing request sub issue: Scientific validity of EPA's approach. The Petitioners object that EPA's approach has not been established as scientifically valid. They claim that data for other carbamates suggests that BMD_{50} s for the carbamates tend to diverge more than the dose levels used to select the PoD (*i.e.*, the BMD_{10} s). In addition, they criticize EPA's approach for incorrectly assuming that the relationship between BMD_{50} s and BMD_{10} s is linear, which they claim overstates the potential differences. They claim that these issues could be avoided by adopting their suggested approach of using within-animal comparisons to determine the relative sensitivity of RBC and brain AChE. The evidence submitted in support of this subissue is the summary presented in the objection.

i. Background. In the proposed rule, EPA explained that its comparisons of the BMD_{50} s for brain and blood relied on an assumption that the magnitude of the difference between RBC and brain AChE inhibition is constant across dose. In other words, EPA assumed that the RBC and brain AChE dose curves are parallel, even though there are no data to test this assumption (73 FR 44873). In their comments, the Petitioners criticized EPA for this assumption, and recommended using ''within animal comparisons'' to avoid having to make this assumption. In the final rule, EPA explained that its decision to rely on comparisons of BMD_{50} s rather than BMD_{10} s was because the RBC data for 10% inhibition levels was insufficient to allow the Agency to generate the necessary estimates. EPA agreed that the dose-response curves were not parallel at these lower doses, (*i.e.*, that the relationship between BMD_{50} s and BMD_{10} s was not linear) but that EPA lacked any data that would allow it to make any other assumption. EPA nevertheless rejected the Petitioners' suggested approach of relying on within-animal comparisons, because, as described in the preceding objection, it is intrinsically flawed and scientifically invalid.

ii. Denial of hearing request. A hearing on this subissue is not appropriate because Petitioners' request is based on mere allegations, general contentions, and speculation (40 CFR 178.32(b)(2)). No evidence has been submitted on any of the issues raised in this objection. Petitioners have provided no evidence that supports their assertion that EPA's assumption that the dose-response curves will remain parallel at lower doses overestimates the ratios. In the absence of data at the low end of the dose-response curve, which Petitioners were required to have developed, there is just as great a likelihood that EPA's assumption underestimates the ratios. Petitioners have not cited to any data from other carbamates to support their contention that BMD_{50} s tend to diverge more than BMD_{10} s; the objection fails to even identify the carbamate chemicals that purportedly support this claim. Further, the claim is untimely, as it was not raised as part of their comments on the proposed rule. For the reasons discussed in Unit VI.D, EPA will not consider such information in support of a request to justify a hearing.

In addition, a hearing on this objection is denied on the ground of materiality (40 CFR 178.32(b)(1)). In the absence of EPA's assumption, EPA would have no basis for deriving an alternate children's safety factor. Thus, EPA would have to raise the children's safety factor from 4X to the statutory

default of 10X, rather than to lower the factor as the Petitioners seek. As discussed at length in the preceding objection subissue, the Petitioners' suggested alternative of within-animal comparisons is scientifically invalid, and provides no useful basis for regulatory action. Accordingly, if Petitioners establish that available information does not support EPA's assumption that the dose-response curves are parallel, then EPA is left with no valid scientific information to determine the correct dose-response curve at lower doses, or to establish a BMD_{10} (21 U.S.C. 346a(b)(2)(C)). Because deviation from a 10X children's safety factor requires some ''reliable data'' on the shape of the dose response curve for RBC AChE, Petitioners' objection on EPA's low dose-response curve assumptions, in combination with the failure to provide a valid alternate approach would result in a higher children's safety factor, and a conclusion that EPA has underestimated carbofuran's risks.

iii. Denial of objection. EPA disagrees that its approach is not scientifically valid. The models used to develop the BMD estimates have been repeatedly reviewed and approved by the SAP (Refs. 34, 35). The most recent occasion was the February 2008 carbofuran SAP, which concluded that ''[t]he dose-response analysis done by the Agency for the EPA–ORD PND11 study was appropriate and led to a very uncertain BMD_{10} * * * This [assumed dose-response] curve fit well in the region where there were data, but there was no way to validate it at low doses'' (Ref. 36 at 54).

EPA acknowledges that it lacks information to confirm its assumption that the dose-response curves remain parallel at lower doses. EPA believes this is the most reasonable assumption, given the absence of information at low doses, since it neither presumes that RBC inhibition will increase or decrease at lower doses. Contrary to Petitioners' naked assertion that EPA's approach overestimates the difference, there is no inherent reason to expect that EPA's assumption would overestimate or underestimate the difference between BMD_{50} s and BMD_{10} s. If indeed data were to show that EPA's assumption overestimated the difference—and Petitioners have submitted none—it would only be as a result of the animal biology, as there is no indication in the mathematical modeling that it overestimates the difference in any way. The mathematical relationship between BMD_{50} s and BMD_{10} s certainly provides no hint that there might be a bias. In this regard, it is notable that the February 2008 SAP concluded that '[w]hat the Panel observed at the low end [of the dose-response curve] made it tempting to assume linearity at this part of the dose-response curve'' (Ref. 36 at 55).

Regarding the Petitioners' claim that data for other carbamates suggests that BMD_{50} s for the carbamates tend to diverge more than the dose levels used to select the PoD (*i.e.*, the BMD_{10} s). EPA cannot confirm the accuracy of this allegation, as Petitioners have provided neither data nor any explanation of a biological basis to support this claim. Nor is EPA able to substantiate this claim based on the information currently available. However, there is no *a priori* reason to expect such a systematic divergence between ratios of BMD_{50}'s and ratios of BMD_{10} s for blood and brain, based either on biology or the mathematical relationship between BMD_{50}'s and BMD_{10} s. It is actually far more probable that the variation from chemical to chemical (due both to real variation among chemicals and to statistical sampling noise) would be large enough to make a conclusive determination from data difficult.

c. *Objection/hearing request sub issue: Combining data from different toxicological studies—i. Background.* In its risk assessment, EPA relied on all of the valid data from the available studies to calculate the estimates that served as the PoD, and to calculate the estimates of BMD_{50} s that serves as quantitative support for derivation of the 4X children's safety factor.

For purposes of the PoD, the Agency used a meta-analysis that combined valid data from all available studies to calculate the BMD_{10} and $BMDL_{10}$ for pups and adults; this analysis includes brain data from studies where either adult or juvenile rats or both were exposed to a single oral dose of carbofuran. The quality brain AChE data from the three studies (2 FMC, 1 EPA–ORD) conducted with PND11 rats, in combination, provides data to describe both low and high doses. By combining the three studies in PND11 animals together in a meta-analysis, the entire dose-response range is covered.

EPA also combined studies in calculating the 4X children's safety factor. EPA derived the ratio of RBC and brain AChE inhibition using the data on administered dose for the PND11 animals from the EPA–ORD studies and the FMC studies combined. In other words, EPA estimated the BMD_{50} for PND11 animals for RBC and brain from each quality study and used the ratio from the combined analysis, resulting in a BMD_{50} ratio of 4.1X. EPA estimated the RBC to brain potency ratio using EPA's data for RBC (the only reliable RBC data in PND11 animals for carbofuran) and all available data in PND11 animals for brain.

In their comments on the proposed rule, Petitioners claimed that EPA's decision to combine data for different strains of rats, sexes, experiments, laboratories, dates, dose preparations, rat ages, and times between dosing and AChE measurement, is problematic, claiming that these differences in study design severely limit the validity of EPA's comparisons. Further, they alleged that differences in data and methods EPA used to estimate its BMD_{50} (brain) and BMD_{50} (RBC) caused EPA to overestimate the difference between brain and RBC, and thereby invalidating any comparison of the estimates. Specifically, Petitioners were concerned that the datasets from the six studies EPA used for brain differ not only because they were from different studies, but also because the data were taken at different times ranging from 15 minutes to 4 hours after dosing.

EPA responded to these comments in full during the rulemaking (74 FR 23055–23057 (May 14, 2009); Ref. 85). Petitioners referenced these comments in their objections, but presented no further argument or evidence on any of these points. Because Petitioners originally raised this claim also with respect to the derivation of EPA's PoD, even though they only raise it in this objection here, the Agency responds to both points below.

ii. Denial of hearing request. The Petitioners have not met the requirements for a hearing on this subissue. Petitioners have not challenged the basis EPA asserted for rejecting their suggested within-animal analyses, and have therefore failed to lodge a relevant objection. Both EPA and FDA precedent make clear that when the agency substantively responds to comments on the proposal, the commenter may only keep that issue alive in its objections by addressing the agency's substantive response (40 CFR 178.32(b)(3)). Nor have they proffered any evidence that calls the substance of EPA's conclusions into question. A hearing is not warranted on the basis of mere denials or contentions (40 CFR 178.32(b)(2)). S*ee* 73 FR 42698–42699 (When an objector does not challenge EPA conclusions in the section 408(d)(4)(iii) order but rather challenges some prior conclusion that was superseded by the section 408(d)(4)(iii) order, the objector has not raised a live controversy as to an issue material to the section 408(d)(4)(iii) order); 53 FR 53176, 53191 (December 30, 1988) (FDA denied a hearing request noting that given FDA's prior conclusion that the

studies relied upon by the objector were unreliable, the ''burden shifted to [the objector] to maintain the viability of its objection by proffering some information that called into question the agency's conclusion on this matter.'')).

Second, this objection is not material. In the case of carbofuran, EPA used a sophisticated analysis of multiple studies and datasets to develop the PoD for the carbofuran risk assessment. Instead of this analysis, EPA could simply have followed the general approach laid out in its BMD policy (Ref. 100), which is used in the majority of risk assessments. Under this general approach, EPA would regulate using the most sensitive effect, study, and/or dataset. If the Agency chose not to combine the data in its analyses, as the commenters' suggested, data collected at or near the peak time of effect (*i.e.*, 30 minutes) would in fact provide the more relevant datasets. If this more simple approach were taken, in accordance with BMD guidance, EPA would select the lowest $BMDL_{10}$. Assuming the commenters' values were used, EPA would have selected a PoD of 0.009 mg/kg/day, instead of the 0.03 mg/kg/day that EPA is currently using in its risk assessment. A lower PoD of 0.009 mg/kg/day would significantly increase carbofuran's level of estimated risk.

iii. Denial of objection. In general, EPA believes that consideration of all available data is the scientifically more defensible approach, rather than the selective exclusion of reliable data. The Agency's Draft BMD Guidance says the following: ''Data sets that are statistically and biologically compatible may be combined prior to dose response modeling, resulting in increased confidence, both statistical and biological, in the calculated BMD'' (Ref. 76). The SAP has reviewed and approved EPA's practice of combining data from studies numerous times (Refs. 34, 35, 36). Most recently, as part of the carbofuran SAP, the SAP was fully aware that the Agency was planning to derive BMD estimates from data sets using different strains of rats (Ref. 36). Accordingly, the Agency's carbofuran analysis has included all available, valid data in its analysis.

By contrast, the Petitioners' suggested analysis ignores relevant, scientifically valid data. Their analysis left out the 30-minute data from MRID no. 47143705 (Ref. 2), but provided no rationale as to why it would be appropriate to selectively exclude data from the time frame in this study most relevant to the risk assessment (*i.e.*, peak AChE inhibition). The Petitioners' analysis of the individual datasets from this study showed that at 30 minutes the females and males provide $BMDL_{10}$ s of 0.009 mg/kg/day and 0.014 mg/kg/day, respectively. When the datasets were combined, inclusion of the 30-minute timepoint from MRID no. 47143705 decreased the $BMDL_{10}$ from 0.033 mg/kg/day to 0.030 mg/kg/day.

Although the Petitioners complain that EPA's approach of combining data across multiple studies is scientifically inappropriate, the Petitioners themselves combined the results of analysis from four datasets in the information presented with their comments and referenced in their objections. Indeed, it is notable that most of the criticisms raised by the Petitioners also apply equally to the Petitioners' own analysis, as described in more detail in EPA's Response to Comments document (Ref. 85).

The Petitioners are also incorrect that differences in the data available for brain and RBC are so great as to invalidate comparisons of the BMD estimates. EPA used all the data available in each case, and used a hierarchical model to account for variability of the BMD among laboratories for the brain endpoint, which the SAP has explicitly reviewed and approved numerous times (Refs. 34, 35, 36).

The Petitioners are correct that data from both sexes were combined for brain but only male data were used for RBC. However, EPA first performed an evaluation of the differences between the sexes. EPA combined data from males and females only after showing that they did not respond differently.[14] The only remaining study to examine AChE activity in RBC in PND11 animals, after FMC's flawed studies were eliminated, contained only male animals. Both BMD_{50} s for brain and RBC in adults were based on 15 minutes, the minimum time interval after dosing when a sample was taken, in each dataset.[15] This is also true for the brain endpoint in PND11 animals. However, the only study available of the RBC endpoint in PND11 animals was conducted at 40 minutes after dosing, and did not include a recovery time course study.

EPA believes that its decision to combine data for purposes of its BMD_{50} estimates supporting the children's safety factor is equally appropriate, and any differences in the way in which the studies were conducted did not impact the validity of EPA's analyses. For example, one of Petitioners' complaints was that it was inappropriate to combine studies because the data in the studies were taken at different times, ranging from 15 minutes to 4 hours after doses. EPA responded to the allegation that this was problematic by conducting the analysis that the Petitioners claimed should have been done to support this. As explained in the final rule, although EPA disagreed with the Petitioners' contention that this was necessary or appropriate, EPA conducted the Petitioners' suggested analysis, and used the dose-time-response model to extrapolate BMD_{50} s to develop a common point of comparison between all studies. Specifically, EPA extrapolated the PND11 brain analysis to estimate BMD_{50} for 40 minutes after dosing for comparison with the existing PND11 RBC BMD_{50}, and extrapolated the PND11 RBC BMD_{50} to 15 minutes after dosing for a range of assumed recovery half-lives, for comparison to the existing PND11 brain BMD_{50}. The results are provided in (Refs. 24, 25). In either approach, the estimate of the RBC to brain potency ratio in PND11 animals is increased, and EPA's safety factor would correspondingly increase to reflect that larger difference. For example, when the PND11 brain BMD_{50} is extrapolated to 40 minutes, the RBC to brain potency ratio grows to 4.7 (Ref. 24 at 46), and when the PND11 RBC BMD_{50} is extrapolated to 15 minutes, using a range of estimates for the recovery half-life of the RBC endpoint, the RBC to brain potency ratio ranges from 4.2 to 4.6 (Ref. 24). The Petitioners' approach would therefore support a children's safety factor of 5X rather than the 4X EPA is currently applying in its risk assessments. Nevertheless, EPA continues to believe that its current use of a 4X factor reflects the most reliable interpretation of existing quality data.

Although it is true that EPA's BMD_{50} for brain was based on data from 6 datasets while the RBC BMD_{50} was based on a single study, this is because scientifically acceptable RBC data are only available from a single study. As discussed, the fact that EPA used all available data sets in its modeling does not affect the validity of its modeling (Ref. 76).

For all of the foregoing reasons, this objection is denied.

d. Objection/hearing request sub issue: Technical Flaws in EPA's statistical comparisons. In their objections, Petitioners claim to have found a number of technical errors and inconsistencies in how the modeling

[14] See pp. 34–35 in the brain document dated October 25, 2007 for adults, pp. 47–48 in the same document for PND11 animals; p. 15 in the RBC document dated October 23 for adults.

[15] See Oct. 5, 2007 reports, page 8 (for the values of the time interval) and page 63 (setting the parameter delta to the minimum non-zero value for that interval) in the RBC report, and page 9, and page 45 for the corresponding report for Brain.

was conducted. Correcting for these errors, they claim, shows that the BMDs for brain and RBC data are essentially the same, which was consistent with the results of modeling conducted by the Petitioners when evaluating the individual animal data. Specifically, Petitioners allege that the approach EPA used to estimate BMD_{50} s for carbofuran is inconsistent with its ''meta-analysis'' approach of combining studies. The Petitioners also argued that EPA's modeling failed to account for significant difference in study methodologies (*e.g.*, time to sacrifice following dosing). For example, EPA's BMD_{50} (Brain) is calculated at 15 minutes after exposure starts whereas EPA's BMD_{50} (RBC) is calculated at 40 minutes after exposure starts. EPA's BMD_{50} (brain) is based on 6 studies whereas EPA's BMD_{50} (RBC) is based on 1 study, and the dose-time-response modeling methodology for combined studies and EPA's BMD_{50} (brain) is different than the dose-time response modeling methodology for a single study and EPA's BMD_{50} (RBC). Petitioners also allege that EPA applied its dose-time-response model inconsistently between the brain and RBC calculations, alleging that the power was fixed to 1.00 for brain, but estimated for RBC.'' They also criticize the modeling on the grounds that EPA did not: (1) Account for differences between the combined datasets; (2) develop a protocol supporting its approach; (3) clearly document its method; (4) accurately document model parameters; (5) rely on a plausible dose-response model, or (6) report its data accurately or transparently. They further allege that ''removing all of these inconsistencies in methodology results in a ratio of 1.3, which corresponds with the ratio that the Petitioners claim to have obtained based on their within animal comparisons.

Petitioners have provided neither further details of their concerns than the explanation above, nor any other evidence to support this objection.

i. Background. EPA addressed all of the commenters' claimed inconsistencies in its final rule and Response to Comments document (74 FR 23055–23056; Ref. 85 at 61–62). For the majority of these claimed flaws and inconsistencies, EPA explained that the Petitioners had misunderstood EPA's analyses, or that the Petitioners' were incorrect. However in response to certain allegations, EPA conducted new analyses to determine whether the suggested alternative approaches would make any significant difference in EPA's modeling outcomes.

Petitioners have provided little detail in their objections on the issues they intend to raise in their testimony; in most instances, they simply allege that EPA's modeling was incorrect. But as the objections reference the Petitioners' comments on the proposed rule, EPA assumes that they intend to raise only the points previously discussed in their comments.

ii. Denial of hearing request. The Petitioners' request for a hearing on the issues raised in this objection is denied on two bases. First, Petitioners have not challenged the substance of EPA's response to their comments or submitted evidence that calls the substance of EPA's conclusions into question. As previously explained, their failure to challenge the actual basis of EPA's final rule affects the materiality of the objection and hearing request (40 CFR 178.32(b)(3)). *See* 73 FR 42698–42699 (When an objector does not challenge EPA conclusions in the section 408(d)(4)(iii) order but rather challenges some prior conclusion that was superseded by the section 408(d)(4)(iii) order, the objector has not raised a live controversy as to an issue material to the section 408(d)(4)(iii) order) 53 FR 53176, 53191 (December 30, 1988) (FDA denied a hearing request noting that given FDA's prior conclusion that the studies relied upon by the objector were unreliable, the ''burden shifted to [the objector] to maintain the viability of its objection by proffering some information that called into question the agency's conclusion on this matter.'')). Further, Petitioners have not rebutted, or even acknowledged, the additional analyses EPA undertook at their suggestion, and discussed in the final rule, which ultimately provided further support for EPA's position. For example, in response to the complaint that EPA should have generated a new dose-response model in order to calculate the BMD_{50} s for brain and RBC, EPA conducted the suggested calculation, and under that analysis, the result is the same as that EPA originally calculated. Similarly, in response to the complaint that EPA should have used the dose-time-response model to extrapolate BMD_{50} s to develop a common point of comparison between all studies, EPA conducted that analysis and described it in the final rule (74 FR 23055–23056 (May 15, 2009)). The result of this reanalysis supported a higher children's safety factor than EPA's 4X. But rather than challenge the new analysis, Petitioners simply repeat the assertions made in their comments. Because the objections on these points fail to account for EPA's analyses, the objections are contradicted by the record, and accordingly, fail to demonstrate a factual dispute (40 CFR 178.32(b)(1)). *See* 73 FR 42698–42699 (Denying NRDC hearing where objection reiterated claims premised on conclusions in EPA's preliminary risk assessment, rather than objecting to EPA's conclusions in the revised assessment prepared for the petition denial); 49 FR 6672 (February 22, 1984) (no hearing if claim based on demonstrably false premise); 57 FR 6667 (February 27, 1992) (''A hearing must be based on reliable evidence, not on mere allegations or on information that is inaccurate and contradicted by the record'').

Second, as in their comments, Petitioners failed to submit the underlying modeling they claim to have conducted in support of their objections. Petitioners' consultants merely assert that the results are as presented in their summarized testimony. In the absence of the underlying scientific analyses, these are effectively no more than mere allegation or general contentions. Hearings will not be granted on this basis. (40 CFR 178.32(b)(2); see also 68 FR 46403, 46406–46407 (August 5, 2003) (FDA denied a hearing involving a challenge to FDA's reliance on consumption pattern data because the objector ''did not present any specific information to dispute P & G's consumption pattern data; instead, [objector] simply asserted that other consumption patterns were likely.''); accord *Community Nutrition Institute* v. *Novitch*, 773 F.2d 1356, 1363 (DC Cir. 1985) (''Mere differences in the weight or credence given to particular scientific studies * * * are insufficient [to show a material issue of fact for a hearing].'').

iii. Denial of Objection. For all of the reasons discussed in the final rule and Response to Comments documents, this objection is denied. A summary of EPA's bases, which were discussed in detail in both the final rule and Response to Comments document, is presented below.

Consistency of EPA approach. In their comments, the Petitioners' explained that the alleged inconsistency with which they were concerned was that ''EPA attempts to extrapolate a BMD_{10} to a BMD_{50} without refitting the data. That is, EPA uses the dose-response model obtained for the BMD_{10} rather than obtaining a new model for BMD_{50}.'' They claimed this was ''especially troublesome since EPA has expressly stated that the model obtained for BMD_{10} (RBC) is unreliable.''

The Petitioners' allegation on this point is incorrect. The model itself does not need to change in order to develop a BMD_{50}. Whether one wants to estimate the BMD_{10} or the BMD_{50}, one would use the same underlying model. EPA simply developed a mathematical expression to adjust parameter values for that fitted model so that, for any given benchmark response level (in particular, for 10% or 50% inhibition), the corresponding BMD could be estimated as a parameter in that model. The same expression makes it possible to compute a BMD for any given response level from estimates based on any other response level. Mathematically, it is not necessary to refit the model to the data to estimate different BMD levels.

However in response to the comments, EPA conducted their suggested calculation, and the ratio of brain to RBC BMD_{50} s in this new analysis is the same as the ratio EPA calculated by using the mathematical expression (Refs. 24, 25). Both provide a ratio of brain to RBCs BMD_{50} of 4X. Specifically, in the just cited documents above, the values are for PND11 brain BMD_{50} are 0.35 (Ref. 24 at 40) and for RBC, 0.086 (Ref. 25 at 20), resulting in a ratio of 4.09.

With regard to the EPA's purported statement that the BMD_{10} model is unreliable, the Petitioners misconstrued EPA's statement. EPA stated that it cannot reliably estimate the RBC BMD_{10} and $BMDL_{10}$ in pups because it lacks data at low doses, not because its model is unreliable. Given the greater amount of data, the estimate for the BMD_{50} is substantially better supported, and thus, less uncertain, than the estimate of the BMD_{10}.

Differences in study methodologies. Both BMD_{50} s for brain and RBC in adults were based on 15 minutes, the minimum time interval after dosing when a sample was taken, in each dataset.[16] This is also true for the brain endpoint in PND11 animals. However, the only study available of the RBC endpoint in PND11 animals was conducted at 40 minutes after dosing, and did not include a recovery time course study.

As noted in the previous objection response, EPA used the dose-time-response model to extrapolate BMD_{50} s to develop a common point of comparison between all studies. Using that approach would support a children's safety factor of 5X rather than the 4X EPA has applied.

[16] See Oct. 5, 2007 reports, page 8 (for the values of the time interval) and page 63 (setting the parameter delta to the minimum non-zero value for that interval) in the RBC report, and page 9, and page 45 for the corresponding report for Brain.

Although it is true that EPA's BMD_{50} for brain was based on data from 6 datasets while the RBC BMD_{50} was based on a single study, this is because scientifically acceptable RBC data are only available from a single study. As discussed in the preceding objection response, the fact that EPA used all available data sets in its modeling does not affect the validity of its modeling (Ref. 76).

Inconsistent application of model. EPA did not apply its model inconsistently; the difference to which the Petitioners refers results from the differences between the available data. In order to generate an estimate of the power parameter, data at both extremes of the dose-response curve are necessary. Despite the comparatively greater amount of brain inhibition data, the brain data did not provide information at both extremes of the curve. A value of 1.00 is the standard default in this situation for all the NMC dose-response analyses. Moreover, despite the limited information at the extremes of the dose-response curve for estimating power in the brain data, a power parameter of 1.00 is consistent with the available brain data. By contrast, because the available RBC data provides the necessary information at higher doses, the power in the RBC data could be directly estimated and was significantly less than 1.0.

EPA is unable to comment on the analyses referenced in the Petitioners' objections as they failed to provide them. However, EPA has previously explained the reasons for rejecting the suggested analysis based on brain RBC comparisons within the same animal. This is discussed at length in the final rule and response to comments, as well as Unit V*I.E.*2.a of this Order.

f. Objection/hearing request sub issue: Consistency in approach between carbofuran and other NMC chemicals—i. Background. In their comments on the proposed rule, the Petitioners argued that EPA's approach to deriving carbofuran's children's safety factor was inconsistent with its approach to deriving the safety factors for other NMC pesticides. They identified only three specific chemicals: Aldicarb, oxamyl, and carbaryl. With respect to aldicarb they argued that although the relative potency of carbofuran is less than aldicarb, the uncertainty factors assigned by EPA presuppose that carbofuran is ten times more toxic that aldicarb. They claim that the aldicarb data show that by all objective measures of toxicity, aldicarb is nearly twice as acutely toxic as carbofuran across all species tested. They further claim that an alternative approach to relative rankings of carbamates proposed by the SAP in its assessment of the NMCs (which also considered the rate of recovery) also showed aldicarb having approximately twice the potency of carbofuran. They further alleged that the children's safety factor for carbaryl was inconsistent with the safety factor applied to carbofuran. Finally, the Petitioners compared the aPAD, aRfD, and uncertainty factors for oxamyl, aldicarb, and carbaryl, concluding that these were inconsistent with EPA's conclusions for carbofuran.

EPA responded to these comments in both the final rule and the accompanying response to comments document (74 FR 23058 (May 15, 2009)).

In their objections, Petitioners have not identified any specific facts that they believe demonstrate inconsistency. They merely allege that the ''relative potency of carbofuran as compared to other N-methyl carbamates does not correspond with OPP's aPAD for carbofuran relative to those same compounds.''

ii. Denial of hearing request. A hearing is denied on this subissue because there is no disputed factual matter for resolution at a hearing. There is no dispute concerning the children's safety factors that EPA applied to the other carbamates, nor how EPA derived those safety factors. Thus, the only question is whether it was reasonable for EPA to account for the fact that other chemicals had a greater amount of toxicity data, and therefore greater uncertainty, in determining the appropriate children's safety factor, when the statute requires EPA to account for ''the completeness of the data'' (21 U.S.C. 346a(b)(2)(C)). This question requires the application of a legal standard to undisputed facts. Hearings are not appropriate on questions of law or policy (40 CFR 178.32(b)(1)). *See*, 73 FR 42706–42707) (denying NRDC hearing request when the only question raised was whether a human study using only adult males met the regulatory requirement of ''scientifically valid and relevant data''. FDA has repeatedly confirmed that the application of a legal standard to undisputed facts is a question of law for which a hearing is not required. (*See*, *e.g.*, 68 FR 46403, 46406 n.18, 46408, 46409 (August 5, 2003) (whether facts in the record show there is a reasonable certainty of no harm is a question of law; whether a particular effect is a ''harm'' is a question of law)).

In addition, Petitioners have not challenged the substance of EPA's response to their comments, but simply reiterated their comments on the proposed rule. Accordingly, a hearing is

not warranted, as the objection is subissue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation (40 CFR 178.32(b)(3)). *See* 73 FR 42698–42699 (July 23, 2008) (When an objector does not challenge EPA conclusions in the section 408(d)(4)(iii) order but rather challenges some prior conclusion that was superseded by the section 408(d)(4)(iii) order, the objector has not raised a live controversy as to an issue material to the section 408(d)(4)(iii) order; 53 FR 53176, 53191 (December 30, 1988) (where FDA responds to a comment in the final rule, repetition of the comment in objections does not present a live controversy unless the objector proffers some evidence calling FDA's conclusion into question)).

Nor have they submitted evidence that calls the substance of EPA's conclusions into question. Petitioner's entire argument concerning this issue is a single conclusory sentence. A hearing will not be granted on ''mere allegations'' or ''general contentions.'' (40 CFR 178.32(b)(2)) (See 53 FR 53176, 53199 (December 30, 1998)) (''Rather than presenting evidence, [the objector] asserts that FDA did not adequately justify its conclusions. Such an assertion will not justify a hearing.'').

iii. Denial of objection. Although it is unclear which precise chemicals the Petitioners believe demonstrate that EPA was inconsistent, the only ones on which any allegations were arguably presented were those identified in their comments on the proposed rule: aldicarb, carbaryl, and oxamyl. Accordingly, EPA denies this objection for the same reasons that EPA explained in its final rule and comment responses.

In their comments, the Petitioners provided information on the oral LD_{50} in rat and the $BMDL_{10}$ for AChE in rat brain or human RBC. The comments also provided uncertainty factors for the three NMCs, the respective aRfD [17] or aPAD [18] and the cumulative risk assessment oral potency factor. The LD_{50} and $BMDL_{10}$, values provided are not completely accurate.

The allegations and the supporting information contained in Petitioners' comments were inaccurate. For example, the LD_{50} values in the oxamyl RED were 3.1 mg/kg (male) and 2.5 mg/kg (female), rather than 30 mg/kg as the Petitioners claimed. Further, the Agency's recent hazard assessments of carbaryl and aldicarb are each consistent with EPA policies and practice, as well as with the Agency's approach to the assessment of carbofuran.

The Petitioners' assertions regarding aldicarb were based on an earlier assessment. At the time the Agency conducted the assessment to which the commenters refer, the Agency was unaware of the difference in sensitivity between PND17 and PND11 animals. Since EPA became aware of the differences, EPA has required the aldicarb registrant to conduct a CCA study in PND11 rats; the Agency anticipates the receipt of this study and the companion range-finding and time course studies in 2009. In the absence of these data, EPA will apply the statutory default children's safety factor to account for the additional sensitivity of PND11 animals, because the Agency lacks any ''reliable data'' that could be used to derive a reduced factor that EPA could determine will be ''safe for infants and children.''

With regard to the carbaryl children's safety factor, the available brain and RBC dose-response data in PND11 pups include data from the lower end of the dose-response curves. ORD's comparative AChE data with carbaryl show that at the lowest dose 20% or near 20% inhibition in brain and RBC AChE was observed. Although not ideal, the carbaryl data provide information closer to the benchmark response of 10%, which allows for a reasonable estimation of the BMD_{10} and $BMDL_{10}$. This is distinctly different from ORD's data with carbofuran in PND11 and PND17 pups where 50% or greater RBC AChE inhibition was observed at the lowest dose.

Petitioners' other comparisons are equally inapposite. The LD_{50}, $BMDL_{10}$, and relative potency factor from the cumulative risk assessment are each measures of chemical potency. Thus, these calculations provide reasonable comparisons of the relative potency of aldicarb, carbofuran, and oxamyl. However, the Petitioners' allegations were based on comparisons of the aPAD, aRfD, and uncertainty factors, which are not measures of potency and should not be interpreted as such (Ref. 79). The magnitude of the uncertainty factors is intended to account for uncertainty in the available data for a particular chemical. For example, it is standard practice to apply a 10X uncertainty factor for extrapolation from animals to humans when ethically and scientifically sound human data are not available for the pesticide of interest. And this explains the difference in the uncertainty factors applied to the three chemicals. Deliberate dosing studies in human subjects conducted with aldicarb and oxamyl were reviewed and accepted by the HSRB for both scientific validity and ethical conduct. This is not the case for carbofuran. As discussed below in Unit VI.G, the HSRB concluded that the carbofuran study was not sufficiently scientifically robust for use in the risk assessment. Therefore, there is less uncertainty in the aldicarb and oxamyl risk assessments since quality data are available in humans and the interspecies factor can be reduced or removed for these chemicals. There are no comparable data for carbofuran.

Accordingly, this objection is denied.

F. *Objections to EPA's Drinking Water Exposure Assessments.*

Petitioners raise separate objections to EPA's estimates of drinking water exposures from contaminated ground water and to the estimates from contaminated surface water. In each objection, Petitioners argue that, based on newly proposed restrictions submitted as part of their objections, the exposure estimates will be significantly lower than EPA's estimates in the final rule.

1. Objections relating to groundwater exposure estimates. Petitioners raise several challenges to the ground water concentration estimates in the final rule. They allege that EPA's estimates are not based on the best available data, but on obsolete data and overly conservative assumptions that are inappropriate because use has been prohibited in all areas like those seen in these data. The objection also claims that the requirements in the new registration proposals to require setbacks from all drinking water wells ranging between 100 and 1,000 feet will ensure that all potential groundwater exposures will be below the level of concern. In support of this objection three analyses were submitted in Exhibits 12, 13, and 14.

a. Objection/hearing request subissue: Reliance on the results of the prospective ground water study (PGW) and historical monitoring to validate groundwater exposure estimates. The Petitioners object that EPA should not have relied for validation on their PGW study or historical monitoring data. They argue that these data are from a period when use was an ''order of magnitude greater.'' Additionally they allege that all areas like those seen in the PGW have now been removed from the carbofuran label, and so the study results do not accurately reflect current risks. In support of this objection, Petitioners reference their comments on the proposed rule, and Exhibit 12.

i. Background. In the proposed rule, EPA relied on a drinking water assessment that used both monitoring data for carbofuran and modeling

[17] aRfD is the acute reference dose.

[18] aPAD is the acute RfD adjusted for the Children's Safety Factor.

methods (Refs. 13, 42, 44, 47, 67). Regarding the potential exposure from contaminated groundwater, the Agency concluded that drinking water taken from shallow wells is highly vulnerable to contamination in areas where carbofuran is used around sandy, highly acidic soil, although sites that are less vulnerable (*e.g.,* deeper aquifer, higher organic matter) could still be prone to have concentration exceeding acceptable exposures. EPA concluded that the results of its modeling were consistent with the results of the available monitoring data, including a PGW study conducted by FMC in the 1980s, when scaled to reflect the current lower rates of application (73 FR 44881).

In their comments, the Petitioners complained that EPA's reliance on the PGW was inappropriate because that study no longer reflected current conditions. Petitioners also summarized the results of their ''National Leaching Assessment'' which used PRZM and ''databases specifically created to provide access to all necessary inputs for a national scale PRZM modeling.'' They claimed that after accounting for the use prohibitions on their September 2008 label, the maximum 1-in-10 year peak concentrations in all potential carbofuran use areas is 1.2–1.3 ppb, while expected concentrations in most areas covered by this assessment are below 1.0 ppb. Neither the ''National Leaching Assessment'' nor the ''National Pesticide Assessment Tool'' upon which the assessment appears to have been based, were submitted to EPA as part of the Petitioners' comments.

In the final rule, EPA revised the assessment conducted for the proposed rule in response to the FMC comments submitted during the comment period, which requested cancellation of the use on a number of crops and imposed a number of restrictions intended to address the potential for groundwater contamination. These restrictions included use prohibitions in certain states, and well setbacks. Taking these into account, ground water concentrations were estimated for all remaining crops on carbofuran labels, using two new Tier 2 scenarios. Based on a new corn scenario in Wisconsin, representative of potentially vulnerable areas in the upper Midwest where use remained, EPA estimated one-in-ten year concentrations for ground water source drinking water of 16 to 1.6×10^{-3} ppb, for pH 6.5 and 7, respectively. Well setback prohibitions of 50 ft were proposed on the new label for the flowable and granular formulations in select counties in Kentucky (7 counties), Louisiana (1 county), Minnesota (1 county), and Tennessee (1 county). Analysis of the impact of these setbacks for the use on corn indicated that the setbacks would not reduce concentrations significantly at locations where exposure to carbofuran in ground water is of concern because at acid pHs, carbofuran does not degrade sufficiently during the travel time from the application site to the well to substantially reduce the concentration.

EPA concluded that the results of the revised corn modeling were consistent with the PGW. Using higher use rates than currently permitted, the peak concentration measured in the PGW study was 65 ppb; when scaled to current use rates, the estimated peak concentration was 11 ppb. The final rule explained that EPA's modeling is also consistent with a number of other targeted groundwater studies conducted in the 1980s showing that high concentrations of carbofuran can occur in vulnerable areas; the results of these studies as well as the PGW study are summarized in References 13 and 67 (74 FR 23079).

ii. Denial of hearing request. For this hearing request, the Petitioners have failed to proffer evidence, which would, if established, resolve a material issue in their favor. First, Petitioners' evidentiary proffer does not support their contention, and consequently, EPA is unable to conclude that there is a reasonable possibility that the issue could be resolved in its favor (40 CFR 178.32(b)(2)). Petitioners' own experts relied on the PGW to validate the modeling submitted in support of this objection and to demonstrate the safety of the tolerances. The Executive Summary of the National Carbofuran Leaching Assessment states

> ''[a] model validation study was conducted in which the results of a prospective groundwater monitoring (PGW) study conducted for cabofuran in Maryland from 1981–1983 were compared to the model simulations that most closely matched the PGW study site in terms of location, soil texture, organic carbon content, and pH. The annual peak concentrations during the simulation are on the order of 9 to 11 ppb, which are similar to the measured concentrations in the PGW study (9 to 10 ppb after adjusting for application rate). The validation provides context that the model predictions are reasonable.''

(Exhibit 12 at 7). *See, e.g.,* 57 FR 33244 (July 27, 1992) (Studies cited by NRDC do not provide a basis for the hearing because they ''support the [FDA] conclusion in question.'').

Second, this objection is premised on inaccurate factual statements that are directly contradicted by the record. For example, the objection disregards the fact that EPA scaled the PGW modeling to reflect the lower current use rates. The Petitioners present no challenge to the methods EPA used to scale the study results; indeed, it is likely that their contractor used the same or similar methodology. Equally, the objection that EPA relied on ''historical monitoring data from a period when carbofuran use was an order of magnitude larger'' is simply incorrect (Ref. Obj at 40). The monitoring results EPA cited in the final rule were from the 1980s, but the targeted monitoring studies were conducted with the same or lower use rates as those permitted under the current labeling (74 FR 23085, May 15, 2009). Such a submission is insufficient to justify a hearing (*See,* 73 FR 42696 (July 23, 2008)(denying hearing where objector incorrectly claimed that EPA had failed to rely on DDVP-specific information in making its children's safety factor determination); 57 FR 6667 (February 27, 1992) (''A hearing must be based on reliable evidence, not on mere allegations or on information that is inaccurate and contradicted by the record.'')

Further, the Petitioners' misrepresentation of EPA's analyses also affects the materiality of the hearing request (40 CFR 178.32(b)(3)). Even if Petitioners were able to successfully refute the validity of the PGW study, it would not affect the validity of the additional monitoring data cited in the final rule (74 FR 23079 (May 15, 2009)), on which EPA also relied to validate its monitoring. *See,* 49 FR 6672 (February 22, 1984) (challenge to one of five related studies; in the absence of any additional data bearing on the clinical study, the objection constitutes nothing more than an allegation).

Finally, the evidentiary proffered with respect to the Petitioners' allegation that all areas with conditions similar to those found in the PGW have been removed from the label is insufficient to warrant a hearing (40 CFR 178.32(b)(2)). To the extent this allegation is based on the information presented as part of the 2008 comments, this claim was rebutted in EPA's final rule, by the modeling based on the Wisconsin corn scenario, and by the lack of any underlying analyses to support of Petitioners' comments. As explained in the final rule, the information provided is insufficient to allow EPA to confirm the Petitioners' contention that there is no overlap between use and all potentially vulnerable ground water (74 FR 23061–23062 (May 15, 2009)).

The evidence submitted along with this objection does not cure this defect. The only evidence proffered in this regard is the Petitioners' comments on

the proposed rule, and the new analysis submitted in Exhibit 12. As previously discussed, mere reiteration of comments made in response to the proposed rule does not provide an adequate basis for a hearing, unless the objector proffers some evidence calling EPA's conclusion into question. Consequently, Petitioners' submission on this issue is irrelevant and therefore immaterial, with regard to EPA's final tolerance revocation (40 CFR 178.32(b)(3)). The analysis in Exhibit 12 appears to be the National Leaching Assessment described in Petitioners' comments, but modified to account for the proposed amendments submitted as part of the objections. As noted previously, neither the National Leaching Assessment nor the model on which it was based was submitted as part of the comments. Because the National Leaching Assessment was available during the comment period but was withheld, this information is considered to be untimely and the Petitioners have waived the right to rely on it. For the reasons discussed in Unit VI.D, EPA therefore will not consider it as an appropriate basis for justifying a hearing on its final rule. *See* 73 FR 42683, 42696 (July 23, 2008); 72 FR 39318, 39324 (July 18, 2007). Further, for the reasons discussed in Unit VI.C, EPA has determined that objections and hearing requests based on the newly proposed amendments, as well as evidence or analyses premised on those amendments, are irrelevant, and therefore immaterial, to EPA's determination in the May 15, 2009 final rule that the carbofuran tolerances were unsafe and could not be sustained under FFDCA section 408. Petitioners are actually not objecting to the conclusions in EPA's final rule; rather, they are suggesting that EPA might reach a different result in a different factual scenario. Objections, however, must be directed ''with particularity [at] the provisions of the regulation or order deemed objectionable'' (21 U.S.C. 346a(g)(2)).

iii. Denial of objection. EPA denies this objection on several bases. Based on the information available, and even accounting for the September 2008 geographic restrictions, the Agency cannot confirm the Petitioners' claim that use has been prohibited in all areas with conditions similar to the PGW study. Based on the information that was timely submitted, the only information provided was in map format. While maps are useful for interpreting results, maps alone are insufficient for a thorough evaluation of the Petitioners' claim, in part because of the maps' spatial resolution. The maps submitted were all on a nation-wide scale, which does not provide the level of detail necessary to verify the combination of paramaters (*e.g.,* soil textures, pH) at locations identified as vulnerable. Further, the maps provided by the Petitioner do not represent all carbofuran use patterns. For example, Figure IV–2 on page 42 of the Petitioners' comments does not address the granular use patterns and proposed label prohibitions. In addition, as a general matter, none of the previously submitted assessments provided a comprehensive analysis of the distribution of soil and water pHs for the Midwest, Northwest or any other region of the country where carbofuran use would be permitted on the September 2008 label, or have the Petitioners provided such an analysis with their objections.

Further, the available scientific information does not support their contentions. EPA examined readily available data with respect to ground water and soil pH in order to evaluate the spatial variability of pH. Data from the USGS and other readily available sources do not necessarily encompass the entire range of ground water pH values present within a state. This is especially true for shallow ground water systems, where local conditions can greatly affect the quality and characteristics of the water. Also, pH in a water body can be higher or lower than the tabulated average values. In addition, average ground water pH values for a given area do not truly characterize the area's temporal and especially spatial heterogeneity. This can be seen by comparing differences in pH values between counties within a state, and by the fact that even within a county individual wells will consistently yield ground water with either above- or below-average pH values for that county. The ground water simulations in Reference 84, Appendix I reflect variability in pH by modeling carbofuran leaching in four different soil and subsurface pH conditions (pH 5.25, 6.5, 7.0, and 8.7), representing the range in the aquifer system in that area. This range also approximates the pH range of natural waters in general. The results of the ground water simulations for corn use showed that a relatively small (0.5) decrease in pH from 7 to 6.5 resulted in an increase in the 1-in-10-year peak concentrations of carbofuran in ground water of 4 orders of magnitude.

The results of EPA's revised corn modeling, based on a new scenario in Wisconsin, are consistent with the results of the PGW study developed by the registrant in Maryland in the early 1980s. Using higher use rates than currently permitted, the peak concentration measured in the PGW study was 65 ppb; when scaled to current use rates, the estimated peak concentration was 11 ppb. EPA's modeling is also consistent with a number of other targeted ground water studies conducted in the 1980s showing that high concentrations of carbofuran can occur in vulnerable areas; the results of these studies as well as the PGW study are summarized in References 13 and 67. For example, a study in Manitoba, Canada assessed the movement of carbofuran into tile drains and ground water from the application of liquid carbofuran to potato and corn fields. The application rates ranged between 0.44–0.58 pounds a.i./acre, and the soils at the site included fine sand, loamy fine sand, and silt loam, with pH ranging between 6.5–8.3. Concentrations of carbofuran in ground water samples ranged between 0 (non-detect) and 158 ppb, with a mean of 40 ppb (Refs. 13 and 67).

Finally, as discussed above, to the extent this objection relies on untimely information and analyses, and on the newly submitted registration amendments, the objection is denied as irrelevant and immaterial.

b. Objection/hearing request subissue: Accounting for FMC's label mitigation measures. Petitioners object that EPA's risk assessment relies on ''unrealistic and overly conservative assumptions about potential concentrations,'' and fails to account for FMC's label mitigation measures. They claim that maximum concentrations of carbofuran in groundwater are expected to be below 1.1 ppb, based on the new proposed geographic restrictions and well setbacks. They allege that, ''only permeable soils (*e.g.*, greater than 90% sand and less than 1% organic matter) with acidic soils and water conditions, and shallow water tables (*e.g.*, less than 30 feet) are vulnerable to carbofuran applications.'' They also claim that vulnerable groundwater only exists along eastern seaboard, and in select counties in the United States, where use has already been prohibited. They argue that further confirmation is provided by the available NAWQA data, which show that detections of carbofuran are rare, and occur only at low levels except in areas where use is now prohibited. Finally, Petitioners allege that in the specific regions where carbofuran will continue to be used under the revised label, groundwater pH data collected under the USGS NAWQA program demonstrate that the average pH is approximately 7.25, and in most regions, moving two standard deviations

away from average, which they claim would capture 95% of all observed values, results in pHs that are still greater than 6.0. According to the Petitioners, under such conditions the combination of hydrolysis and drinking water well setbacks would ensure that any carbofuran that might reach ground water sources would degrade to only *de minimis* concentrations less than or equal to 1.1 ppb.

In support of this objection, Petitioners cite the analyses submitted as part of their comments, and the new analyses in Exhibits 12, 13, and 14. Exhibits 12 and 13 contain the revised modeling of the estimated groundwater concentrations from carbofuran use, based on the label restrictions proposed as part of the objections. Exhibit 14 consists of a statistical summary of groundwater pH statistics from the USGS NAWQA database. Means, standard deviations, and numbers of groundwater measurements in the database are summarized by state and land use within each state.

i. Background. In the proposed rule EPA concluded that drinking water taken from shallow wells is highly vulnerable to contamination in areas where carbofuran is used around sandy, acidic soil, although sites that are less vulnerable (*e.g.*, deeper groundwater, less coarsely textured soils) could still be prone to have concentrations exceeding acceptable exposures (73 FR 44881–44883 (July 31, 2008)). EPA also described the available NAWQA monitoring data, and explained the reasons that the monitoring data tends to underestimate exposure for acute risks, such as those carbofuran presents, and so are not sufficiently robust to be used as an input into a quantitative risk assessment or to serve as a lower bound (73 FR 44880–44881 (July 31, 2008)).

As part of their comments on the proposed rule, FMC requested that EPA amend their registration to include a number of geographic use restrictions and migitation measures intended to address the risks to groundwater. In their comments, Petitioners claimed that ''[g]roundwater sources are vulnerable to carbofuran leaching only under certain conditions, namely where permeable soils (*e.g.*, areas with soils greater than 90% sand and less than 1% organic matter), acidic soil and water conditions, and shallow water tables predominate (*e.g.*, where ground water is less than 30 feet).'' The commenters claimed that these conditions are rare in areas where carbofuran would be used under the new label proposed as part of their comments. They further asserted that in ''most states where carbofuran is used, less than 2% of the entire surface areas possess sandy soil texture'' and that ''low pH conditions are not found in carbofuran use areas allowed under the registrant's amended label'' (Ref. 18 at 33–34). They described, but did not submit analyses they claimed to have conducted to demonstrate this. The summary consisted primarily of maps depicting areas identified as vulnerable.

On December 24, 2008, FMC again requested that EPA amend their registration to include additional restrictions intended to further mitigate carbofuran's risks to groundwater.

In response to the September 2008 proposed label restrictions submitted as part of the comments, EPA revised its risk assessment to take into account the new geographic restrictions, as well as the proposed risk mitigation measures. Based on its revised assessment, EPA explained in the final rule that it disagreed that the criteria on the September 2008 label defined 100% of the conditions where ground water sources would be vulnerable to carbofuran leaching. EPA noted that no comprehensive analysis had been provided that evaluated how the Petitioners had reached this conclusion. As discussed in greater detail in EPA's Response to Comments, the information provided as part of the Petitioners' comments—primarily maps depicting areas identified as vulnerable—was not sufficient to allow the Agency to evaluate their claim (Ref. 84).

EPA also disagreed that the commenters provided sufficient information to support their general claim that only high pH conditions (pH above 7) existed in all the areas in which carbofuran could be used under FMC's September 2008 revised label. EPA presented its assessment of the newly submitted label in its Response to Comments document and these issues were addressed in substantial detail there (Ref. 84).

EPA did not evaluate the mitigation measures proposed in the December 24, 2008 submission. The mitigation measures in that submission were incorporated into the measures proposed by the Petitioners as part of their objections on June 30, 2009.

ii. Denial of hearing request. EPA is denying the hearing requested on this objection because, in large measure, if not entirely, it rests on the newly submitted mitigation measures accompanying Petitioners' objections. As discussed in Unit VI.C, EPA has determined that these objections do not warrant a hearing because they are irrelevant, and therefore immaterial, to EPA's determination in the May 15, 2009 final rule that the carbofuran tolerances were unsafe and could not be sustained under FFDCA section 408 (40 CFR 178.32(b)(3)). Petitioners are actually not objecting to the conclusions in EPA's final rule; rather, they are suggesting that EPA might reach a different result in a different factual scenario. Objections, however, must be directed ''with particularity [at] the provisions of the regulation or order deemed objectionable'' (21 U.S.C. 346a(g)(2)). In addition, for the reasons discussed in Unit VI.D, EPA has determined that the new risk mitigation measures are not appropriately considered at this stage of the administrative process, and will not grant a hearing on this basis.

Petitioners' objections provide no further clarification as to what is meant by their claim that EPA's assessment relied on ''unrealistic and overly conservative assumptions.'' Therefore, this objection, and the attendant hearing request, is denied based on Petitioners' failure to state with ''particularity * * * the basis for the objection * * *'' (40 CFR 178.25(a)(2)). As Petitioners raised similar allegations in their comments, EPA has assumed that they intended to incorporate all of the issues raised in the comments on the proposed rule.

To the extent this objection relies on the September 2008 mitigation measures, EPA denies the hearing request because the evidentiary proffer in support of this objection is insufficient to warrant a hearing. The record is clear on its face that EPA did account for the mitigation measures in its revised risk assessment supporting the final rule. A hearing can only be based on a genuine issue of disputed fact (40 CFR 178.32(b)(1)). Where a party's factual allegations are contradicted by the record, there is no genuine dispute (73 FR 42701–42702 (July 23, 2008) (Denying NRDC's hearing request where EPA had revised its residential exposure assessment to address the issue complained of); 57 FR 6667, 6668 (February 27, 1992) (''A hearing must be based on reliable evidence, not on mere allegations or on information that is inaccurate and contradicted by the record.'')).

The objection also suffers from a further defect; many of the allegations in this objection merely reiterate points Petitioners had raised in their earlier comments. For example, EPA addressed the claim that the NAWQA data from 1993–2006 rarely show detections of carbofuran, and that in ''almost every instance'' the observed concentrations are low. EPA also addressed the claim that only areas with permeable soils (*e.g.*, areas with soils greater than 90% sand and less than 1% organic matter), acidic soil and water conditions, and

where shallow water tables predominate (*e.g.*, where ground water is less than 30 feet) present significant risks of leaching. As previously discussed, mere reiteration of comments made in response to the proposed rule does not provide an adequate basis for a hearing, unless the objector proffers some evidence calling EPA's conclusion into question (40 CFR 178.32(b)(3)). *See, e.g*, 73 FR 42701–42702 (July 23, 2008); 53 FR 53176 (December 30, 1988).

The evidence submitted in Exhibits 12–14 does not cure these defects. As a preliminary matter, much of this evidence is untimely. The analyses in Exhibits 12 and 13 appear to be the National Leaching Assessment described in Petitioners' comments, but modified to account for the proposed amendments submitted as part of the objections. As noted previously, neither the National Leaching Assessment nor the model on which it was based was submitted as part of the comments. Certainly, there is no justification for Petitioners' refusal to provide the analyses that were available during the comment period. Because the National Leaching Assessment was available during the comment period but was withheld, this information is considered to be untimely and the Petitioners have waived the right to rely on it. Accordingly, as discussed in Unit VI.D, because this evidence was not presented as part of the Petitioners' comments, EPA considers that the evidence submitted in support of this objection is not appropriately considered as a basis for justifying a hearing on the final rule. *See* 73 FR 42683, 42696 (July 23, 2008); 72 FR 39318, 39324 (July 18, 2007). And in the absence of this evidence, this portion of the objection consists of mere allegations and denials, which do not warrant a hearing (40 CFR 178.32(b)(2)).

But even assuming that the evidence was appropriately considered, the evidence is insufficient, even if established, to justify the factual determination urged (40 CFR 178.32(b)(3)). Nothing in Exhibits 12–13 provides any information that substantively differs from the information summarized in the comments. Second, even assuming that the analysis in Exhibit 14 is valid, on its face the submission states that the analysis only addresses 95% of the samples chosen by the study; no information was provided to explain how the samples relate to the state or other geographic area in which carbofuran would be used. This is important because NAWQA samples were not evenly distributed across most states, but tended to be concentrated in particular regions; in statistical parlance, the samples were not collected randomly. The maps in Exhibit 14 clearly demonstrate that the study samples were not randomly distributed across the state but were primarily in the southern and eastern portions of each state, even though carbofuran use is not restricted to those portions of the states. In other words, no evidence was provided that would allow the Agency to determine the percentage of the carbofuran use area represented by the 95% of the samples the Petitioners' analysis addressed. Nor was any information provided to document the significance of the remaining 5% of the samples that were not captured by their analysis; for example, although this may have only represented 5% of the samples, it is not clear whether this 5% relates to only 5% of the areas where carbofuran may be used, or whether it actually represent a far greater percentage of the use area.

iii. Denial of objection. EPA denies this objection on several bases.

The contention that the NAWQA monitoring data—or indeed any available carbofuran monitoring data—provide an adequate basis for concluding that concentrations will remain low in the areas where use is now permitted is incorrect. The NAWQA program focuses on ambient water rather than on drinking water sources, is not specifically targeted to the high use area of any specific pesticide, and is sampled at a frequency (generally weekly or bi-weekly during the use season) insufficient to provide reliable estimates of peak pesticide concentrations in surface water. For example, significant fractions of the data may not be relevant to assessing exposure from carbofuran use, as there may be no use in the basin above the monitoring site. Unless ancillary usage data are available to determine the amount and timing of the pesticide applied, it is difficult to determine whether non-detections of carbofuran were due to a low tendency to move to water or from a lack of use in the basin. As a consequence, the data do not support relying on the non-detections as a lower bound, or relying on the detections as an upper bound. The program, rather, provides a good understanding on a national level of the occurrence of pesticides in flowing water bodies that can be useful for screening assessments of potential drinking water sources, especially for those assessments concerned with chronic, rather than acute toxicants.

While there have been additional groundwater monitoring studies that included carbofuran as an analyte, there has been no additional monitoring targeted to carbofuran use in areas where aquifers are vulnerable, and the locations of sampling and the sampling frequencies generally are not sufficient to capture peak concentrations of the pesticide in a watershed or aquifer where carbofuran is used. Capturing these peak concentrations is particularly important for assessing risks from carbofuran because the toxicity end-point of concern results from single-day exposure (acute effects). Pesticide concentrations in ground water are generally the result of longer-term processes and less frequent sampling can often adequately characterize peak ground water concentrations. However, such data must be targeted at vulnerable aquifers in locations where carbofuran applications are documented in order to capture peak concentrations. As a consequence, monitoring data tends to underestimate exposure for acute endpoints.

EPA also disagrees that the Petitioners' criteria of soils composed of 90% sand and less than 1% organic matter, and wells of less than 30 feet define all of the conditions under which ground water sources are vulnerable to carbofuran leaching. No comprehensive analysis was provided evaluating how they reached this conclusion. Although the Petitioners proposed these criteria as restrictions on the carbofuran label, the spatial extent of the label restrictions was not provided. Moreover, as discussed in greater detail in EPA's Response to Comments, the information provided as part of the Petitioners' comments (primarily maps depicting areas identified as vulnerable) was not sufficient to allow the Agency to evaluate their claim (Ref. 84). For example, the percent sand, one of the criteria used in this analysis, varies significantly across a field and the whole range of soil textures may occur at a county-level. The national map provided purports to represent this parameter and several others aggregated together to identify vulnerable locations. This national-scale map does not provide the level of detail needed to verify the combination of paramters at locations identified as vulnerable.

While the assertion that soils with 90 percent sand are the most vulnerable to leaching is in part true, it is misleading. While many states have only small areas of sandy soils, several of the states in which carbofuran would continue to be used under the Petitioners' proposals have quite extensive areas. For example, according to the Petitioners' own assessment of states with high amounts of carbofuran application (Ref. 6), Texas had 4.2% of soils classified ''as sand'', Michigan had 21.3% and Nebraska had

26.3%. In addition, the Petitioners' statements imply that soils that are sandy textured define the universe of soil textures that are vulnerable to leaching. It is possible that more fine-textured soils, for example sandy loams or silt loams, could also be sufficiently permeable to result in carbofuran leaching as it has not been established how much of a reduction in leaching might occur as texture becomes finer. Furthermore, finer textured soils tend to have more cracks and root channels and thus are more prone to preferential flow.

Petitioners' claims regarding pH concentrations are also incorrect. As an initial matter, their analysis fails to prove that pH values in all use areas will ensure that concentrations are below the level of concern because the analysis in Exhibit 14 is based on a flawed statistical analysis. The methodology on which the Petitioners relied—the use of the mean minus two standard deviations—to estimate the 5th percentile (*i.e.,* 95% of the samples above the value) of the distribution of ground water pHs in a state depends strongly on the shape of the distribution. This method relies on three assumptions: 1) That the data is randomly sampled, 2) that the samples are normally distributed (*i.e.,* a bell-shaped distribution), and 3) that the samples are independent (*i.e.,* the sampling locations do not share common characteristics and are not clustered). The maps in Exhibit 14 clearly demonstrate that the study samples were not randomly collected across each state but were primarily in the southern and eastern portions of the states, even though carbofuran use is not restricted to those portions of the states. For example, Figure 1 in Exhibit 14 clearly shows that the vast majority of the wells sampled in North Dakota and South Dakota are in the eastern half of the state, and in Nebraska in the southern and eastern parts. Therefore the wells sampled will not be representative of the full distribution of wells in the state. On the second assumption, the analysis provided by the Petitioners did not determine whether the distribution was normal; the accuracy of percentiles at the tails of the distribution, such as the 95th percentile, are very sensitive to the accuracy of this assumption. Environmental data are usually not normally distributed; log-normal distribution is more typical (Ref. 60). If the shape of the distribution is not known, a non-parametric or 'empirical' estimation of the percentiles is better because it does not depend on the same assumption of normal distribution. Finally, the pH in various wells may or may not be statistically independent. Samples taken across the landscape are usually spatially correlated up to a certain distance. Beyond that distance, they are statistically independent. Unfortunately, this was not determined as part of this analysis. While pH is clustered across the state, there is considerable spatial variability in pH conditions for both the subsurface and surface environments. This is especially true for shallow ground water systems, where local conditions can greatly affect the quality and characteristics of the water. This can be seen by comparing differences in pH values between counties within a state, and noting that even within a county individual wells will consistently yield ground water with either above- or below-average pH values for that county. Furthermore, even if the statistical calculations was correct, by definition this evidence would not support a determination that groundwater concentrations would never exceed 1.1 ppb, as 5 percent of the samples would result in concentrations that are higher.

In conducting its modeling for the final rule, EPA examined readily available data with respect to ground water and soil pH to evaluate the spatial variability of pH in Wisconsin. As part of the final rule, EPA explained that ground water pH values can span a wide range; this is especially true for shallow ground water systems, where local conditions can greatly affect the quality and characteristics of the water (higher or lower pHs compared to average values). As noted even within counties in the same state, wells will consistently yield ground water with either above- or below-average pH values for that county. Thus, EPA concluded that average ground water pH values for a given area do not truly characterize the (temporal and especially spatial) heterogeneity common in most areas. The actual significance of using a single pH even if it is a 95th percentile value, which as described above was not demonstrated to be accurately calculated, is not clear. For this reason, EPA bracketed potential exposure using a range of pH values.

As further explained in the final rule, the considerable spatial variability in pH conditions for both the subsurface and surface environments is significant because the pH has a large effect on the persistence of carbofuran. This is demonstrated by the results of the ground water modeling simulations from the South-Central Wisconsin scenario, which show that what might appear as relatively small variations in soil pH can have a significant impact on estimates of carbofuran in ground water. Under more acidic conditions, the hydrolysis half-life increases from 28 days at pH 7 to years or more at pHs less than 6. Further, the results of EPA's corn ground water simulations (bounded by the high and low pH values of the aquifer system underlying the scenario location) showed that a relatively small (0.5) decrease in pH from 7 to 6.5 resulted in an increase by 4 orders of magnitude in the 1-in-10-year peak concentration of carbofuran.

The ground water simulations reflect variability in pH by modeling carbofuran leaching in four different pH conditions (pH 5.25, 6.5, 7.0, and 8.7), representing the range in the Wisconsin aquifer system. The upper and lower bound of pH values that EPA chose for this assessment were measured values from the aquifer, and the remaining two values were chosen to reflect common pH values between the measured values. Estimated 1-in-10-year peak ground water concentrations at pH 7 are 1.6×10^{-3} ppb; however, the estimated 1-in-10-year peak ground water concentration at pH 6.5 is 16 ppb, nearly 4 orders of magnitude greater. EPA explained that, because of carbofuran's sensitivity to pH, the Agency had concerns that any given set of mitigation measures would not successfully protect groundwater source drinking. Data indicate that pH varies across an agricultural field, and also with depth (Ref. 49). In particular, the pH can be different in groundwater than in the overlying soil. The upper bound of the carbofuran concentrations estimated by EPA at pH 6.5 is much greater than the concentrations the Petitioners reported in their objections. EPA's complete assessment of the 2008 revised label can be found in its Response to Comments document and these issues were addressed in more detail there (Ref. 84).

For all of these reasons, the objection is therefore denied.

c. Objection/hearing request subissue: Consistency with groundwater concentration in NMC–CRA. Petitioners object that EPA's estimates in the final rule are inconsistent with the groundwater concentration estimates EPA developed for the NMC (CRA). However, they do not identify any specific inconsistency, they simply make the general allegation. They allege that, by contrast, their assessment, which estimated maximum concentrations of 1.1 ppb, is consistent with the NMC CRA.

i. Background. The NMC CRA examined carbofuran at two sites, northeastern Florida and the Delmarva Peninsula. In Florida, concentrations

were found to be below levels of concern because of high pH, but in Delmarva, both in corn and in melon scenarios EPA estimated that 90% of daily concentrations could be as high as 20.5 and 25.6 ppb, respectively. In the proposed and final rules, EPA cited the modeling conducted for the NMC to support its estimates. In addition, EPA used the same methodology used to develop the estimates for the NMC CRA, to conduct the modeling for the additional crops and locations on which carbofuran use occurs.

Although the Petitioners alleged that their estimates were consistent with the NMC CRA in their comments on the proposed rule, they did not identify any specific inconsistency between EPA's groundwater estimates for the proposed rule and its estimates for the NMC CRA.

ii. Denial of hearing request. EPA denies the request for a hearing on this subissue because there is no disputed factual matter for resolution. There is no dispute as to the methodology EPA used to conduct its modeling in either assessment. Petitioners have not identified any specific inconsistency between EPA's groundwater exposure assessment conducted for this rule and the assessment conducted for the NMC CRA. Instead, they rely on mere allegations and denials. As EPA's regulations make clear, a mere ''denial'' of an EPA position is not sufficient to satisfy the standard for granting a hearing (40 CFR 178.32(b)(2)). Moreover the question of whether EPA's assessments are consistent requires the application of a legal standard to undisputed facts, and is thus a legal or policy question. Hearings are not appropriate on questions of law or policy (40 CFR 178.32(b)(1)). (73 FR 42696–42697) (denying a hearing on EPA's decision to reduce the children's safety factor, in the absence of data from the endocrine screening program, on the ground that the objection constituted a legal issue). FDA has repeatedly confirmed that the application of a legal standard to undisputed facts is a question of law for which a hearing is not required. (*See, e.g.,* 68 FR 46403, 46406 n.18, 46408, 46409 (August 5, 2003) (whether facts in the record show there is a reasonable certainty of no harm is a question of law; whether a particular effect is a ''harm'' is a question of law)).

Neither does the claim that their modeling is consistent with the NMC CRA justify a hearing on this question. As EPA explained in the final rule, the values estimated in the modeling conducted for the NMC CRA are greater than the 1 ppb that FMC claims is the maximum expected 1-in-10-year peak concentration. A hearing is not warranted where the claim is clearly contradicted by the record (40 CFR 178.32(b)(2)). *See, e.g.,* 57 FR 6667 (February 27,1992) (''A hearing must be based on reliable evidence, not on mere allegations or on information that is inaccurate and contradicted by the record.''); 49 FR 6672 (February 22, 1984) (hearing denied where claim was based on demonstrably false premise).

iii. Denial of objection. As discussed in the final rule and response to comments document, the Petitioners' results are not consistent with the estimates developed for the NMC CRA. The NMC CRA examined carbofuran at two sites, northeast Florida and the Delmarva Peninsula. In Florida, concentrations were found to be below levels of concern because of high pH, but in Delmarva, both in corn and in melon scenarios EPA estimated that 90% of daily concentrations could be as high as 20.5 and 25.6 ppb, respectively. These values are greater than the 1 ppb that Petitioners claim is the maximum expected 1-in-10-year peak concentration.

2. Objections relating to surface water exposure estimates—a. Objection/ hearing request subissue: Use of percent of the crop treated (PCT) in surface water modeling. The Petitioners object to the assumption in the surface water assessments in the final rule that 100% of the crops in a watershed will be treated with carbofuran. The Petitioners argue that actual carbofuran sales data on a county basis from 2002-present demonstrate that the current carbofuran PCT is less than 4.25%. Using this PCT, and taking into account the recently submitted ''no application buffers,'' the Petitioners allege that the modeling in Exhibit 15 demonstrates that carbofuran concentrations in surface water will not exceed 1.1 ppb, ''which is below the level of concern.''

In support of this objection, the Petitioners reference county level sales data that were submitted to the Agency on November 7, 2008, after the close of the comment period. They also reference the use tracking system proposed in their recent registration amendments (Exhibit 2) and the modeling contained in Exhibit 15.

i. Background. To conduct an assessment of a pesticide's potential to contaminate surface water, EPA estimates the percentage of farmland in a watershed on which a particular crop is grown (*e.g,* corn); this is referred to as the percent cropped area (PCA). EPA then assumes that 100% of the cropped area is treated with the pesticide that is the subject of the assessment. In the proposed rule, EPA explained that the reason for its assumption that 100% of PCA in a watershed is treated is due to the large uncertainties in the actual PCT on a watershed-by-watershed basis. EPA developed an extensive discussion of the uncertainties in PCT and how they impact drinking water exposure assessment in its proposed rule (73 FR 44885 (July 31, 2008)), and in a background document previously provided to the SAP considering the draft carbofuran NOIC (Ref. 45). The data are generally not available on the scale necessary to allow for reliable estimates of pesticide use in a watershed. Such data are generally available only on a statewide basis, and if such estimates are used to account for PCT, it will underestimate the risks for some drinking water facilities in the state, as these estimates represent only a state-wide average. In some cases this underestimate can be substantial, because usage may not be evenly distributed across the landscape; due to differences in factors like pest pressure, local consultant recommendations, and weather, it may be much higher in some areas. Further, temporal uncertainties can result in changes in use that might be driven by weather, changes in insect resistance over time, and changes in agronomic practices. To date, methods that account for this uncertainty, given the nature of the available data, have not been developed. EPA explained that as a consequence, the Agency could not accurately estimate a drinking-water watershed scale PCT that, when used in a quantitative risk assessment on a national or regional basis, standing alone, provides the necessary level of certainty to allow the Agency to confidently conclude that exposures will meet the FFDCA section 408 safety standard. EPA also described the results of a sensitivity analysis conducted using a low PCT estimate.

In their comments on the proposed rule, the Petitioners criticized the Agency for this assumption, arguing that because carbofuran is used on such a low percentage of crops nationally that it is unrealistic to assume that such a large percentage of any individual watershed would be treated. To support their claims that the PCT would generally be below 4%, they referenced county-level ''use'' data, but failed to provide either the data or methodology on which they relied until after the close of the comment period.

In the final rule, EPA explained at length the reasons that the information provided during the comment was insufficient to allow the Agency to reliably estimate a lower PCT for carbofuran. EPA did not review the information submitted after the close of

the comment period. However, based on the information that could be gleaned from the description in the comments, EPA explained that the data on which they relied did not appear to be ''use'' data, but sales data, and that both the data and methodology failed to support the claims made in the Petitioners' comments. The Agency also described the results of a sensitivity analysis conducted to determine the impact that PCT could have on the risk assessment, which demonstrated that even assuming that a low percentage of a watershed is treated with carbofuran, exposures will still be unsafe for infants.

ii. Denial of Hearing Request. To the extent Petitioners' objection is limited to EPA's refusal to use a 4% PCT in estimating drinking water concentrations, EPA has concluded that the objection does not warrant a hearing because the Petitioners' objection on this subissue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation. The Petitioners have not responded to EPA's explanation in the final rule of the reasons that the information and methodology on which they relied to estimate a 4% PCT was flawed. As discussed in the final rule, EPA had assumed that the data on which they were relying was sales data, and so the resubmission of the information sent in after the close of the comment period only confirms that the Agency's analysis was correct; it does not rebut EPA's substantive concern that such information is insufficient to support the conclusions the Petitioners assert. In essence, the Petitioners ignored EPA's extensive analysis of this issue in the final rule and simply refiled their comments on the proposal as if EPA's determination in the final rule did not exist. The statute, however, requires that objections be filed on the final rule not the proposal. By ignoring EPA's final rule on this issue, Petitioners have failed to lodge a relevant objection. When an objector does not challenge EPA's conclusions in the final rule, but merely reiterates comments made on the proposed rule, without submitting some evidence that calls EPA final rule conclusions into question, the objector has not raised a live controversy as to an issue material to the final rule (*See* 73 FR 42698–42699 (July 23, 2008) (denying several NRDC hearing requests because the objections were based on EPA's preliminary DDVP risk assessment, rather than the revised risk assessment published with the final order); 53 FR 53176, 53191 (December 30, 1988) (where FDA responds to a comment in the final rule, repetition of the comment in objections does not present a live controversy unless the objector proffers some evidence calling FDA's conclusion into question)).

An additional flaw in this objection is that the proffered evidence is untimely and insufficient. Neither the proposed registration amendments nor the evidence submitted as part of this objection, including the modeling in Exhibit 15, was provided to the Agency during the comment period. The modeling in Exhibit 15 was available, because it was summarized in Petitioners' comments; however the underlying modeling was withheld. Equally, there is no evident reason that the sales data could not have been submitted as part of the Petitioners' comments. Petitioners relied on this data to perform analyses completed in 2006–2007, for purposes of the January 2008 SAP review of the draft carbofuran NOIC, so the information was available long before their comments needed to be filed. Accordingly, as discussed in Unit VI.D, this information is not appropriately considered as a basis for justifying a hearing on its final rule. Moreover, as explained below, because no evidence was submitted in support of the newly proposed use tracking system, reliance on that proposal to support a low PCT constitutes nothing more than an allegation. This is not an adequate basis on which to grant a hearing (40 CFR 178.32(b)(2)). Finally, to the extent this objection relies on Petitioners' recently proposed risk mitigation measures, as discussed in Units VI.C and D, objections and hearing requests based on these new risk mitigation measures are not appropriately considered at this stage of the administrative process, and are denied as immaterial (40 CFR 178.32(b)(3)).

iii. Denial of objection. While the Agency typically uses PCT in developing estimates of pesticide residues in food, this is entirely different than developing estimates of the percent of a watershed that is treated for purposes of estimating drinking water exposures. Food is generally randomly distributed for sale across the nation without regard to where it is grown. This tends to even out any PCT variations that may arise on local levels. By contrast, the source of water consumption (and consequently exposure) is localized, either in a private well or a community water system. The PCT in any watershed will therefore directly impact the residues to which people living in that watershed will be exposed.

For this reason, among others, for drinking water exposure estimation, the Agency assumes that 100% of the cropped area (or 100% PCT) is treated with the pesticide. EPA also makes this assumption due to the large uncertainties in the actual PCT on a watershed-by-watershed basis. EPA included an extensive discussion of the uncertainties in PCT and how they impact drinking water exposure assessment in its proposed rule (73 FR 44834) and in a background document provided to the SAP considering the draft carbofuran NOIC (Ref. 45). Because usage is often not evenly distributed across the landscape, due to differences in factors like pest pressure, local consultant recommendations and weather, it may be much higher in some areas. Further, temporal uncertainties can result in changes in use that might be driven by weather, changes in insect resistance over time, and changes in agronomic practices. To date, methods that account for this uncertainty, given the nature of the available data, have not been developed. Consequently, EPA cannot accurately estimate a drinking-water watershed scale PCT that, when used in a quantitative risk assessment on a national or regional basis, standing alone, provides the necessary level of certainty to allow the Agency to confidently conclude that exposures will meet the FFDCA section 408 safety standard.

In most cases, EPA agrees that it is unlikely that 100% of the crop will be treated with a single pesticide in most watersheds, particularly in larger watersheds. However, for small watersheds, it is reasonable to assume that an extremely high percentage of the crops in the watershed may be treated.

Moreover, EPA has an obligation to evaluate all legally permitted use practices under the label, and to ensure that all such use meets the requisite statutory standards, not simply to base its decisions on the practices the majority might typically use. The September 2008 proposed label, submitted during the comment period, imposes no restriction on the application of carbofuran related to whether a particular percent of the watershed has been treated. Thus, even with the restrictions on FMC's September 2008 labels, it remains legally permissible for 100% of the watershed to be treated with carbofuran.

Nor is EPA aware of an enforceable mechanism to ensure that farmers applying pesticide to their individual fields will have the ability to indendently determine whether a particular percentage of the watershed has been treated. There are significant practical difficulties inherent in implementing such label directions, as

they force individual growers to have continual knowledge of the variances of the behavior of other farmers across the entire watershed. While for small watersheds that involve only one or two farms it might be feasible for neighbors to independently coordinate applications with respect to adjacent fields, for larger watersheds or for smaller watersheds with multiple farms, the practical difficulties increase significantly. And as explained below in Unit VI.F.2.D, significant questions remain regarding the efficacy of Petitioners' proposed use tracking system.

However, in the final rule, EPA conducted a sensitivity analysis to explore the impact of the PCT assumption on dietary risk using an assumed 10% PCT, a figure proposed previously by FMC (74 FR 23065–23066). The results of that analysis demonstrated that even at these low percentages, which may significantly underestimate exposures, particularly in small watersheds, carbofuran exposures from drinking water contribute significantly to children's dietary risks. EPA conducted a similar sensitivity analysis for the final rule, discussed below in Unit VI.F.3, which demonstrates that even assuming that a low percentage of a watershed is treated, exposures will still be unsafe for infants.

Since EPA's 2006 determination that carbofuran does not meet the safety standard, FMC has submitted three assessments that relied in part on what they refer to as ''county-level usage data'' (Refs. 29, 74, and 89). Based on the information provided with the objections, the original source of the ''county-level usage data'' is sales data, apparently collected at the distributor level. The Petitioners claim to have augmented these sales data in an unspecified manner, by incorporating information from the distributors, which was used to allocate carbofuran usage at the county level. In their comments on the proposed rule, the Petitioners provided maps representing county level and watershed-scale use estimates, but did not provide the actual usage estimates in any clearly understandable format.

The Petitioners did submit these sales data as part of their objections, but have provided only a limited description of how these data were collected and no description of how they were actually analyzed or validated; what was characterized as ''careful and proven techniques to capture this data'' were not described. The method used to attribute carbofuran sales to counties was not described. Nor have they explained what is meant by negative usage estimates.

The Agency agrees that county-level use data would be useful in generating reasonable estimates of PCT that might be appropriately used in drinking water assessments. However, no usage data have been provided. Rather, the Petitioners only provided county-level use estimates for Illinois, although they have not submitted the analyses that presumably are the basis for the estimates. County-level estimates to support other risk assessments have not been submitted by the Petitioners. Further, the Petitioners have provided limited characterization of the source data, noting that these data were derived from FMC billings and ''EDI data'', but they did not provide either the billings or the EDI data, nor explain how they were collected.

There are two major problems in equating sales information with use information: (1) Mapping the point and time of sale to the point and time of use and (2) allocating the amount sold across the crops on which it can be used. The submission did not explain how either of these two problems was resolved.

The first problem is highlighted by the fact that for some county/crop/year combinations in the submitted tables, estimated usage is negative. Use of a pesticide clearly cannot be negative, but sales at a particular point and time can be negative because buyers can return unused product. The fact that some usage estimates are negative suggests that buyers are returning carbofuran product purchased in an earlier time period or from another location. But if farmers are returning carbofuran purchased in a previous time period, any assessment must also account for the possibility that they also could use stocks purchased previously. Thus, use in a given year may be greater than sales in that year. Similarly, if farmers are returning carbofuran purchased in another location, it must be recognized that they could be using carbofuran purchased in another location. Thus, use in any given county or watershed could be greater than sales in that locality. That is, regardless of whether the issue is use over space, time, or both, the results are that usage will be underestimated in some localities. Further, zeroing out the negative values will not result in appropriate estimates; the negative usage estimates merely make the problem manifest. Even total sales at a point in time may underestimate actual use.

The second problem arises with the allocation of product sales across the crops on which it can be used. The data provided as part of the objections were aggregated for all crops, including crops on which use is no longer allowed, such as cotton or alfala; the data were not collected based on the individual crops. No explanation is provided to indicate how the Petitioners divided the quantity sold between the amount used on cotton, on alfalfa, and on all other crops. Since part of the purpose of the Petitioners' assessment is presumably to show that eliminating the use on the cancelled crops, such as alfalfa, will sufficiently reduce any risks, it is critical to know how they determined the amount used on alfalfa as opposed to other crops, and it is difficult to imagine how this could be done with any accuracy. For example, one could assume that the chemical is used on equal proportion of all crops, but there is no basis for such an assumption. It might not matter if all EPA were interested in was the total amount used in an area, but this is not useful for purposes of assessing the risk on a smaller scale, such as in the present case.

The method the Petitioners used to generate use estimates from the sales data does not account for the uncertainties described above nor for the potential for use to be locally concentrated due to pest pressures. The method that is summarily described as having been used to allocate county-level usage estimates to watersheds appears to be similar to a method that has been used by others to calculate ''best-estimate'' county-level PCT (Ref. 73) to map nationwide pesticide usage. However, these methods are not appropriate for calculating PCTs for surface drinking water sources or watersheds that drain to community water systems, because they do not adequately account for the uncertainty in the data at the appropriate spatial scale. This methodology produces an estimate that is a measure of central tendency and, as such, roughly half the estimated values will underestimate the PCT. Furthermore, because pesticide use varies from year to year, and can in some cases be patchy, with high levels of use in small areas and little use in most areas, the underestimates of PCT can be substantial in small watersheds. As previously noted, methods for calculating PCT that account for these uncertainties have not been developed. Accordingly, EPA denies this objection.

b. Objection/hearing request subissue: Results of FMC modeling. The Petitioners claim that the prior surface water assessments submitted to the Agency demonstrated that carbofuran concentrations in surface water were not expected to exceed 1.1 ppb. They claim

that these studies provide further confirmation of the results of the new modeling conducted to support their objections, which also concluded that concentrations would be less than 1.1 ppb. In support of this objection, the Petitioners reference the previously submitted studies, along with the modeling provided in Exhibit 15. The modeling in Exhibit 15 appears to be the modeling that was originally summarized in their comments, but that the Petitioners withheld. The modeling was also supplemented to account for the newly proposed registration amendments submitted as part of the objections.

i. Background. In their comments, the Petitioners alleged that the results of their modeling showed that concentrations of carbofuran in surface water would not exceed 1.1 ppb. The comments referenced two surface water assessments that they had submitted to the Agency prior to the proposed tolerance revocation: a surface water assessment based on an Indiana Community Water System (CWS) (Refs. 89 and 90) and an assessment based on the Watershed Regressions for Pesticides (WARP) model. They also summarized additional surface water modeling that had been conducted to support their comments on the proposed rule, a Nationwide Community Water System Assessment (Ref. 57), but did not submit the actual modeling, or identify or describe in detail the model on which they relied.

In the final rule, EPA explained the flaws in all of the Petitioners' assessments that caused the Agency to reject the studies' conclusions. For the two assessments that had actually been submitted to the Agency, EPA was able to definitively explain the flaws. With respect to the Nationwide CWS modeling that was summarized in their comments, EPA evaluated the modeling based on the information it was able to glean from the description provided in the comment discussion.

ii. Denial of hearing request. A hearing is denied on this subissue because EPA has concluded that Petitioners' objection on this issue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation (40 CFR 178.32(b)(3)). In the final rule, and in other rulemaking documents, EPA provided a detailed explanation of the bases for its conclusions that the previously submitted assessments were invalid (74 FR 23062–23064 (May 15, 2009)). Petitioners have not challenged EPA's explanation, nor explained how the resubmission of the same studies addressed the substantive issues EPA raised. Because Petitioners ignored EPA's extensive analysis of this issue in the final rule, they have essentially refiled their comments on the proposal as if EPA's determination in the final rule did not exist. The statute, however, requires that objections be filed on the final rule, not on the proposal (21 U.S.C. 346a(g)(2)). By ignoring the EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Petitioners' resubmission of the exact same information does nothing to call EPA's conclusion into question, which is what is required to maintain their claim at this stage of the proceeding. When an objector does not challenge EPA conclusions in the final rule, but merely reiterates comments made on the proposed rule without submitting some evidence that calls EPA final rule conclusions into question, the objector has not raised a live controversy as to an issue material to the final rule. (See 73 FR 42700–42701 (July 23, 2008) (hearing request denied where NRDC failed to challenge EPA's conclusion that challenged study is consistent with several other studies, but merely reiterated assertions from its original petition that the study is not representative); 53 FR 53176, 53191 (December 30, 1988) (where FDA responds to a comment in the final rule, repetition of the comment in objections does not present a live controversy unless the objector proffers some evidence calling FDA's conclusion into question)).

With respect to the modeling submitted in Exhibit 15, this evidence is untimely. The modeling submitted in Exhibit 15 appears to be a fuller description of Petitioners' National CWS Assessment, which was described but not provided as part of their comments on the proposed rule. The modeling also has been revised to account for the newly proposed risk mitigation measures. However, even with the greater detail provided, the information contained in Exhibit 15 still fails to address many of the deficiencies EPA identified in the final rule. For example, although some further detail has been provided of how the Petitioners modeled the vegetated buffer strip, the complete information EPA would need to assess the modeling was not provided; the material provided is insufficient to understand how the simulations were performed or how the simulations were parameterized. Nor have the Petitioners submitted the inputs used in modeling estimated concentration from spray drift. As discussed in Unit VI.D, because the modeling in Exhibit 15 was not provided during the comment period, and to the extent that the detailed information EPA identified as lacking in the final rule has still not been provided, the evidence submitted in Exhibit 15 is not appropriately considered as a basis for justifying a hearing on its final rule. And in the absence of this evidence, this objection consists of mere allegations and general denials, which are inadequate to justify a hearing (40 CFR 178.32(b)(2)).

Further, to the extent that this objection relies on the ''no application buffers,'' or the proposed use tracking system newly submitted as part of their objections to support the models' assumption of a low PCT, the hearing request is denied as irrelevant, and therefore immaterial, to EPA's determination in the May 15, 2009 final rule, for the reasons discussed in Unit VI.C. Petitioners are actually not objecting to the conclusions in EPA's final rule; rather, they are suggesting that EPA might reach a different result in a different factual scenario. Objections, however, must be directed ''with particularity [at] the provisions of the regulation or order deemed objectionable'' (21 U.S.C. 346a(g)(2). And, as explained below, because no evidence was submitted in support of the newly proposed use tracking system, reliance on that proposal to support a low PCT constitutes nothing more than an allegation. This is not an adequate basis on which to grant a hearing (40 CFR 178.32(b)(2)).

iii. Denial of objection. To the extent this objection relies on Petitioners' newly submitted registration amendments, the objection is denied as immaterial. EPA also denies the remaining objections because, based on its review of the submitted modeling, EPA has concluded all of the modeling has substantial flaws that render the model results invalid. EPA has previously reviewed these assessments, and provided a detailed explanation of the reasons for the Agency's conclusions, most recently, in the final rule and the associated response to comments (74 FR 23060–23064, Ref. 84). EPA's reasoning is summarized briefly below.

Indiana CWS Assessment

EPA has previously reviewed the Indiana surface water assessment, and has provided comments on that submission (Ref. 45), many of which were reiterated at length in the final rule and response to comments documents (74 FR 23062–23064, Ref. 84). The Petitioners originally submitted this study to demonstrate that ''EPA's standard index reservoir scenario

overestimates surface water concentrations compared with expected concentrations in actual Indiana CWS where carbofuran is used.'' The Index Reservoir is designed to be used as a screen, and as such, represents watersheds more vulnerable than most of those that support a drinking water facility. It is thus protective of most drinking water on a national basis. That, however, does not mean that EPA believes this scenario overestimates concentrations for all drinking water reservoirs. EPA agrees that it is an appropriate refinement to simulate local and regional watersheds, and has in fact done so (Refs. 44, 46, 47, 48, and 84). However, for the reasons discussed below, EPA does not believe that the Petitioners' assessment demonstrates that carbofuran concentrations will not exceed 1.1 ppb in Indiana surface water sources of drinking water. Even accepting the Indiana surface water assessment at face value, the estimated 1-in-10-year peak concentrations at some facilities were as high as 6.88 µg/L, and these concentrations substantially exceed the 1.1 ppb concentration the Petitioners now claim represent reasonable estimates.

The study also fails to support the Petitioners' other conclusions. The study was originally intended to demonstrate two points: (1) That the vulnerability of the Indiana CWS ''brackets'' the Index Reservoir, and (2) that the concentrations they estimated for these locations are significantly less than EPA estimates. Regarding the vulnerability of the CWS, the assessment describes their approach for modifying the parameters of the Index Reservoir scenario to represent 15 reservoir-based watersheds in Indiana cropped in corn. The study indicates the Petitioners have included data that, based on EPA's review of these submissions, are not available at the appropriate scale to determine all site-specific parameters. The Petitioners modified some of the parameters based on available data to represent more localized conditions that are more or less vulnerable than for the Index Reservoir. From the description, the Petitioners' approach is similar to the methods that EPA uses to develop new scenarios, in that soil and weather data are varied in order to represent different locations. However, for other parameters, EPA believes the modifications are inconsistent with fundamental assumptions upon which the modeling is based. In previous submissions to the Agency, FMC has described that they have made modifications to scenarios to reflect local conditions of each CWS in Indiana by modifying the soil and weather data and altering the ratio of watershed drainage area to the reservoir capacity (Ref. 89). EPA agrees that soil and weather data can be modified to reflect conditions at local watersheds. However, EPA disagrees that altering the ratio of watershed drainage area to the reservoir capacity (*i.e.*, the DA/NC) is a reasonable modification.

The DA/NC parameter is associated with increased concentrations in drinking water reservoirs to a certain point. The Petitioners adjusted their EDWCs for each drinking water facility by a factor representing the ratio of the DA/NC for each reservoir divided by the DA/NC for the Index Reservoir (which is 12). EPA does not believe this is appropriate for two reasons. First, the relationship between concentrations and the DA/NC is not strictly linear. Small DA/NCs imply a small watershed combined with a large reservoir. As the DA/NC increases, the relative watershed size increases, and thus the runoff volume going into the reservoir also increases. This is also means the reservoir's ability to dilute the runoff decreases; the result is that concentrations increase with an increase in the DA/NC. However, at some point, the runoff volume exceeds the reservoir capacity, and rather than increasing the pesticide concentration, the excess runoff flows out of the reservoir, carrying the pesticide with it. Thus, because pesticide concentrations are not linearly related to the DA/NC, it is not appropriate to multiply the model output by a linear DA/NC adjustment factor. Secondly, the PRZM model, which is used to simulate the watershed for the Index Reservoir, is a field-scale model. As the watershed size (and the DA/NC) increases, assumptions upon which PRZM relies (namely: uniformity of soils, equal and simultaneous movement of runoff to the reservoir, and uniform weather across the watershed) no longer hold and the model becomes less valid for simulating the runoff processes. The geometry of the Index Reservoir was chosen partly to avoid these two limitations (Ref. 43).

The study authors also calculated their own PCA values [19] for this assessment. EPA uses the maximum PCA calculated for any HUC8 (8-digit hydrologic unit code) watershed in exposure estimates. HUC8s are cataloging units for a watershed developed by the USGS and are used as surrogates for drinking water watersheds. The process by which PCAs were developed and how they are used by the Agency has been vetted with the FIFRA SAP (Refs. 30 and 31). The Agency has developed PCAs for four major crops—corn, soybeans, wheat, and cotton—and uses a default PCA based on all agricultural land for characterizing other crops. The Agency has also calculated regional default PCAs for use in characterizing regional differences in drinking water exposure. EPA limited further development of PCAs for additional crops in response to the FIFRA SAP peer review, which concluded that the data were not available at the appropriate scale to do so. The Petitioners' assessment estimated PCAs for specific watersheds in Indiana, but did not provide sufficient detail in their descriptions of how they calculated those PCAs to enable EPA to assess their validity.

Regarding the statement that the concentrations estimated for the study locations in Indiana are significantly less than EPA estimates, EPA has determined that the Petitioners included an adjustment factor to account for the percent of a crop that is treated with carbofuran. As previously discussed, EPA does not believe that it is appropriate to base its aggregate risk estimates on PCT within watersheds. This is because data and/or methods are not available that would allow EPA to develop PCT at the watershed scale with the necessary level of confidence to allow EPA to make a safety finding. The PCT factors that the Petitioners applied would generate significantly lower concentrations than those estimated by EPA.

WARP Assessment

EPA has reviewed the WARP assessment previously and has provided comments on the submission (Refs. 45 and 86). The WARP model has not been fully evaluated for quantitative use in exposure estimation by the Agency, although it has been preliminarily reviewed by the SAP (Ref. 32). EPA used WARP to select monitoring sites for the herbicide atrazine, based on predicted vulnerability of watersheds to atrazine runoff within the corn/sorghum growing regions. EPA presented its approach to the FIFRA SAP in December 2007. The SAP report concluded that ''WARP appears to be a logical approach to identify the areas of high vulnerability to atrazine exposure,'' endorsing EPA's use of this tool only for atrazine, and for the limited purpose of designing a monitoring program. The SAP noted that the most important explanatory variable with WARP was use intensity, which underscores the

[19] The PCA is the fraction of the drinking water watershed that is used to grow a particular crop.

importance of having the most accurate data for this parameter.

WARP is a regression model developed by the USGS to estimate concentrations of the pesticide atrazine in rivers and streams. As a regression model, it is based on monitoring data from 112 USGS NAWQA monitoring locations. WARP does not directly estimate daily concentrations, but predicts the percent of the time in a randomly selected year that concentrations of the pesticide are less than a specified value, with a specified level of confidence. USGS attempted to develop an approach to estimate annual time series for other pesticides, and concluded that ''further data collection and model development may be necessary to determine whether the model should be used for areas for which fewer historical data are available * * * Because of the relative simplicity of the time-series model and because of the inherent noise and unpredictability of pesticide concentrations, many limitations of the model need to be considered before the model can be used to assess long-term pesticide exposure risks'' (Ref. 92).

The Petitioners had previously relied on their WARP assessment to support the conclusion that the ''maximum 1-in-10-day estimated concentrations of carbofuran at the 90th percentile level in Illinois, Indiana, Iowa, and Nebraska * * * will be less than or equal to 0.3687 ppb.'' This is erroneous. WARP does not provide direct estimates of return frequency, *i.e.*, 1-in-10 days, but rather percentiles of the expected distribution of measurements. This may be similar but not identical to the return frequency expressed as a percentile, depending on the number of measurements used to support the regression. EPA lacked the information necessary to determine whether the contractor calibrated the model correctly. However, taking the conclusion at face value, the value the Petitioners predicted using WARP, 0.3687 ppb, appears to represent the maximum of the estimated values of the annual 90th percentile among all the sites evaluated. Such a site would be expected to have higher concentrations than 0.3687 ppb about 37 days a year (10% of the year). Generally, the 90% prediction intervals tend to be about plus or minus an order of magnitude. Thus, roughly 5% of such sites could have about 37 days a year greater than about 3.7 ppb, or over 3-fold higher than the 1.1.ppb concentrations the Petitioners now claim will be the maximum concentrations in surface water.

The Agency also disagrees that the differences between the Petitioners' and EPA estimates are only due to Petitioners' use of county-level use estimates. Most importantly, the Petitioners relied on estimates of 1-in-10-day concentrations, rather than the 1-in-10-year peak concentrations estimates used routinely by EPA. 1-in-10-day concentrations are not the measurement endpoint EPA uses for human health risk assessment and are not appropriate for estimating drinking water exposure. The Agency uses 1-in-10-year peak concentrations for screening level assessments, and the full time series (typically 30 years) of daily concentration values for refined assessments. EPA's reliance on the 1-in-10-year peak concentration has been reviewed and approved by the FIFRA SAP (Ref. 30).

A concentration that occurs 1-in-10 days occurs 350 times as often as a 1-in-10-year event. Using this value instead of the one EPA used would result in significantly lower estimates of pesticide water concentration and human exposure. For example, EPA's estimate of the 1-in-10-year peak concentration from the simulation of corn in Kansas with a 300 ft buffer was 31.8 ppb. By contrast, EPA's estimate of the 1-in-10-day concentration from the same simulation was 4.5. Use of the 1-in-10 day concentration to assess dietary risk would be inconsistent with the SAP's advice and EPA's typical practice, as well as with EPA's statutory requirement to protect human health.

EPA disagrees with the Petitioners' claim that ''the extreme nature of a 1-in-10-year event would result in dilution effects that cancel out any increased loading.'' The Index Reservoir scenario has been validated against monitoring collected at the site it was designed to represent, Shipman City Lake in Illinois (Ref. 43). This assessment showed that the 1-in-10-year event EPA modeled was similar in magnitude to the peak value of the pesticide concentrations shown in 5 years of monitoring data collected at that site. The 1-in-10-year peak concentration calculated for that pesticide (not carbofuran), using the Index Reservoir was 33 ppb, while the peak value from 5 years of monitoring was 34 ppb.

EPA cannot determine the validity of the use intensities assumed for the Petitioners' assessment. The source of county level use data appears to have been sales data at the distributor level, similar to the data provided in the Petitioners' November 7, 2008 submission. However, as previously explained, the method chosen to estimate county level use estimates from the sales data was not provided. The county level estimates used in the assessment for 2002 to 2004 for Illinois were provided in a table. These estimates for each county were averaged over the 3 years for input to the model. A summary description of how watershed-scale use estimated from county level use data was provided, but because the sales data for the individual crops and the method that was used to generate county level estimates were not available, the validity of this assessment cannot be evaluated.

Nationwide CWS Assessment

EPA has previously reviewed the Petitioners' ''Nationwide CWS Assessment'' and provided a response to the submission as part of the final rule and Response to comments (Ref. 45). As a preliminary matter, this assessment only included use intensity for reservoir-based systems, and excluded use intensity for all stream- or river-based systems from their assessment. Therefore, this assessment provides no evidence to demonstrate that carbofuran can be safely used in stream or river-based community water systems.

Similar to the Indiana CWS study discussed above, this study relied on county-level usage estimates to estimate use intensity. The National CWS Assessment concluded that a use intensity below 2.1 lbs a.i/mi^2 would assure that surface water concentrations will be below the level of concern.

To evaluate the study, it is therefore important to understand how the use intensities were derived. The Petitioners' methods have been poorly described, but EPA has been able to piece together a general sense of the methods from the various reports provided to EPA. To summarize, the Petitioners relied on sales data to generate the use intensity estimates, but the method used to generate the county-level use estimates from the sales data is not described. The actual county level use estimates used in the use intensity calculations were not provided. There is a limited description indicating only that the county level use estimates were apportioned to different crops, but the method used to do this was not provided. The Petitioners appear to have used an objective method to group the county-level use estimates into 5 classes, but the method is only briefly described. Thus, because EPA cannot determine how use intensity was estimated, the Agency cannot determine if the conclusions made in the National CWS Assessment are justified by the underlying data.

In the absence of this information, EPA is unable to substantiate the study conclusion that 75% of the permissible use areas have a carbofuran use intensity below 2.1 lbs a.i/mi²—even assuming that reliance on only 75% of the use areas would be protective, and nothing has been submitted to substantiate that conclusion. Use intensity maps that were provided with the Petitioners' comments appear to indicate that carbofuran use varies year by year, and it is not clear for which year or years, the Petitioners are relying to support their claim that use intensity will be below 2.1 lbs a.i/mi². No further support for this claim was provided with the Petitioners' objections, even though EPA presented its conclusions in the final rule.

As noted, the National CWS Assessment assumed that a use intensity below 2.1 lbs a.i/mi² would assure that surface water concentrations will be below the level of concern. EPA agrees that using lower rates of carbofuran will result in lower exposure. But EPA does not agree that it has been demonstrated that a use intensity below 2.1 lbs a.i./mi² will assure that surface water concentrations will be below the applicable level of concern. The National CWS Assessment does not justify such a finding, nor has any other assessment that has been submitted to date. The Agency modeled use rates for carbofuran on corn based on the label proposed in September 2008, which are the rates at which farmers are legally allowed to apply carbofuran, and the results clearly demonstrate that estimated exposures will substantially exceed safe levels. The results of EPA's assessments are described in more detail in Unit V.E. of this order, the final rule and in Reference 111.

EPA is equally unable to confirm the study's claim that the no-application buffers on the September 2008 labels will adequately mitigate the risks ''in areas with historical use intensities greater than 2.1 lbs a.i./sq. mi.'' On the September 2008 labels, FMC included buffers of 300 feet on water bodies in Kansas, and 66 feet around water bodies in other places, but EPA cannot evaluate how these buffers relate to areas where carbofuran use intensities exceeded a specific value, for all of the reasons stated above. EPA did, however, model the effects from the buffers proposed on the September 2008 labels and found that these buffers reduce exposure by 5.1% (33.5 to 31.8 ppb) for corn in Kansas with a 300-foot spray drift buffer and 4.7% (29.9 to 28.5 ppb) for corn in Texas with a 66-foot spray drift buffer. However, even with the buffers, EPA's analyses clearly demonstrate that estimated exposures will substantially exceed safe levels. These results are described in more detail in Unit V.E. of this order, the final rule, and Reference 84, Appendix I. For all of these reasons, the objection is denied.

c. Objection/hearing request subissue: Challenges to EPA use of NAWQA monitoring data. The Petitioners object to EPA's discussion in the final rule of the extremely high concentrations detected in Zollner Creek in Oregon. They argue that reliance on these concentrations to confirm the results of EPA's modeling is not supportable because Zollner Creek is a small isolated creek, not a drinking water source, and that because of its size, is not representative of potential drinking water anywhere else. They also argue that the majority of the concentrations in the NAWQA data, including those detected at Zollner Creek, are extremely low—below the 1.1 ppb they claim is supported by their modeling. They also contend that the higher observed concentrations in the NAWQA monitoring data are the result of use patterns that are no longer permitted, and that allowed a much higher use rate than is currently permitted.

i. Background. In the proposed rule, EPA described the available monitoring data that characterized carbofuran concentrations in surface water. EPA described that the highest concentrations of carbofuran are reported from a sampling station on Zollner Creek, which EPA acknowledged ''is not directly used as a drinking water source'' (73 FR 44883). USGS monitoring at Zollner Creek from 1993 to 2006 detected carbofuran annually in 40–100% of the samples. EPA stated that although the majority of the concentrations detected were in the sub-part per billion range, concentrations have exceeded 1 ppb in 8 of the 14 years of sampling (Id.). The maximum measured concentration was 32.2 ppb, observed in the spring of 2002. EPA compared its modeling results to the concentrations seen in all of the USGS monitoring, Safe Drinking Water Act (SDWA) monitoring, and to the results of the available field scale studies. EPA concluded that the concentrations estimated in its modeling were consistent with the results of all of the available monitoring and studies (73 FR 44883–44884).

In their comments on the proposed rule, the Petitioners alleged that comparisons between EPA's modeling concentrations and Zollner Creek detections were inappropriate because they were based on ''older data [that] are not reflective of future carbofuran use areas and/or intensities'' (Ref. 18 at 55). In support, they claimed that ''carbofuran was once used at several nurseries and strawberry farms in the Zollner Creek watershed at estimated application rates of up to 15 lbs. a.i./acre (5 times higher than the maximum rate on the current label, and 15 times higher than the most common use rates)'' (Id at 56).

In the final rule, EPA explained that it had not relied solely on Zollner Creek concentrations to validate its modeling. EPA again described the results of all available modeling, which included the detections at Zollner Creek, but also included results from all other NAWQA sites, SDWA post-treatment monitoring, and the results of field studies. Based on all of these data, EPA concluded that the results of the revised modeling conducted for the final rule was consistent with the available monitoring data.

ii. Denial of hearing request. This subissue does not meet the standard for a hearing. The objections regarding Zollner Creek are not material. EPA did not rely in on the concentrations detected at Zollner Creek to provide significant support its assessment.

In the final rule, EPA was clear that it considered the levels seen at Zollner Creek to be a rare circumstance:

> While available monitoring from other portions of the country suggests that the circumstances giving rise to high concentrations of carbofuran may be rare, overall, the national monitoring data indicate that EPA cannot dismiss the possibility of detectable carbofuran concentrations in some surface waters under specific use and environmental conditions.

(74 FR 23081). The final rule was clear that EPA placed greater reliance on the concentrations detected in Safe Drinking Water Act (SDWA) post-treatment monitoring, showing concentrations ranging between 4 and 7 ppb (74 FR 23079–23080). EPA also discussed the results of the UK tile drain studies as supplemental confirmation of its modeling (74 FR 23082).

Petitioners' contentions regarding the NAWQA monitoring also fail to present a genuinely-disputed issue of material fact. In both the proposed and final rules, EPA acknowledged the large percentage of non-detections and low concentration levels in the majority of the NAWQA monitoring data, and repeatedly explained the reasons that these data cannot serve as lower or upper bounds (73 FR 44882–44883; 74 FR 23081). Petitioners do not dispute those conclusions, or submit evidence to rebut them. When an objector does not challenge EPA conclusions in the final rule, but merely reiterates

comments made on the proposed rule, without submitting some evidence that calls EPA final rule conclusions into question, the objector has not raised a live controversy as to an issue material to the final rule. (See 73 FR 42700–42701 (denying hearing request where NRDC failed to object to the basis EPA asserted in its petition denial for rejecting their original challenge). Finally, no evidence has been submitted to support the contention that all of the higher concentrations exclusively result from uses or higher use rates that are no longer permitted. Hearings will not be granted on mere allegations (40 CFR 178.32(b)(2)).

iii. Denial of objection. Data compiled in 2002 by EPA's Office of Water show that carbofuran was detected in treated drinking water at a few locations. Based on samples collected from 12,531 ground water and 1,394 surface water source drinking water supplies in 16 states, carbofuran was found at no public drinking water supply systems at concentrations exceeding 40 ppb (the MCL). Carbofuran was found at one public ground water system at a concentration of greater than 7 ppb and in two ground water systems and one surface water public water system at concentrations greater than 4 ppb (measurements below this limit were not reported). Sampling is costly and is conducted typically four times a year or less at any single drinking water facility. The overall likelihood of collecting samples that capture peak exposure events is, therefore, low. For chemicals with acute risks of concern, such as carbofuran, higher concentrations and resulting risk is primarily associated with these peak events, which are not likely to be captured in monitoring unless the sampling rate is very high.

Unlike drinking water derived from private ground water wells, drinking water from public water supplies (surface water or ground water source) will generally be treated before it is distributed to consumers. An evaluation of laboratory and field monitoring data indicate that carbofuran may be effectively removed (60–100%) from drinking water by lime softening and activated carbon; other treatment processes are less effective in removing carbofuran (Ref. 81). The detections between 4 and 7 ppb, reported above, represent concentrations in samples collected post-treatment. As such, these levels are of particular concern to the Agency. An infant who consumes a single 8-ounce serving of water with a concentration of 4 ppb, as detected in the monitoring, would receive approximately 130% of the aPAD from water consumption alone.

To further characterize carbofuran concentrations in surface water (*e.g.,* streams or rivers) that may drain into drinking water reservoirs, EPA analyzed the extensive source of national water monitoring data for pesticides, the USGS NAWQA program. The NAWQA program focuses on ambient water rather than on drinking water sources, is not specifically targeted to the high use area of any specific pesticide, and is sampled at a frequency (generally weekly or bi-weekly during the use season) insufficient to provide reliable estimates of peak pesticide concentrations in surface water. For example, significant fractions of the data may not be relevant to assessing exposure from carbofuran use, as there may be no use in the basin above the monitoring site. Unless ancillary usage data are available to determine the amount and timing of the pesticide applied, it is difficult to determine whether non-detections of carbofuran were due to a low tendency to move to water or from a lack of use in the basin. The program, rather, provides a good understanding on a national level of the occurrence of pesticides in flowing water bodies that can be useful for screening assessments of potential drinking water sources.

The national monitoring data indicate that EPA cannot dismiss the possibility of detectable carbofuran concentrations in some surface waters under specific use and environmental conditions. Even given the limited utility of the available monitoring data, there have been relatively recent measured concentrations of carbofuran in surface water systems at levels above 4 ppb and levels of approximately 1 to 10 ppb measured in streams representative of those in watersheds that support drinking water systems (Ref. 81). Based on this analysis, and since monitoring programs have not been sampling at a frequency sufficient to detect daily-peak concentrations that are needed to assess carbofuran's acute risk, the available monitoring data, in and of themselves, are not sufficient to establish that the risks posed by carbofuran in surface drinking water are below thresholds of concern. Nor can the non-detections in the monitoring data be reasonably used to establish a lower bound of potential carbofuran risk through this route of exposure. Nevertheless, these results are consistent with the results of EPA's surface water modeling (Refs. 12, 47, 67). For all of these reasons, the Petitioners objection is denied.

d. Objection/hearing request subissue: New label restrictions and revised terms of registration. As discussed in Units VI.C and D, FMC submitted a request to amend its existing registration to incorporate a requirement intended to ensure that no more than 2% of any watershed will be treated with carbofuran. Petitioners allege that these new use restrictions will ensure that drinking water concentrations will not exceed 1.1 ppb. In support, the objection presents a June 30, 2009 letter describing the restrictions, along with proposed revisions to the carbofuran labels.

i. Background. On June 30, FMC requested that EPA amend its registration to incorporate a requirement that, within five days of applying the product, all applicators report to FMC the following information: the location that the product will be used; crop, use rate, application method, acreage, and quantity applied. Based on this information, FMC would track the percentage in each watershed. ''Whenever it appears that carbofuran has been applied to 1.75% of any watershed,'' the registrant would report that information immediately to EPA, ''cease further sales in any county that overlaps with such a watershed for that use season, and shall attempt to recall all unused carbofuran within such counties by offering to repurchase such unused product'' (Exhibit 3). In addition, FMC requested that its registration be amended to require that ''based on watershed boundaries, FMC * * * prior to each uses season, allocate to its distributors in a manner which will attempt to ensure that no distributor receives more for carbofuran for sale than can be accommodated by the 2% watershed area cap in any watershed supplied by that distributor.''

ii. Denial of hearing request. EPA denies this hearing request on two grounds. First, discussed in VI.C, Petitioners' objections and hearing requests are denied as irrelevant, and therefore immaterial, to EPA's determination in the May 15, 2009 final rule that the carbofuran tolerances were unsafe and could not be sustained under FFDCA section 408. Petitioners are actually not objecting to the conclusions in EPA's final rule; rather, they are suggesting that EPA might reach a different result in a different factual scenario. Objections, however, must be directed ''with particularity [at] the provisions of the regulation or order deemed objectionable'' (21 U.S.C. 346a(g)(2)). Further, as discussed in Unit VI.D, this objection is untimely, because it was not raised in comments. Neither this specific proposal, nor any other proposal regarding a potential tracking system, was presented to EPA by the close of the September 29, 2008 comment period. EPA therefore

considers this issue waived, and will not consider this as an appropriate basis for justifying a hearing on its final rule.

However, there is a further equally material defect in this hearing request. The Petitioners have submitted no evidence to support their allegation that these proposed requirements would be effective in ensuring that carbofuran would be applied to no more than 2% of any watershed. The only submission was the description provided in the June 30 letter (Exhibit 3), and repeated above. However, this vague description leaves several critical questions unanswered. For example, the critical component of this proposal is a post-use reporting scheme, with a five-day delay between use and reporting. Even assuming that one accepts that reporting an address would allow for complete identification of the location within an individual watershed—a point on which no evidence has been submitted—no evidence, or even an explanation, has been provided to demonstrate how this after-the-fact reporting requirement will prevent application to greater percentages of the watershed. For smaller watersheds, as discussed in the final rule, application to only one or two farms may be sufficient to substantially exceed 2% of the watershed. In such cases, since applicators are only required to report within five days after application, it is likely that FMC would not be informed until after the 2% cap had been exceeded. Further, there will inevitably be some delay between FMC's attempt to repurchase the product and the reports suggesting (or confirming) that the cap either has been or will shortly be exceeded. Given the inevitable delay, it is not unlikely that further application would occur before FMC could even attempt to repurchase the product. No details whatsoever have been provided regarding the timing or mechanism by which this would occur. Further, this program operates in the absence of any enforceable use restriction, and no description of the means by which this would be enforced is provided. Although the company would ''attempt to recall the product'' or make it less available by ''attempting'' to direct sales to particular distributorships, in the absence of some mechanism to prevent sales or use, such as a permitting process, there is no real assurance that these voluntary measures would be effective (Exhibit 3). This is further complicated by the extremely low percentages contemplated by this proposal.

Additionally, this scheme rests on a variety of assumptions that no evidence has been submitted to substantiate. For example, the proposal to restrict sales to distributors in particular watersheds rests on an assumption that farmers always purchase products from a distributor within their watershed. It also assumes that growers and distributors will accept FMC's offer to repurchase unused stock of the products, rather than seeking to stockpile the product for use in the next growing season.

In the absence of any evidence to demonstrate the efficacy of these proposed restrictions, any objection based on these proposed amendments constitute no more than mere allegations or denials. Hearings will not be granted on such a basis (40 CFR 178.32(b)(2)).

iii. Denial of objection. For the reasons discussed above, even if it were appropriate to consider the proposed registration amendments, EPA is unable to conclude that those amendments would ensure that concentrations of carbofuran in drinking water derived from surface water will not exceed 1.1 ppb. Accordingly, the objection is denied.

e. Objection/hearing request subissue: Consistency with NMC surface water estimates. Petitioners object to EPA's surface water exposure estimates on the ground that they are inconsistent with the estimates EPA developed for purposes of the NMC CRA. Petitioners further claim that their revised surface water assessment is consistent with the EPA estimates in the NMC cumulative risk assessment. The evidence proffered for this objection consists of the modeling in Exhibit 15.

i. Background. In comments on the proposed rule, the Petitioners complained that as part of the NMC CRA, EPA relied on actual ''county-or multi-county level pesticide use information, based on agricultural chemical use surveys'' to develop its estimates of potential exposure, rather than assuming 100% PCT.'' In the final rule, EPA provided a lengthy and detailed explanation of the reasons that its approach to assessing individual chemicals and its approach to assessing the cumulative risks of multiple chemicals differed (74 FR 23067–23068 (May 15, 2009)).

ii. Denial of hearing request. To the extent Petitioners base this objection on the concerns raised in their comments, EPA denies the hearing request on this subissue because there is no disputed factual matter for resolution at a hearing. There is no dispute that EPA assumed 100% PCT for carbofuran in its surface water modeling, nor that EPA developed lower estimates in the NMC CRA, that accounted for the percent of the crop that was likely to be treated with each individual NMC chemical in order to more accurately account for the likelihood of pesticide co-occurrence at a single drinking water facility. Thus, the only question is whether EPA's basis for adopting a different approach between the assessment of a single chemical's aggregate exposure and the assessment of the cumulative exposures from several chemicals is reasonable. This question requires the application of a legal standard to undisputed facts. Hearings are not appropriate on questions of law or policy (40 CFR 178.32(b)(1)); (73 FR 42706–42707 (July 23, 2008)). FDA has repeatedly confirmed that the application of a legal standard to undisputed facts is a question of law for which a hearing is not required. (*See, e.g.,* 68 FR 46403, 46406 n.18, 46408, 46409 (August 5, 2003) (whether facts in the record show there is a reasonable certainty of no harm is a question of law; whether a particular effect is a ''harm'' is a question of law)).

In addition, Petitioners have not challenged the substance of EPA's response to their comments or submitted evidence that calls the substance of EPA's conclusions into question (40 CFR 178.32(b)(3)). Consequently, the Petitioners' objection on this issue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation because Petitioners ignored EPA's extensive analysis of this issue in the final rule and essentially resubmitted their comments on the proposal as if EPA's determination in the final rule did not exist. The statute, however, requires that objections be filed on the final rule, not on the proposal (21 U.S.C. 346a(g)(2)). By ignoring the EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Both EPA and FDA precedent make clear that when the agency substantively responds to comments on the proposal, the commenter may only keep that issue alive in its objections by addressing the agency's substantive response. *See* 73 FR 42698–42699 (When an objector does not challenge EPA conclusions in the section 408(d)(4)(iii) order but rather challenges some prior conclusion that was superseded by the section 408(d)(4)(iii) order, the objector has not raised a live controversy as to an issue material to the section 408(d)(4)(iii) order; 53 FR 53176, 53191 (December 30, 1988) (where FDA responds to a comment in the final rule, repetition of the comment in objections does not present a live controversy unless the objector proffers some evidence calling FDA's conclusion into question)).

To the extent this objection is simply an allegation that the results of the modeling are consistent with the surface water estimates in EPA's NMC risk assessment, the hearing request also suffers from a fatal flaw. The modeling is based on the assumption the recently proposed label restrictions are effective, and that the PCT will be 2%. Because the objection and hearing request are inextricably intertwined with the Petitioners' newly submitted proposed FIFRA registration amendments, the objection and hearing request are denied as irrelevant, as discussed in Unit VI.C. Further, as discussed, no evidence was submitted to support the assumption that the newly submitted use tracking proposal will be effective. The only evidence submitted in this regard is the results of the modeling in Exhibit 15, which as previously discussed is untimely, and therfore provides an inappropriate basis for a hearing. This evidence, therefore, on multiple grounds is insufficient to support a reasonable possibility that the issue will be resolved in the Petitioners' favor. No hearing is warranted under such circumstances (40 CFR 178.32(b)(2)).

iii. Denial of objection. While it is true that in the NMC assessment EPA used PCT numbers to estimate the cumulative exposure from the contamination of such pesticides in surface water, this was done in order to more accurately account for the likelihood of pesticide co-occurrence at a single drinking water facility. But this does not mean that use of PCT is appropriate in conducting an assessment of aggregate exposure from carbofuran residues in surface water. This difference in approach between the assessment of a single chemical's aggregate exposure, and the assessment of the cumulative exposures from several chemicals, stems from the differences in the purpose and scope of the two assessments. These differences inevitably require the application of different methodologies.

In evaluating the acute risks associated with a single chemical's contamination of drinking water, EPA must consider all of the variations permitted under the label. Drinking water exposures are driven by uniquely local factors; not only is the source of drinking water local (*i.e.,* a person drinks water from his or her local water system, not from a combination of water systems from across the United States), but the likelihood and degree of contamination of any particular, local drinking water source, whether it is a reservoir or well, varies widely based on local conditions (*e.g,* from local pest pressures, weather). Given this local variability, EPA must evaluate how all of the practices permitted under the label will affect drinking water exposures, because all are legally allowed, and farmers may choose any of them based on their particular individual local conditions. This means that even if growers, on a national or regional basis, do not frequently use a particular practice, EPA must still evaluate whether aggregate exposures from that practice would be safe because the practice is legally permissible and may be used due to local conditions. Thus, for example, even if most growers tend to apply the chemical only to a portion of the field, or typically only apply one-half of the maximum application rate, EPA must determine whether use by all or some growers on the entire field or at the maximum rate in a local watershed would result in unsafe drinking water concentrations.

By contrast, it is not feasible to conduct the identical analysis for a cumulative assessment of related chemicals. Since the potential combinations of variations in pesticide use practices for the group of pesticides to be assessed are essentially infinite, even with computer modeling it would be impossible to model or evaluate all of the combinations allowed under the labels. EPA therefore needed to narrow its evaluation of the possible combinations to those deemed ''likely'' to occur. In contrast to the single chemical assessment, a cumulative assessment is intended to develop a snapshot in time of what is likely occurring at the moment. Moreover, the purpose of a cumulative assessment is to identify major sources of risk that could potentially accrue due to the concurrent use of several pesticides that act through a common mechanism of toxicity. Thus, EPA is primarily interested in the subset of circumstances in which residues from such pesticides occur concurrently (or co-occur).

In addition, one of the important attributes of a cumulative risk assessment is that its scope and complexity can potentially lead to inflated estimates of risk due to compounding conservatisms, which would reduce the interpretability and ultimately the utility of the assessments. Because many data sets need to be combined, reducing the impact and likelihood of compounding conservative assumptions and over-estimation bias becomes very important in constructing a reasonable cumulative risk assessment.

When little or no information is available to inform potential sources of exposure, such as a reasonable or maximum watershed scale PCT, it is both scientifically and legally reasonable for a single chemical assessment to incorporate conservative assumptions to reflect reasonable worst-case exposure estimates. But in a cumulative risk assessment, the incorporation of such conservative assumptions would imply multiple simultaneous reasonable worst-case exposure estimates for each individual chemical. This is so unlikely that the results would no longer represent even a reasonable worst-case estimate of the likely risks. Consequently, some of the conservative assumptions appropriately used in the single chemical risk assessments are not appropriate or reasonable for use in a cumulative risk assessment, and vice versa.

As a result, EPA chose in the NMC to work with those data that most closely reflect ''representative'' exposures, and developed ''representative'' estimates of PCT in regional watersheds. However, to be clear, the PCT values used in the NMC assessment do not represent estimates of 50% of watersheds, or even the ''average'' watershed; rather, they represent values that are expected to be as likely to be accurate as not, based on a random selection of watersheds. A comparable example is the statistic that the average American family has approximately 2 children; this may or may not be true for any individual family, but there is an equally good chance that it will be accurate for any randomly selected family, as that it will not be accurate. For the cumulative assessment, EPA is able accept this level of uncertainty in these estimates, precisely because it has confidence that aggregate exposures from the individual chemicals will be safe, based on the level of conservatism in the single chemical assessments. But given the statute's mandate to ensure a ''reasonable certainty of no harm,'' EPA could not rely on the approach used under the cumulative assessment in the absence of the more conservative single-chemical assessment that evaluates the full range of exposures permitted by the registration.

Nevertheless, as discussed in the final rule, in response to FMC's concerns EPA performed a sensitivity analysis of an exposure assessment using a PCT in the watershed to determine the extent to which some consideration of this factor could meaningfully affect the outcome of the risk assessment. The results suggest that, even at levels below 10% CT, exposures from drinking water derived from surface waters can contribute significantly to the aggregate dietary risks, particularly for infants and children. Accordingly, these assessments suggest that use of a reasonably conservative PCT estimate,

even if one could be developed, would not meaningfully affect the carbofuran risk assessment, as aggregate exposures would still exceed 100% of the aPAD.

f. Objection/hearing request subissue: Natural surface water pH conditions. The Petitioners contend that the low PCT levels guaranteed by the recent proposed use tracking system, along with natural surface water pH conditions in the areas where use is permitted under the revised label will ensure potential exposures are *de minimis.* In support they reference the analysis in Exhibit 16, which they claim demonstrates that the NAWQA USGS data show that average surface water pH is above 7.5 and that ''in most regions, moving 2 standard deviations away from average (which would capture 95% of all observed values) results in pHs that are still greater than 7.5.''

i. Background. In the proposed rule, EPA explained that the variation in pH across the landscape was a significant uncertainty in EPA's analysis. The proposal stated, that ''while it is well established that carbofuran will degrade at higher rates when the pH is above 7, and lower rates when below pH 7, due to the high variation of pH across the country for many of the scenarios, a neutral pH (pH 7) default value was used to estimate water concentrations (73 FR 44883). Petitioners raised no issue regarding surface water pH in their comments.

ii. Denial of hearing request. EPA denies this hearing request because the objection, as well as the proffered evidence is untimely. EPA clearly described the potential impact that pH could have on its estimates, and noted that this was a significant uncertainty in its assessment. None of the analyses in Exhibit 16 were provided as comments on the proposed rule. Nor were any of the issues inherent in this objection raised as comments on the proposal. Since the proposed rule was clear that the issue was relevant, and the NAWQA data were available, Petitioners could have conducted these analyses and raised the issue as part of their comments. Consequently EPA has determined that the evidence submitted in support of this objection is not appropriately considered as a basis for justifying a hearing on its final rule. And in the absence of this evidence, the objection consists of mere allegations and general denials, which do not warrant a hearing (40 CFR 178.32(b)(2)). Further, to the extent the objection and the evidence in Exhibit 16 rely on use tracking system and risk mitigation proposals submitted as part of their objections, this hearing request is denied as irrelevant, and therefore immaterial, as discussed in Unit VI.C. Petitioners are actually not objecting to the conclusions in EPA's final rule; rather, they are suggesting that EPA might reach a different result in a different factual scenario. Objections, however, must be directed ''with particularity [at] the provisions of the regulation or order deemed objectionable'' (21 U.S.C. 346a(g)(2)). In addition, for the reasons discussed in Unit VI.D, any hearing request premised on the new mitigation measures is considered untimely, and not appropriately considered at this stage of the administrative process as a basis for granting a hearing under the FFDCA.

EPA is also denying the requested hearing on the grounds that the evidence, even if established, is insufficient to justify the action urged (40 CFR 178.32(b)(3)). The analyses presented in Exhibit 16, as the Petitioners explicitly acknowledge, only capture 95% of the values; five percent of exposures are not, *per se, de minimis.* Second, just as with the groundwater pH analyses presented in Exhibit 14, no information was provided to explain how the samples relate to the state or other geographic area in which carbofuran would be used. This is important because NAWQA samples were not evenly distributed across most states, but tended to be concentrated in particular regions; in statistical parlance, the samples were not collected randomly. In other words, no evidence was provided that would allow the Agency to determine the percentage of the carbofuran use area represented by the 95% of the samples the Petitioners' analysis addressed. Nor was any information provided to document the significance of the remaining 5% of the samples that were not captured by their analysis; for example, although this may have only represented 5% of the samples, it is not clear whether this 5% relates to only 5% of the areas where carbofuran may be used, or whether it actually represents a far greater percentage of the use area. Because this information, even if established, would provide an insufficient basis on which EPA could reasonably conclude that the drinking water exposures would be ''safe,'' this issue is not determinative.

iii. Denial of objection. For the reasons presented above, the Petitioners' objection is denied. Further, there are several significant defects with the analysis in Exhibit 16. First, the analysis was based on statewide averages, which ignores the fact that pH is not evenly distributed, but randomly clustered. Second NAWQA contained no data for Kansas (KS), Oklahoma (OK), and South Dakota (SD); Petitioners simply assert that the ''given the similarity between these states and the other High Plains states, it is reasonable to extend the observations from Colorado (CO), Nebraska (NE), and North Dakota (ND)'' (Exhibit 16 at 4). Although the 'High Plains' states all have extensive areas of grassland, they also have extensive geographic soil and climatic differences—*e.g.* the Black Hills and Badlands (SD), Sand Hills (NE), Flint Hills, Cheyenne Bottoms and Quivira wetlands (KS), Red Hills and Cross Timbers region (OK). These differences are not surprising since the distance from the Canadian border in ND to OK is over 1000 miles. Consequently it is not reasonable to extend observations from CO, NE, and ND to KS, OK, and SD.

g. Objection/hearing request subissue: Effect of existing drinking water treatment systems. The Petitioners contend that a review of drinking water treatment systems in areas under revised labels indicates that the majority of the ''total population in affected states obtain their drinking water from surface water sources subject to lime softening or activated charcoal filters. They allege that ''60% of the total population in affected states'' will have their water treated by methods that will substantially reduce or entirely remove carbofuran concentrations. For the remaining 40%, they claim that a significant portion use ground water sources, which are already protected by the Petitioners' other mitigation measures, and the remainder are protected by the Petitioners' proposed use reporting scheme. In support of this objection, Petitioners rely on the analysis in Exhibit 17.

i. Background. In the proposed rule, EPA explained that one of the more significant uncertainties in EPA's analysis was that EPA failed to account for the potential effect of treatment in removing carbofuran from finished drinking water before it is delivered to the consumer supply system. EPA explained that an evaluation of laboratory and field monitoring data indicate that carbofuran may be effectively removed (60–100%) from drinking water by lime softening and activated carbon; other treatment processes are less effective in removing carbofuran (Ref. 81). Although the Agency was aware of the mitigating effects of specific treatment processes, the processes employed at public water supply utilities across the country vary significantly both from location to location and throughout the year, and therefore EPA was unable to quantitatively incorporate this factor into its drinking water exposure

estimates. For example, lime softening would likely reduce carbofuran concentrations. That process is used in 3 to 21% of drinking water treatment systems in the United States (Ref. 14). Activated carbon has been shown to also reduce carbofuran concentrations, but is used in 1 to 15% of drinking water treatment facilities (Id.). Petitioners noted this discussion in their comments, and relied on it to support their argument that their drinking water exposure assessments were conservative, because they did not account for the effect of treatment (Ref. 18 at 46–55). However they submitted no comments raising any of the issues or evidence presented in this objection.

ii. Denial of hearing request. EPA denies this hearing request on the grounds that both the objection and the proffered evidence are untimely. EPA clearly described the potential impact that treatment could have on its estimates. None of the analyses in Exhibit 17 were provided as comments on the proposed rule. Nor were any of the issues inherent in this objection raised as comments on the proposal. Since the proposed rule clearly identified the issue, and the USGS data were available, the Petitioners could have conducted these analyses, or at least raised the issue, as part of their comments. Consequently, as discussed in Unit VI.D, EPA has determined that the evidence submitted in support of this objection is not appropriately considered as a basis for justifying a hearing on its final rule. In the absence of this evidence, the objection consists of mere allegations and general denials, which do not warrant a hearing (40 CFR 178.32(b)(2)). Further, to the extent the objection and the evidence in Exhibit 17 rely on the new registration proposals submitted in June 2009 as part of their objections, this evidence as well is deemed both immaterial and untimely. As discussed in Units VI.C and D, the new risk mitigation measures are not appropriately considered at this stage of the administrative process, and no hearing is warranted on this basis.

EPA is also denying this hearing request on the grounds the Petitioners' evidentiary proffer is insufficient to justify the factual issue urged (40 CFR 178.32(b)(2)). The analysis in Exhibit 17 is based on the percentage of the total population across all states combined, not the percentage of the local populations served by an individual surface water source—or even the percentage within each state. Even assuming that the 60% figure could legitimately be translated to a state-by-state basis, their own analysis shows that some percentage of the population in individual states will remain unprotected. In Colorado, only 24% of the population obtains their drinking water from groundwater, and in Illinois, only 33% of the population obtains their drinking water from groundwater. Sixteen percent of Colorado's population is not *de minimis.* Consequently, even if the analysis were accurate, it would not provide a sufficient basis on which to conclude that exposures from drinking water would be ''safe.''

A further consideration in this regard is that drinking water exposures are driven by uniquely local factors; not only is the source of drinking water local (*i.e.,* a person drinks water from his or her local water system not from a combination of water systems from across the United States), but the likelihood and degree of contamination of any particular, local drinking water source, whether it is a reservoir or well, varies widely based on local conditions (*e.g.,* from local pest pressures, weather). Examining a population across an entire state—let alone across several states—is an entirely inappropriate basis on which to conclude that drinking water exposures will be safe.

The evidence submitted therefore does not support their contention that 60% of the population in ''affected states'' obtain their drinking water from public systems that use the treatment processes effective at mitigating carbofuran residues. For example, Exhibit 17 shows that a major Chicago surface water drinking water system, which serves a population of 9,000,000, has neither lime softening processes nor filters. Petitioners have submitted no evidence that this population is protected. The fact that a small population remains unprotected is not outweighed by the fact that a larger population in another community or state is protected. Their own evidence also shows that only 26 of 141 of community water systems use lime softening/filters (Exhibit 17 at 4–9), which supports the conclusion in the final rule that approximately 20% facilities have appropriate treatment. See 57 FR 33244 (7/27/92) (Studies cited by NRDC do not provide a basis for the hearing because they ''support the [FDA] conclusion in question.''); 57 FR 6667 (2/27/1992) (''A hearing must be based on reliable evidence, not on mere allegations or on information that is inaccurate and contradicted by the record.''); 49 FR 6672 (2/22/84) (no hearing if claim based on demonstrably false premise).

iii. Denial of objection. For the reasons discussed above, this objection is denied. A further consideration is that treatment does not necessarily remove all residues. As previously noted, in both the proposed and final rules EPA discussed the SDWA monitoring detections between 4 and 7 ppb, which represent concentrations in samples collected post-treatment. As such, these levels are of particular concern to the Agency. An infant who consumes a single 8-ounce serving of water with a concentration of 4 ppb, as detected in the monitoring, would receive approximately 130% of the aPAD from water consumption alone. An infant who consumes a single 8-ounce serving of water with the higher detected concentration of 7 ppb, as detected in the monitoring, would receive approximately 220% of the aPAD from water consumption alone.

G. Objections to EPA's Dietary Risk Assessment

Petitioners raise two related objections to the way in which EPA evaluated the aggregate dietary exposures to carbofuran residues. First they raise several technical challenges to the way in which EPA calculated the two recovery half-lives that were used in the risk assessment supporting the final rule to account for the potential for individuals to recover from the effect of ingesting carbofuran residues between exposures. Second, they object to the fact that in the final rule EPA included both aggregate exposure estimates that did not account for the potential for individuals to recover from the effects between exposures as well as estimates that did account for such recovery. In support the Petitioners cite to Exhibits 9 and 10. Exhibit 9 is a memorandum prepared by Robert Sielken and Ciriaco Valdez-Flores. Exhibit 10 is a published literature study by Elsa Reiner that presents data on the rates of spontaneous reactivation of phosphorylated and carbamylated cholinesterases.

1. Objection/hearing request subissue: Inclusion of exposure estimates that do not incorporate recovery in final rule. The Petitioners object to the fact that the final rule presented aggregated exposure estimates that did not incorporate the anticipated recovery from carbofuran's effects between exposures, in addition to those that did account for recovery. They claim that recovery time should be included in EPA's ''primary'' risk assessment.

i. Background. As discussed in Unit V, EPA's standard acute dietary exposure assessment calculates total dietary exposure over a 24-hour period; that is consumption over 24 hours is summed and no account is taken of the

fact that eating and drinking occasions may spread out exposures over a day. This total daily exposure generally provides reasonable estimates of the risks from acute dietary exposures, given the nature of most chemical endpoints. Due to the rapid recovery associated with some chemical toxicity (*e.g.,* AChE inhibition), 24-hour exposure periods may or may not be appropriate. To the extent that a day's eating or drinking occasions leading to high total daily exposure might be found close together in time, or to occur from a single eating event, minimal AChE recovery would occur between eating occasions (*i.e.,* exposure events). In that case, the ''24-hour sum'' approach, which sums eating events over a 24-hour period, would provide reasonable estimates of risk from food and drinking water. Conversely, to the extent that eating occasions leading to high total daily exposures are widely separated in time (within 1 day) such that substantial AChE recovery occurs between eating occasions, then the estimated risks under any 24-hour sum approach may be overstated. In that case, a more sophisticated approach—one that accounts for intra-day eating and drinking patterns and the recovery of AChE between exposure events—may be more appropriate. This approach is referred to as the ''Eating Occasions Analysis'' and it takes into account the fact that the toxicological effect of a first dose may be reduced or tempered prior to a second (or subsequent) dose.

In the proposed rule, EPA conducted an Eating Occasion analysis based on two half-lives: 150 minutes and 300 minutes (73 FR 44887 (July 31, 2008)). These half-lives were not specific to carbofuran, but were calculations derived for the NMC Cumulative Risk Assessment. EPA concluded that incorporating these analyses into the risk assessment had little impact on the risk estimates from exposures from food alone, but that risk estimates from combined exposures from food and water were reduced by approximately 2–3X (Id). However, because many of EPA's risk concerns stemmed from a single exposure (*e.g.,* one meal) and because, even when recovery was accounted for, aggregate exposures far exceeded safe levels, EPA concluded that ''risks to carbofuran is indeed not substantively overestimated using * * * the 24-hour approach'' (Id).

In their comments, Petitioners complained that EPA had failed to incorporate recovery into their risk assessment. They further argued that EPA should calculate the per capita 99.9th percentile based on all person minutes rather than all person-days. In addition, they submitted an aggregate dietary risk assessment they had conducted using a 150-minute half-life input. They submitted no explanation for using only the 150-minute half-life rather than also including estimates based on the 300-minute half-life that EPA has used for the proposed rule.

In the final rule EPA explained that it had conducted a revised Eating Occasion analysis to evaluate the impact of carbofuran's rapid reversibility on its risk estimates (74 FR 23086 (May 15, 2009)). EPA concluded that incorporating Eating Occasion Analysis and the 186-minute or 426-minute recovery half-lives for carbofuran did not significantly change the risk estimates for food exposures alone (74 FR 23086 (May 15, 2009)). EPA concluded that risk estimates based on combined food and drinking water exposures are reduced considerably—by a factor of two or more in some cases, but nonetheless still substantially exceed EPA's level of concern for infants and children. EPA also explained that the Agency remains concerned about the risks from single eating or drinking events. Finally, EPA noted that the Eating Occasion Analyses underestimate exposures to the extent that they do not take into account carry-over effects from previous days, and because drinking water concentrations are randomly picked from the entire 30-year distribution (Id at 23087).

ii. Denial of hearing request. EPA is denying this hearing request on two grounds. First, the objection fails to present a disputed issue of material fact. The record is clear that EPA did incorporate recovery into its analysis; indeed, one of Petitioners' objections relates to the manner in which EPA incorporated recovery into its risk assessment (Obj at 30–33). Rather, their only challenge is that the final rule should have only presented risk estimates that accounted for recovery. The sole issue is whether it was reasonable for EPA to have also communicated aggregate risks that did not account for recovery, when (1) EPA's estimates showed that accounting for recovery demonstrated that EPA's standard 24-hour estimates were not substantially overstated; (2) EPA's approach to accounting for recovery underestimates some risks; and (3) EPA's risk assessments concluded that infants received unsafe exposures from a single meal (eating occasion). This is a policy issue, and hearings are not appropriate on such (40 CFR 178.32(b)(1)).

Second, the fact that EPA relied on 24-hour aggregate exposures in addition to analyses that accounted for recovery is not material. As documented in the final rule, EPA would still have concluded that revocation of all tolerances were warranted on the grounds that, even accounting for recovery, aggregate exposures are not ''safe.'' Even though accounting for recovery resulted in a 2–3X reduction in exposure estimates, many of EPA's estimates for aggregate exposures ranged between 2700% aPAD and 9400% aPAD for infants. Accounting for recovery does not, therefore, demonstrate that aggregate exposures will be safe for infants. Of greater significance in this regard is EPA's finding that infants are at risk from a single exposure. Recovery is only relevant, by definition, where the risk is derived from multiple exposures over time.

iii. Denial of objection. The reason for not simply adopting the assessment incorporating recovery time was that the Agency has concerns that other aspects of its exposure model tends to understate exposure. If the assessment using recovery time had suggested that carbofuran risks may be acceptable, EPA would have had to further examine how exposure was assessed. However, because both the assessment based on 24-hour exposure and the one incorporating recovery time showed carbofuran exposures to be well over the safe level, EPA concluded that its exposure assessment was reasonable. As explained in the final rule, incorporating Eating Occasion Analysis and the 186-minute or 426-minute recovery half-lives for carbofuran resulted in a reduction in the risk estimates for which food and drinking water are jointly considered (*i.e.,* Food + Drinking Water) by a factor of two or more in some cases. But even though the risk estimates from aggregate exposure are reduced, they nonetheless still substantially exceed EPA's level of concern for infants and children. Using drinking water derived from the surface water from the Idaho potato surface water scenario, which estimated one of the lowest exposure distributions, aggregate exposures at the 99.9th percentile ranged from 328% of the aPAD under the scenario for which infants rapidly metabolize carbofuran (*e.g.*, 186-minute half-life), to a high of 473% of the aPAD under the scenario for which infants metabolize carbofuran more slowly *(e.g.*, scenarios in which a 426-minute half life is assumed). Either way, the tolerances are unsafe.

Moreover, even accounting for the estimated decreased risk from accounting for carbofuran's rapid reversibility, for which recovery between exposures is irrelevant. The Agency remains concerned about the

risks from single eating or drinking events, as illustrated in the following example, based on an actual food consumption diary from the CSFII survey. A 4-month old male non-nursing infant weighing 10 kg is reported to have consumed a total of 1,070 milliters (ml) of indirect water over eight different occasions during the day. The first eating occasion occurred at 6:30 a.m., when this 4 month old consumed 8 fluid ounces of formula prepared from powder. The FCID food recipes indicate that this particular food item consists of approximately 87.7% water, and therefore, 8 ounces of formula contains approximately 214 ml (or grams) of indirect water; with the powder (various nutrients, dairy, soy, oils, etc.) accounting for the remaining 12.3%. This infant also reportedly consumed a full 8-ounce bottle of formula at 12 p.m., 4 p.m., and 8 p.m. that day. The food diary also indicates that the infant consumed about 1 tablespoon of water (14.8 ml) added to prepare rice cereal at 10 a.m., about 2 ounces of water (59.3 ml) added to pear juice at 11 a.m., another ½ tsp of water (2.5 ml) to prepare more rice cereal at 8:30 p.m.; and finally, he consumed another 4 ounces of formula (107 ml) at 9:30 p.m.

The infant's total daily water intake (1,070 ml, or approximately 107 ml/kg/day) is not overly conservative, and represents substantially less than the 90th percentile value from CSFII on a ml water/kg bodyweight (ml/kg/bw) basis. As noted, carbofuran has been detected in finished water at concentrations of 4 ppb. For this 10 kg body weight infant, an 8-ounce bottle of formula prepared from water containing carbofuran at 4 ppb leads to drinking water exposures of 0.0856 micrograms of active ingredient/kilogram of bodyweight (µg ai/kg bw), or 114% of the aPAD from that bottle alone. Based on the total daily water intake of 1,070 ml/day (no reversibility), total daily exposures from water at 4 ppb concentration would amount to 0.4158 µg ai/kg bw, or 555% of the aPAD; this is the amount that would be used for this person-day in the Total Daily Approach.

Peak inhibition occurs following each occasion on which the infant consumed 8 fluid ounces of formula (6 a.m., 12 p.m., 4 p.m. and 8 p.m.); however, the maximum persisting dose occurs following the 9:30 p.m. eating occasion, based on a 186-minute half-life parameter. This produces a maximum persisting dose of 0.1457 µg ai/kg bw, or about 30% of the total daily exposure of 0.4158 µg ai/kg bw derived above, or expressed as a fraction of the level of concern, the maximum persisting dose amounts to about 194% of the aPAD (or 30% of 554%). Note that with drinking water concentration at 4 ppb, an infant consuming one 8 oz bottle of formula—prepared from powder and tap water containing carbofuran at 4 ppb will obtain exposures of approximately 114% of aPAD. Since many infants consume the equivalent of this amount on a single eating occasion, accounting for reversibility over multiple occasions is not essential to ascertain that infants quite likely have obtained drinking water exposures to carbofuran exceeding the level of concern based on drinking water concentrations found in public drinking water supplies.

The approach discussed above is used to evaluate the extent to which the Agency's 24-hour approach to dietary risk assessment overestimates risk from carbofuran exposure. The results of both approaches indicate that the risk from carbofuran is indeed not substantively overestimated using the current exposure models and the 24-hour approach.

In this regard, it is important to note EPA's Eating Occasion Analyses underestimate exposures to the extent that they do not take into account carry-over effects from previous days, and because drinking water concentrations are randomly picked from the entire 30-year distribution. As discussed previously, DEEM–FCID is a single day dietary exposure model, and the DEEM-based Eating Occasion Analysis accounts for reversibility within each simulated person-day. All of the empirical data regarding time and amounts consumed (and corresponding exposures based on the corresponding residues) from the CSFII survey are used, along with the half-life to assess an equivalent persisting dose that produced the peak inhibition expected over the course of that day. This is a reasonable assumption for food alone; since the time between exposure events across 2 days is relatively high (compared to the half-life)—most children (>9 months) tend to sleep through the night—and the time between dinner and breakfast the following morning is long enough it is reasonable to ''ignore'' persisting effects from the previous day. A single day exposure model will underestimate the persisting effects from drinking water exposures (formula) among infants, and newborns in particular (<3 months), since newborns tend to wake up every 2 to 4 hours to feed. Any carry over effects may be important, especially if exposures from the previous day are relatively high, since the time between the last feeding (formula) of the day and the first feeding of the subsequent day is short. A single day model also does not account for the effect of seasonal variations in drinking water concentrations, which will make this effect more pronounced during the high use season (*i.e.*, the time of year when drinking water concentrations are high). Based on these analyses, the Agency concludes that the current exposure assessment methods used in the carbofuran dietary assessment provide realistic and high confidence estimates of risk to carbofuran exposure through food and water.

In summary, there are several factors that may cause EPA's exposure/risk model to either understate or overstate exposure/risk. It is unreasonable to present risks only incorporating factors that tend to reduce exposure/risk estimates (*e.g.*, recovery time), as Petitioners suggest. EPA's approach of evaluating the impact that these factors may have on the risk assessment is an appropriate method of taking all relevant factors into account. Petitioners' objection to EPA's policy decision to present acute risks in terms of 24-hours of exposure is therefore denied because EPA's policy approach here is reasonable.

2. Objection/hearing request subissue: Technical challenges to EPA's calculated half-lives. Petitioners contend that EPA's calculation of carbofuran half-lives of 186 minutes and 426 minutes were flawed, and that the data instead support the use of a 150-minute half-life. Petitioners identify three specific challenges: (1) Because one of the time course studies showed that the time-to-peak effect was one hour, EPA's assumption that the time-to-peak effect in each study was 15 minutes is incorrect; (2) EPA included the control rats in its modeling, which distorts the estimated recovery half-life because it incorporates AChE from animals that were not dosed and did not need to recover; (3) Biochemically, the recovery half-lives of all NMC chemicals should be the same, which supports the use of a 150-minute half-life. In support of these claims, Petitioners offered a summary of written testimony from Drs. Sielken and Valdez-Flores (Exhibit 9) and a published study (Exhibit 10).

i. Background. In the proposed rule, EPA relied on half-lives of 150 minutes and 300 minutes (73 FR 44887). These values were calculated for the NMC cumulative risk assessment and so were intended to encompass the half-lives for all of the NMC pesticides.

In the final rule, EPA calculated half-lives specific to carbofuran to ensure that its analyses accurately reflected carbofuran's risk. Using the two FMC

time course studies in rat pups EPA calculated half-lives for recovery of 186 and 426 minutes (Id). The two values were derived from two different studies using rat pups of the same age (Refs. 24, 25); the two values provide an indication that half-lives to recovery can vary among juvenile rats. By extension, children are expected to vary in their ability to recover from AChE inhibition where longer recoveries would be associated with a potentially higher ''persisting dose.''

ii. Denial of hearing request. The issue of the appropriate half-lives for carbofuran is not material. Petitioners have proffered no evidence to show that reliance on a 150-minute half-life rather than a 186-minute half-life would make a significant difference to their estimates. By contrast, in the risk assessment supporting the final rule, EPA's estimates show that the use of a 150-minute or 186-minute half-life makes little or no difference. For example, EPA's estimated exposures from food alone for children 1–2 were 43% of the aPAD, assuming a 186-minute half-life, and 41% of the aPAD, assuming a 150-minute half-life. Similarly, for infants, the estimates ranged from 31% aPAD, assuming a 186-minute half-life, and 30% of the aPAD, assuming a 150-minute half-life. For all other age groups, the estimated exposures were identical, whether one assumed a 150-minute or 186-minute half-life.

In any event, Petitioners' objection would have ultimately no effect on the Agency's conclusion that the carbofuran tolerances are not ''safe.'' Given EPA's assessments showing that a single exposure can result in excessive risks to infants—a conclusion that Petitioners have not challenged—the extent of recovery between subsequent exposures is irrelevant. This conclusion alone provides an adequate basis to revoke the carbofuran tolerances. Accordingly, because the action would be the same even if the factual issue were resolved in the manner sought, this request does not meet the standard for granting a hearing (40 CFR 178.32(b)(3)).

There is yet a further consideration affecting the materiality of this objection. EPA's recalculation of half-lives in the final rule would ordinarily mean that Petitioners could appropriately challenge EPA's methodology for deriving the revised half-lives for the first time in their objections. This is because the Petitioners would have had no prior opportunity to challenge the manner in which these estimates were developed, as EPA had not previously relied on carbofuran-specific estimates. However in this case, the Petitioners never commented on the 300-minute estimate EPA used in the proposal, nor raised any issue to challenge the reliance on a longer half-life to account for the variation in children's sensitivity. For the reasons discussed in Unit VI.D, they have therefore waived any objection to use of a 300-minute half-life. Accordingly, the question of whether the Petitioners' half-life of 150-minutes or EPA's estimated half-life of 186-minutes is immaterial, since the lower amount of recovery associated with the longer 300-minute half-life would be expected to have a far greater impact than the use of a 186-minute half-life.

EPA is also denying the hearing request because the evidentiary proffer in support of this objection is inadequate. Petitioners have not provided the underlying analyses conducted in support of their calculated half-lives. The remainder of Exhibit 9 consists of contentions that EPA's analyses were mistaken. In the absence of the analyses that support their claim that the data support a half-life of 150 minutes, Petitioners' evidentiary proffer consists of no more than mere allegations and denials. Hearings will not be granted on this basis (40 CFR 178.32(b)(2)) (See 73 FR 42706 (July 23, 2008) (''NRDC does no more than state '[w]e are aware of no statistical test' which would support EPA's use of the Gledhill data. As EPA's regulations make clear, a mere 'denial' of an EPA position is not sufficient to satisfy the standard for granting a hearing'') (citations omitted); 53 FR 53176, 53199 (December 30, 1998) (''Rather than presenting evidence [the objector] asserts that FDA did not adequately justify its conclusions. Such an assertion will not justify a hearing.'').

The published paper in Exhibit 10 does not cure this defect. The paper was submitted to support the claim that the Petitioners' 150-minute half-life is consistent with the ''available literature on the AChE recovery'' (Obj at 32). This evidence is immaterial. The Reiner paper relates to the reactivation of the AChE enzyme; however the relevant issue is not the reactivation of the cholinesterase enzyme, but the level of chemical in that target tissue, which this study does not address. Moreover, this study concludes that ''[I]t follows from the data in Tables 1 and 2 that the rate of spontaneous reactivation cannot be predicted, but must be separately determined for each compound and each enzyme source (Exhibit 10 at 1). The paper did not include data specifically on carbofuran, and it is therefore difficult to see how this could be argued to support the Petitioners' half-life of 150-minutes.

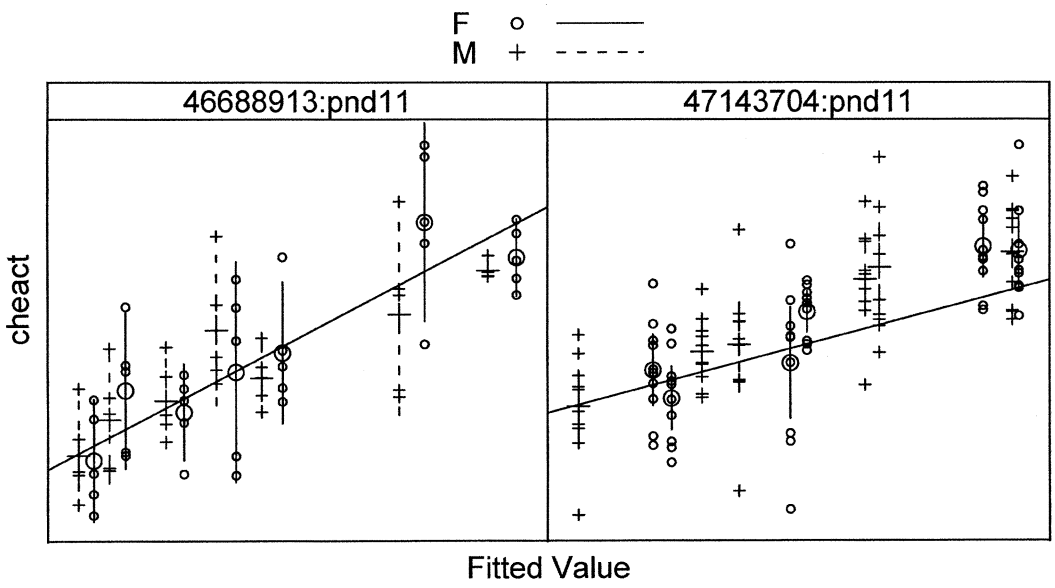
iii. Denial of objection subissue. All of Petitioners' claims are incorrect.

Appropriate time to peak effect. The Petitioners claim that the time to peak effect in the study with MRID 47143704 (Ref. 2) should have been 1 hour instead of the 15 minutes EPA calculated. Petitioners chose this value simply by choosing the data point with the highest level of inhibition. But this approach is flawed in a number of regards: First as a practical matter, using the same criteria on which the Petitioners rely, the time to peak effect in MRID 46688913 (Ref. 3) is 15 minutes. Petitioners have presented no basis for excluding those results.

More significantly, the Petitioners' approach fails to account for the variability of the estimated AChE activity at each time point. As a point of background, the level of the highest inhibition is not something that can be observed, in the way that motor activity is observed. To determine inhibition, samples are taken and measured—the samples may or may not capture the highest point of inhibition; the technician has not external indicia that will determine the moment of the ''peak.'' Determining peak inhibition is estimated based on the available measurements. But because measurements are generally variable—the animals differ and the sampling itself is not identical, as people cannot perfectly replicate their actions time after time—in order to accurately capture the peak levels, the variability needs to be accounted for. When, as here, the individual values are quite variable, then for a half-life as long as carbofuran's, the sampling variability will make the study means bounce up and down around a trend line representing the true recovery rate. Figure 2 illustrates the sampling variability of the measured AChE activity and its relationship to EPA's modeling estimates for PND11 pups. In brief, this plots observed versus predicted for all the data. Each little point is an individual animal, while the time-group mean is the larger version of the same plotting symbol. The vertical lines are the 95 percent confidence intervals for each mean, the vertical lines. The diagonal line in each figure is the identity line—*i.e.,* the line all the data would fall on if there were no variability and the model were perfect. Normally, one would expect some random scatter about the identity line. In such a case, simply visually picking the time with the lowest mean, which is what the Petitioners have done, will

not be a very reliable way to estimate the time to peak effect.

Figure 2



Inclusion of data from control animals. It is standard scientific practice to include concurrent control animals (*i.e.*, animals that are not dosed with the test substance) as part of any experimental design. The purpose of controls is to determine the effects of the inevitable, unexpected, and uncontrolled variations in experimental practice, such as the biological variation between individual living animals. EPA's model simply used control levels to establish a baseline against which to evaluate the recovery of the treated animals. For example, as discussed above, measurements of AChE activities may change, and that concurrent controls are set up so that the same non-dose-related factors that affect treated animals will also affect control animals. Thus, EPA measured activity and computed inhibition based on measures of activity in treated animals and concurrent control animals. Thus, if the control animals showed that measured levels of AChE typically varied by 5 percent, if the dosed animal showed inhibition levels of 20 percent, EPA would consider that only 15 percent of the inhibition would be related to the chemical exposure. EPA did not estimate a half-life of recovery for the control animals and incorporate that into the estimated half-lives, which seems to be the Petitioners' allegation.

Biochemically, the recovery half-lives of all NMC chemicals should be the same. Although the Petitioners' claim that the recovery rate of AChE inhibited by carbamate compounds is dictated by the commonly-shared NMC carbamyl group is theoretically plausible, in reality, it is not supported by the data on the NMC compounds. EPA had originally hoped, based on the same mechanistic argument Petitioners make, that half-lives would be the same across all NMCs, thus greatly simplifying the cumulative risk assessment. It turned out, though, in the NMC data sets analyzed for the NMC cumulative risk assessment, that estimated recovery half-lives changed (generally, they got longer) as dose increased, which is counter to the results that would be predicted from the Petitioners' simple mechanistic argument (Ref. 81). Ultimately, this is due to the fact that the relevant question is not the abstract reactivation of the cholinesterase enzyme, but the level of chemical in the living animal's target tissue, which is a function both of the pharmacokinetics of the NMC (*i.e.*, the rate at which the chemical is absorbed, distributed among tissues, and eliminated) in the animal and the rate of hydrolysis of the leaving group off the AChE molecule. These parameters vary at least somewhat for the different carbamates, accounting for the differences in half-lives between the NMC pesticides.

H. Objection to EPA's Decision Not To Rely on Carbofuran Human Study

Petitioners object to EPA's reliance on a default 10X interspecies factor, which accounts for the uncertainties inherent in extrapolating from animal data to the anticipated effects in humans. They argue, for several reasons, that EPA should have instead used a 3X interspecies factor. All of their arguments, however, depend on EPA consideration of an oral carbofuran dosing study conducted in humans. EPA did not rely on the cited human study because it found, taking into account the advice of the HSRB, that the study was scientifically invalid. EPA's Human Research rule prohibits EPA from considering scientifically invalid human studies (40 CFR 26.1701). In their objections, Petitioners argue that the HSRB's, and presumably EPA's, evaluation of the scientific validity of the human study was flawed because (1) the human study was not considered in light of the animal data on carbofuran; (2) insufficient weight was given prior independent reports on the value of the Arnold study which reached the opposite conclusion from the HSRB; (3) the ''technical'' concerns raised by the HSRB are addressed by ''the data within the study'' and that these ''technical'' deficiencies do not render the Arnold study unreliable.

1. Background. There are three intentional dosing human studies conducted with carbofuran that were conducted by J.D. Arnold in 1976, 1977, and 1978. One study was an oral ingestion toxicity study and two studies were intended to evaluate toxicity from dermal exposure (Refs. 7, 8, 9). The oral study conducted with carbofuran was carried out in nine healthy male

volunteers using an ascending dose schedule and single doses of 0.05, 0.1 and 0.25 mg/kg (Ref. 7). The two dermal toxicity studies were found to have significant ethical deficiencies and the EPA's Human Studies Review Board recommended against their use. The Petitioners do not challenge the decision to disregard these studies.

As previously noted, EPA did not rely upon any of the existing intentional dosing human toxicity study deriving an acceptable level of exposure for carbofuran. Instead, EPA relied on data conducted with rats, and applied the default 10 × interspecies factor to account for the potential uncertainty in extrapolating from animal data. EPA's decision not to rely on the Arnold studies was made pursuant to its Human Research rule. As explained in Unit III.B, that rule establishes different ethical standards for the review of completed human studies depending on whether they were initiated before or after the effective date of the rule on April 7, 2006. For an intentional human exposure study such as the Arnold studies, that was initiated prior to April 7, 2006, EPA is barred, subject to a very limited exception, from relying on it if there is clear and convincing evidence that the conduct of the research was fundamentally unethical or significantly deficient with respect to the ethical standards prevailing at the time the research was conducted (40 CFR 26.1704, 26.1706). Further, the rule limits the human research that can be relied upon by EPA to ''scientifically valid and relevant data'' (40 CFR 26.1701). Finally, because the Arnold study was conducted with the purpose of identifying or measuring a toxic effect, EPA is required by the rule to submit its determination regarding these issues to an independent expert advisory body known as the Human Studies Review Board (''HSRB'') for review. These procedures were followed with regard to the Arnold study.

The HSRB reviewed the Arnold oral and dermal carbofuran human studies at its May, 2006 meeting (Refs. 7, 8, 9). The Board found numerous technical deficiencies regarding the conduct of the oral study and that overall, the weaknesses of the studies far outweigh the strengths. These deficiencies included: (1) There was no justification or rationale for the selection of doses used in any of the three studies. (2) The sample size was very small (typically two subjects per dose or condition) with few or no controls (no more than two control subjects in any study). Such a design prevented evaluation of statistical significance for any parameter measured in the studies. (3) The values obtained for RBC and plasma cholinesterase levels were highly variable. Factors that contributed to this variability included the small sample size, the inclusion of only a single baseline sample collected immediately prior to dosing used to compare all post-dosing samples, the small number of control subjects, and an uncommon method for analytical determination of cholinesterase activities. The contribution of potential laboratory error cannot be ruled out. (4) Plasma cholinesterase levels were highly variable in all studies so as to preclude any useful interpretation. In general, plasma cholinesterase levels were not consistent with changes in RBC cholinesterase activities. (5) One subject who presented with abnormal vestibular mechanisms in the pre-dose evaluation was used in the oral study and showed serious symptoms after treatment. (6) Subjects were allowed to smoke during the study period.

In response to a specific request from the Agency, the Board provided additional analysis concerning the potential for the data in human subjects for carbofuran to be applied to: (1) The calculation of a benchmark dose (BMD_{10}) and identification of the $BMD_{10}L$ (lower confidence limit); (2) the identification of a NOAEL or LOAEL for effects or (3) the comparison to other species for possible adjustments to uncertainty factor for the cumulative assessment. The HSRB provided the following additional perspective relative to the Agency's question:

> The utility of the human studies with carbofuran was limited by the very small sample size used in all of the studies. The Agency proposed to use the RBC cholinesterase data for determination of the $BMDL_{10}$. However, under conditions where the group size was only two, it would be imperative to have highly accurate, valid, reliable and consistent measures of RBC cholinesterase activity in both control and carbofuran-treated subjects. This rigor was simply not achieved in the human studies. Rather, RBC cholinesterase activities were compared to a single baseline value, were highly variable across subjects, including controls, and did not show any consistency with plasma cholinesterase levels. As such, although EPA scientists calculated a $BMDL_{10}$ from the time course of changes in RBC cholinesterase values in the nine subjects evaluated in the oral study, the HSRB concluded that the accuracy and reliability of this calculation was limited by the technical shortcomings noted for the study. Therefore, the HSRB reiterated its recommendation that the $BMDL_{10}$ calculated by the Agency from the human data should not be used.
>
> In a similar manner, the small sample size, compounded by the lack of consistent changes in cholinesterase activities in all studies, the inappropriate methods used for dermal application of the compound in the dermal studies and the inclusion of at least one subject who presented with abnormal vestibular function in a pre-dose assessment limited the general utility of the data. Collectively, the weaknesses in the conduct and outcomes of the carbofuran human studies cast doubt on the utility of the data for identifying a NOAEL or LOAEL or for comparing across species in consideration of the interspecies uncertainty factor for the cumulative risk assessment. Thus the majority of HSRB members agreed the human oral data should not be used to identify a NOAEL or LOAEL, and there was unanimous agreement that the human dermal data should also not be used for these evaluations.

The HSRB concluded that while these studies were informative, due to the numerous technical issues regarding the conduct of the oral study, overall, the weaknesses of the studies far outweigh the strengths. Describing the studies as ''poor science,'' the HSRB recommended against the use of the oral study conducted with carbofuran in human subjects for the single chemical assessment or in informing the interspecies uncertainty factor for the cumulative assessment.

In their comments opposing EPA's proposal to revoke carbofuran tolerances, Petitioners essentially raised the same arguments they present in their objections.

In responding to Petitioners' comments, EPA explained that it agreed with the HSRB's conclusions that the studies were scientifically flawed, and that, therefore, under the Human Research rule, EPA was barred from considering them (Ref. 85 at 9).

2. Denial of hearing request. The critical issue here is EPA's determination under the Human Research rule that the Arnold study was scientifically invalid. All of Petitioners' arguments concerning the choice of the interspecies safety factor rely on EPA's consideration of the Arnold study. As noted above, Petitioners make three arguments as to why EPA erred in its determination. For the reasons discussed below, none of those arguments satisfy the regulatory standard for granting a hearing. Further, as explained in Unit VI.H.3., Petitioners' objections to EPA's determination have no merit. Thus, there is no need to consider Petitioners' more general arguments about EPA's decision to use a 10X interspecies factor in assessing carbofuran's risk.

Petitioners' first argument as to why EPA erred in its determination that the Arnold study was scientifically invalid is that EPA failed to consider the animal data on carbofuran in assessing the scientific quality of the Arnold study. This claim is not material and thus not

appropriate for a hearing (40 CFR 178.32(b)(3)). Under the Human Research Rule, the relevant question is whether the Arnold study is scientifically valid, not whether consideration of the Arnold study in conjunction with the animal data could justify a lower interspecies factor. EPA, and the HSRB, found the Arnold study to be flawed at its core—due primarily to its small sample size and the high variability in measurement of AChE inhibition—and no amount of data from other studies in animals can cure these defects in the Arnold study. Thus, Petitioners' claim here is irrelevant and immaterial to EPA's decision. Ultimately, Petitioners' objection is a challenge to the policy established in the Human Research rule that EPA will not routinely consider all human data. They contend that ''[s]ince [human] data exist for carbofuran, they should have been used to select the interspecies uncertainty factor.'' However, this policy question is not open for debate under the terms of the Human Research rule. And more importantly, such a question does not provide a basis for a hearing (40 CFR 178.32(b)(1)).

Second, Petitioners argue that insufficient weight was given the prior independent reports on the Arnold study. However, the weight EPA should give under the Human Research rule to pre-rule independent reviews as opposed to the conclusions of the HSRB—the body established by the rule for the purpose of aiding EPA's implementation of it—is a legal/policy question and not a factual one. Hearings will not be granted on legal/policy issues (40 CFR 178.32(b)(1)).

Finally, Petitioners' claims that EPA and the HSRB identified merely ''technical'' deficiencies in the Arnold study and that these deficiencies are ''address[ed]'' by ''data within the study itself'' and, therefore, do not render the study ''unreliable'' are no more than mere allegations and thus provide an insufficient basis for the granting of a hearing (40 CFR 178.32(b)(2)). Petitioners have proffered no evidence regarding the ''technical'' nature of the deficiencies in the Arnold study or how the deficiencies in sample size or variability are addressed within the study. Moreover, the record is clear that the deficiencies in the study are fundamental in nature and a hearing will not be granted on bald objections that are contradicted by the record (73 FR 42696 (July 23, 2008) (hearing denied when objection was contradicted by record and no evidence proffered in support)).

3. Denial of objection. Petitioners have offered no response to EPA's explanation for accepting the HSRB's reasoning as to the weaknesses of the studies that rendered them scientifically invalid. Specifically, Petitioners do not address the HSRB's conclusion, adopted by EPA, that ''the weaknesses in the conduct and outcomes of the carbofuran human studies cast doubt on the utility of the data for * * * comparing across species in consideration of the interspecies uncertainty factor.'' Nor do Petitioners offer any reason as to why the HSRB's conclusion is not ''justifiable'' in light of the individual peer review reports from Drs. Brimijoin, Chambers, and Pope. Actually, there are several very good reasons for EPA to place primary weight on the HSRB's report compared to the three individual reports from Drs. Brimijoin, Chambers, and Pope prepared in 1997. First, the prior reports were not produced under the rubric of the Human Research rule, which has a different scope of inquiry than a traditional peer review. Second, Drs. Brimijoin, Chambers, and Pope made their recommendation regarding use of the Arnold study for a RfD in the context of a very different overall database for carbofuran. A significant number of new toxicity studies have been submitted since 1997. Third, Drs. Brimijoin, Chambers, and Pope all noted the severe deficiencies in the Arnold study but proposed that they be dealt with through the use of additional safety factors. Given these considerations it was reasonable for EPA to place primary reliance on the HSRB's report.

The bulk of Petitioners' argument concerning EPA's determination on the scientific validity of the Arnold study is devoted to suggesting that the HSRB's review of the Arnold study was somehow ''inadequate'' because two members of the HSRB (Drs. Brimijoin and Chambers) were recused from the review due to their prior participation in a prior independent peer review. Petitioners also assert that the HSRB was hampered because EPA ''never informed the HSRB that it could call upon these experts for questioning or information regarding their prior peer review of the human studies, nor was it informed of—or provided with—those prior reviews.''

These claims are wholly without merit. As laid out in a letter responding to FMC's complaint regarding the recusal of Drs. Brimijoin and Chambers from the HSRB review of the carbofuran human studies, the recusal was entirely appropriate, and consistent with EPA's policies and regulations. The facts outlined in that letter also demonstrate that the HSRB's review was in no way restricted or hampered by the limited recusal of the two Board members.

First, the HSRB was fully apprised of the earlier peer review reports. EPA relied on the reports because EPA's position before the HSRB was that the Arnold study should be found to meet the standard of the Human Research rule and would be useful in establishing points of departure for the carbofuran's single chemical assessment and in informing the interspecies uncertainty factor for the NMC CRA. It was clearly in EPA's interest that the HSRB be made aware of the earlier reports. In fact, the background materials provided to the Board included the peer review reports by Drs. Brimijoin, Chambers, and Pope, and the Agency's Weight-of-the-Evidence presentation to the HSRB which noted the contributions of these reviewers. Further, both the peer review reports and EPA's Weight-of-Evidence presentations were included in the public docket for the HSRB review. To the extent that the HSRB was still somehow unaware of the prior reports, FMC clearly referenced them in both its written and oral comments to the Board.

Second, EPA's determination on the recusal of Drs. Brimijoin and Chambers was clearly consistent with Agency policy and well with EPA's discretion. The EPA's Peer Review Handbook (3rd Edition) (Ref. 80) provides guidance about peer review processes of the Agency. Of particular relevance is the Handbook's guidance regarding independent peer reviewers. While the Handbook notes that there is no prohibition against using the same peer reviewer more than once on the same product, it nevertheless advises that ''it is preferable to use different people each time to provide a broader perspective (Ref. 80 at 13). Further the Handbook advises that the review of experts who ''have participated substantially in the development of a product * * * may not qualify as unbiased, independent peer review * * *'' (Id.). Therefore, EPA concluded that, under the circumstances, a question could be raised regarding the impartiality of Drs. Brimijoin and Chambers from the particular matter under review by the HSRB. Further support on this point can be found in the regulations at 5 CFR 2635.502(a)(2), and in the preamble to the original regulation (56 FR 33778 (July 23, 1991)).

In light of these considerations, EPA addressed the appearance issue regarding Drs. Brimijoin and Chambers by determining whether authorization by the Agency designee should be invoked (see, 5 CFR 2635.502(d)). Three factors were particularly relevant to the determination of Drs. Brimijoin and Chambers (see, 5 CFR 2635.502(d)(4), (5), and (6)): the sensitivity of the

matter, the difficulty of reassigning the matter to another employee, and adjustments that may be made in the employee's duties that would reduce or eliminate the likelihood that a reasonable person would question the employee's impartiality. After considering these factors, the Agency decided the prudent course was be to recuse Drs. Brimijoin and Chambers from the HSRB carbofuran discussion but to authorize limited, as needed, participation.

As documented in Dr. William Farland's May 1, 2006 memorandum entitled, ''Ethics Determination for Participation at the May 2–3, 2006 EPA Human Studies Review Board Meeting'' (Ref. 39), EPA authorized the HSRB to ask Drs. Brimijoin and Chambers clarifying questions regarding their 1997 review, in the event that the HSRB deemed it necessary as part of their deliberations. At no point during the meeting did any of the HSRB's members indicate in any way that they wanted to consult with their recused colleagues. Nor did any of the members state that they wanted clarification on any point associated with the study.

For all of the above reasons, Petitioners' objection on this point is denied.

I. Objections to Revocation of Import Tolerances

Petitioners object to EPA's revocation of the tolerances for imported foods along with the tolerances associated with domestic uses. Petitioners allege that the revocation of the import tolerances is not supported by the available data because EPA's own risk assessments conclude that, when considered separately from the domestic uses, the residues from imported foods covered by these tolerances are ''safe.'' Petitioners further argue that EPA ''has not asserted any claim or rationale in the Final Order justifying its conclusions that the import tolerances are unsafe'' and therefore the revocation is unjustified.

1. Background. In the proposed rule, EPA explained that its finding that aggregate exposure from all of the existing uses of carbofuran is not safe does not necessarily mean that no individual tolerance or group of tolerances could meet the FFDCA 408(b)(2) safety standard and be maintained (73 FR 44865 (July 31, 2008)). Rather, to the extent parties wanted to retain a particular subset of existing tolerances, the onus was on commenters to identify those uses and to submit information to demonstrate that the tolerance(s) meet the statutory standard. Indeed, EPA specifically identified the import tolerances as a subset that might meet the safety standard (Id.).

No one submitted any comments alleging the need to retain individual tolerances for purposes of imports, or indicated an intention to seek to maintain those tolerances. The only subset of tolerances that commenters suggested was safe was the subset identified by the Petitioners, which included the import tolerances along with four domestic food uses.

In the final rule, EPA analyzed the aggregate exposures from the subset of tolerances the Petitioners sought to retain, and concluded that the aggregate residues from food covered by those tolerances and from residues in drinking water are unsafe (74 FR 23084–23088).

2. Denial of hearing request. A hearing is denied on this subissue because there is no disputed factual matter for resolution at a hearing. As the objection notes, EPA and Petitioners' risk assessment both concluded that the residues from imported food alone fell within the risk cup (Obj. at 52–54). The only issue this objection raises is whether EPA should have independently determined to retain a subset of the tolerances that Petitioners sought to maintain. This is a legal issue, and hearings are not appropriate on such issues (40 CFR 178.32(b)(1)). (*See* 73 FR 42696–42697 (July 23, 2008) (denying NRDC's request for a hearing on objection that children's safety factor could not be reduced in absence of endocrine screening data). FDA also has repeatedly confirmed that the application of a legal standard to undisputed facts is a question of law for which a hearing is not required. (*See, e.g.*, 68 FR 46403, 46406 n.18, 46408, 46409 (August 5, 2003) (whether facts in the record show there is a reasonable certainty of no harm is a question of law; whether a particular effect is a ''harm'' is a question of law)).

In addition, Petitioners failed to raise this issue as part of their comments on the proposed rule, and never requested retention of only the import tolerances. Accordingly, as discussed in Unit VI.D, EPA considers this issue to have been untimely raised, and therefore waived. (See, 73 FR 42,696 (July 23, 2008) (denying NRDC's hearing request on claims not presented in their original petition); 72 FR 39318, 39324 (July 18, 2007) (ruling that parties may not raise new issues in filing objections to EPA's denial of original petition)).

3. Denial of Objection. Petitioners incorrectly allege that EPA provided no rationale for the revocations of the import tolerances. In the final rule, EPA clearly found that the aggregate exposures to carbofuran residues from all remaining uses, when combined with residues found in drinking water, were unsafe (74 FR 23084–23088 (May 15, 2009).

EPA can only maintain tolerances that it can determine will be ''safe'' within the meaning of section 408(b)(2)(A)(ii). In making this determination, EPA must consider aggregate exposures from ''dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources'' (21 U.S.C. 346a(b)(2)(D)(vi)). At the time of the final rule, EPA evaluated the safety to the public from all dietary exposures to residues of carbofuran, which included not only the import tolerances, but also from residues on foods associated with domestic registrations and from residues in drinking water contaminated by the domestic uses. Indeed, until domestic use ceases—or at least until EPA has a reasonable basis to believe that it will cease—the Agency has no discretion to ignore the exposures from those uses. And revocation of the tolerances themselves does not necessarily resolve the issue, given the circumstances here. Until the registrations are cancelled, residues from contaminated drinking water, which is the primary contributor to the risks, must be included in EPA's risk assessment (Id).

The consequence of this requirement is that, when one tolerance is unsafe, all tolerances are equally unsafe until aggregate exposures have been reduced to acceptable levels. Accordingly, in circumstances where aggregate exposures exceed the risk cup, there are potentially multiple variations of the potential subset of tolerances that might meet the safety standard. FFDCA section 408 does not compel EPA to determine the appropriate subset that would meet the safety standard. EPA is compelled ''to revoke or modify a tolerance if [EPA] determines it is not safe,'' but the statute grants EPA the discretion to determine how to proceed where more than one tolerance is unsafe. EPA's general policy in such situations is not to independently select the subset that meets the standard, but to rely on the pesticide registrant and the public to determine which of the various subsets of tolerances are of sufficient importance to warrant retention. There are a number of reasons EPA adopted this policy; it would be an unreasonable burden for the Agency to evaluate every possible combination of tolerances that might fit within the risk cup. In addition, if there were multiple different combinations that might within the risk cup, it is not clear that any party would

agree that EPA had selected the appropriate combination of tolerances. This is particularly relevant, since EPA relies on individual entities to maintain the tolerance, by continuing to submit necessary data to demonstrate the continuing safety of the covered residues.

J. Summary of Reasons for Denial of Petitioners' Objections and Hearing Requests

1. General Denial. All of Petitioners' objections and hearing requests are denied because they are irrelevant, and thus immaterial, to EPA's final regulation revoking carbofuran tolerances. The lack of relevance stems from Petitioners' decision to object not to the safety decision EPA made in its final revocation regulation but to instead argue that EPA should reach a different decision based on FMC's proposed changes to the carbofuran registration that were submitted to EPA 44 days after the regulation published in the **Federal Register**. These proposed registration changes are central to and inextricably intertwined with the contention that underlies all of Petitioners' objections—that the carbofuran tolerances are safe, because in order to retain the contested tolerances, Petitioners must succeed on all of their objections. There exist statutory and regulatory procedures under FIFRA for FMC to pursue an amended carbofuran registration. As part of seeking an amended registration, FMC may petition to reestablish the revoked carbofuran tolerances. However, it is not proper to object to a final FFDCA tolerance revocation regulation based on the assertion that subsequently-filed, and as of yet unapproved FIFRA registration amendments, may change the risk picture under the FFDCA.

FMC has had ample opportunity prior to issuance of the final tolerance revocation regulation to amend its FIFRA registration, whether during the comment period on the proposed rule, the extended reregistration process, or the public process initiated as part of the NOIC for carbofuran. And FMC has requested a number of modifications to its registrations during that time period. Yet, FMC has waited until EPA issued a final revocation regulation finding that carbofuran tolerances are unsafe, particularly as to infants and children, before filing its latest series of proposed FIFRA registration amendments. For this FFDCA proceeding, that is too late. The FFDCA commands that EPA ''shall modify or revoke a tolerance if the Administrator determines it is not safe'' (21 U.S.C. 346a(b)(2)(A)(i)). The statute also places EPA under a special injunction to protect infants and children from the risks of pesticides (21 U.S.C. 346a(b)(2)(C)). EPA has made a final determination that carbofuran tolerances are unsafe and further determined that that lack of safety falls hardest on infants and children. Petitioners had the statutory right under FFDCA to challenge the accuracy of EPA's safety finding on carbofuran tolerances. FMC also has the statutory right under FIFRA to request amendment of its registration. What Petitioners may not do is prolong the FFDCA tolerance revocation process by challenging EPA's safety determination based on proposed FIFRA registration changes that were not before EPA at the time of its final revocation decision.

2. Alternate Grounds for Denial. Despite the fact that Petitioners' objections and hearing requests are facially defective for reliance on newly-proposed FIFRA registration amendments, EPA has carefully examined each of Petitioners' objections and hearing requests and found that, in every instance, there are alternate grounds for denial. Those grounds are summarized below.

There are multiple problems with Petitioners' hearing requests. Many of these problems stem from the Petitioners' decision to withhold analyses and information from the notice-and-comment rulemaking portion of this proceeding. Thus, despite EPA's clear warning that issues not raised in comments on the proposed rule, and information not submitted in that same timeframe, would be considered waived, Petitioners included several new issues, and numerous documents and analyses for the first time with their objections although they were clearly available earlier. Petitioners also have, for the most part, ignored how EPA responded to the comments they did submit in the notice-and-comment rulemaking, and instead have often merely recycled their earlier comments as objections without addressing the reasons why EPA found them lacking in the first instance. This strategy, unfortunately for Petitioners, is fatal to many of their hearing requests and objections. EPA will not grant hearings on issues that have been waived, on issues where supporting documents were untimely submitted, or on claims that have become stale in that EPA addressed them in the final rule and Petitioners have not responded by clarifying where disputed issues still remain.

It is not as if Petitioners lacked warning that EPA would take such an approach. Not only did EPA clearly state in the proposed rule that comments and information must be submitted in the comment period to be preserved but in 2007 EPA denied a hearing to a party who treated the notice-and-comment rulemaking process in a similarly cavalier fashion. In that instance, the party in question, like Petitioners, filed objections that largely mirrored its earlier submissions to the Agency without taking into account how EPA's final action had altered the nature of issues in dispute (See, *e.g.*, 73 FR 42693 (''NRDC's objections largely restate the claims in its petition. Significantly, NRDC does not acknowledge or respond to the DDVP dietary and residential risk assessments made in response to the NRDC petition.'')). Such objections and hearing requests were denied for a lack of materiality (73 FR 42698–42699 (''When an objector does not challenge EPA conclusions in the section 408(d)(4)(iii) order but rather challenges some prior conclusion that was superseded by the section 408(d)(4)(iii) order, the objector has not raised a live controversy as to an issue material to the section 408(d)(4)(iii) order.'').

a. Children's Safety Factor Objection. In support of their objection on the children's safety factor, Petitioners put forward several arguments; EPA summarizes below the various reasons for rejecting Petitioners' hearing requests and objections on each argument. Given the voluminous number of arguments asserted by petitioners in support of this objection, it is easy to lose track of the fact that all of the arguments relate to a single decision by EPA—the decision to reduce the presumptive 10X children's safety factor to 4X, rather than to 1X or 2X as the Petitioners desire.

(i) Subissue: Are brain AChE measures in juveniles adequately protective of CNS effects in juveniles? EPA based its determination to reduce the children's safety factor to 4X on the ratio of sensitivity shown between carbofuran's effects on RBC AChE and brain AChE in juvenile rats. It is EPA's general policy to rely on RBC AChE as a surrogate for effects on the PNS but Petitioners failed to provide adequate RBC AChE data in juveniles to fully characterize the dose level of concern for PNS effects in infants and children. Petitioners claim EPA was wrong from the start. They claim that once EPA determined it had adequate data on brain AChE, the RBC data was irrelevant because brain AChE is an adequately-protective surrogate for PNS effects.

Petitioners' hearing requests and objections on this issue are denied for identical reasons: the available evidence

identified by petitioners is ''insufficient to justify the factual determination urged'' (40 CFR 178.32(b)(2)). The critical issue with regard to EPA's children's safety factor decision is whether EPA has reliable data to ensure that residues of carbofuran in food will not cause adverse effects on infants and children's PNS. Petitioners claim that carbofuran data on brain AChE in juveniles is such reliable data. However, the evidence they proffer to support such an assertion is facially insufficient. Primarily, Petitioners cite data involving comparisons of brain AChE and PNS effects in adult animals. But evidence from adult animals is beside the point; the question is whether brain AChE in juveniles is protective of the PNS in juveniles. For at least 25 years, EPA has required toxicity tests be performed with pre- and post-natal animals as well as adult animals because young animals can be more sensitive and affected in a different manner than adults. Further, the only studies Petitioners cite that compared brain AChE in juveniles with PNS effects in juveniles, were conducted using other pesticides. For good reason, EPA requires that pesticides be individually tested in toxicity studies. Moreover, the majority of the data cited by Petitioners in other chemicals actually fails to demonstrate that the brain is more sensitive than the PNS, and the remainder of the evidence is, at best, merely equivocal on this point.

To reiterate, if EPA chooses to select a children's safety factor different than 10X, it bears the statutory burden of showing that reliable data support its determination that the selected factor is safe for infants and children. Thus, Petitioners, in seeking to establish that EPA erred by not selecting an even lower children's safety factor for carbofuran (in fact, no such factor at all), similarly bear the burden of showing that there are reliable data for the proposition that juvenile brain AChE data for carbofuran are protective of PNS effects in children. Petitioners' equivocal and largely irrelevant proffer cannot meet that standard, particularly where EPA is lacking data it has traditionally-required on cholinesterase-inhibiting pesticides to protect against PNS effects, and the data EPA does have on measures of PNS effects indicate that effects on the juvenile PNS occur at lower doses than effects on brain AChE.

(ii) Subissue: Are RBC AChE measures adequately reliable evidence of CNS effects? As a corollary to their claim that brain AChE measures are adequately protective of PNS effects, Petitioners also argue that RBC is not an appropriate surrogate for CNS effects in most circumstances. A hearing is not warranted on this subissue because Petitioners' evidentiary proffers either concern matters of undisputed fact (*e.g.*, RBC AChE inhibition is not an adverse effect, RBC AChE can be variable at low doses) or inadequate and irrelevant data on other pesticides. Further, Petitioners' claim basically reduces to an argument over which is the ''preferred'' surrogate for PNS effects in the absence of data directly measuring such effects. Thus, this subissue is an argument about science policy and EPA's regulations are clear that hearings will not be held on policy matters. Even more problematic to Petitioners' hearing request on this subissue is its lack of materiality. Having failed in the previous subissue to proffer sufficient evidence to show carbofuran brain AChE data in juveniles is protective of carbofuran's effect on the PNS in juveniles, Petitioners' attempt to attack EPA's basis for addressing carbofuran's effects on the PNS in juveniles can only undercut Petitioners' ability to demonstrate the safety of the carbofuran tolerances. With the demise of Petitioners' brain AChE argument, EPA's analysis of the RBC AChE data is the only remaining basis for reducing the children's safety factor. If Petitioners are successful in showing that RBC AChE data are not a reliable measure of PNS effects in juveniles, EPA would have no reliable data on such impacts and would be required to retain the full children's safety factor. As such, Petitioners' claim is immaterial; even if the claim were upheld, it would not justify the ultimate relief sought by Petitioners.

As to Petitioners' objection to EPA's science policy decision to use RBC cholinesterase as a surrogate for PNS effects, EPA explains in detail in Unit VI.E, the biological basis for its policy decision, the multitude of data supporting its approach, and the frequent consultations with the SAP concerning the wisdom of using such an approach. The equivocal data submitted by Petitioners does not raise a serious question regarding EPA's policy. In any event, as noted with regard to the hearing request, this subissue lacks materiality in that success on this subissue by Petitioners would retard rather than advance their challenge to EPA's action.

(iii) Subissue: Is ''lip-smacking'' a CNS or PNS effect? Petitioners object that EPA's evidence of ''lip smacking'' in a carbofuran adult developmental rat study does not support concern for potential PNS effects because lip smacking is more properly correlated to CNS, rather than PNS inhibition. A hearing is denied on this issue because Petitioners did not raise this issue in its comments on the proposed tolerance revocation. A hearing on this issue is also inappropriate because the issue is immaterial. EPA's decision that a 4X children's safety factor is appropriate did not rest exclusively—or even significantly—on the effects observed in this developmental study. Rather, EPA retained the children's safety factor based on the lack of data in the PNS and/or a surrogate at the low end of the response curve, and the fact that the available pup RBC data at higher doses affirmatively indicate that the PNS appears to be significantly more sensitive than the CNS.

Petitioners' objection on this subissue is denied because both parties agree that muscle fasiculations, which are the movements EPA described at the SAP meeting and in the proposed and final rules, are PNS-mediated effects. Further, it is unclear that the effects described in the studies Petitioners submitted are actually the same effects seen in the carbofuran study; other factors in the studies suggest that the movements being studied are not purely cholinergic, which calls into question whether the effects are the same. For the same reason, this calls into question the contention that the effects are exclusively CNS-related. Finally, the cited studies fail to support Petitioners' remaining contentions. Since it is unclear that the studies actually describe the same effects, and Petitioners have failed to demonstrate that the effects are exclusively CNS-related, the evidence does not, therefore, rebut EPA's conclusions regarding the movements described in the carbofuran study.

(iv) Subissue: Did EPA err by relying on studies not conducted pursuant to EPA's GLP regulations? Petitioners claim that EPA's reliance on the ORD data is problematic because the data were not conducted in accordance with EPA's GLP regulations at 40 CFR part 160. Petitioners have not cited any evidence suggesting there is a substantive problem with the ORD data or made any arguments to such effect. Thus, this subissue presents only a legal question and legal questions are not appropriate grounds for a hearing. EPA denies Petitioners' objection on this point because EPA regulations make clear its GLP regulations only apply to studies in support of a pesticide registration or tolerance (40 CFR 160.1(a), 160.3). In any event, non-compliance with the GLP regulations does not automatically disqualify a study from EPA consideration but rather goes to reliability (40 CFR 160.17(a)).

(As noted, Petitioners have made no claim that the ORD data is not reliable.).

(v) Subissue: Was EPA's selection of a 4X children's safety factor consistent with EPA's approach to other carbamate pesticides? Petitioners object that EPA was inconsistent in retaining a 4X children's safety factor for carbofuran given that EPA removed the children's safety factor for other carbamates. A hearing is not appropriate on this subissue because it presents a purely legal question. There is no dispute regarding the facts of EPA's decision in each case, the only question is whether EPA acted appropriately on carbofuran given its decision on the children's safety factor for other carbamate pesticides, such as carbaryl. The objection is denied because EPA's decisions in each case were consistent; EPA applied a different children's safety factor to carbofuran than to the other carbamate pesticides based on the different facts in each case. For example, the data showed that carbaryl differed significantly from carbofuran in terms of each chemical's relative sensitivity in juveniles with regard to brain and RBC AChE inhibition. For carbofuran, EPA concluded that RBC AChE inhibition in juveniles was more sensitive than brain AChE inhibition in juveniles by a factor of 4X. For carbaryl, the AChE inhibition in brain and RBC of juveniles was essentially equal.

(vi) Subissue: Did EPA err in not using within-animal brain to RBC AChE inhibition comparisons to derive the children's safety factor? EPA derived an alternate to the default 10X children's safety factor based on the ratio of RBC and brain AChE inhibition. In their comments on the proposed rule, Petitioners criticized this approach, arguing that EPA should have compared the RBC and brain AChE inhibition levels at the same time in the same rat when these rats are exposed to carbofuran. Petitioners claimed to have done such an analysis and that the analysis showed that within rat inhibition levels in brain and RBC AChE were roughly equivalent. Although the results of the statistical analyses were summarized in the comments, the underlying analysis was not submitted. In the final tolerance revocation regulation, EPA extensively reviewed the ''within animal'' approach and rejected it as fundamentally flawed in several regards. Additionally, EPA noted that EPA's review of the Petitioners' suggested approach showed that it produced results, which are in fact consistent with EPA's conclusions. In their objections, Petitioners do not respond to EPA's rejection of the within animal approach in the final tolerance revocation rule either by explaining their disagreement with EPA's critique or proffering evidence to counter EPA's conclusion. Rather, Petitioners simply resubmitted essentially the same comments they provided on the proposed rule. Petitioners also again failed to submit the underlying analysis supporting their within animal calculations.

A hearing on this subissue is not appropriate for two reasons. First, Petitioners' repeated failure to submit the analysis supporting their claim reduces this objection to a mere allegation. Under EPA's regulations, hearings will not be granted on the basis of mere allegations. More importantly, Petitioners' objection on this subissue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation because Petitioners ignored EPA's extensive analysis of this subissue in the final rule and refiled their comments on the proposal as if EPA's determination in the final rule did not exist. The statute, however, requires that objections be filed on the final rule, not on the proposal. By ignoring the EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Both EPA and FDA precedent make clear that when the agency substantively responds to comments on the proposal, the commenter may only keep that issue alive in its objections by addressing the agency's substantive response. In other words, the final rule is the focal point for determining whether issues remain that must be resolved by the objection and hearing process. Any other approach relegates the notice-and-comment rulemaking stage of the revocation process to a meaningless exercise.

Petitioners' objections on this subissue are denied as irrelevant to the conclusions reached in the final rule. The final rule explains why Petitioners' arguments are without a basis, and Petitioners have failed to address that explanation. For essentially the same reasons, EPA denies the objection.

For essentially the same reasons, EPA denies the hearing request and objection designated above as *Objection/hearing request sub issue: Technical Flaws in EPA's statistical comparisons.* Petitioners' objection and hearing request on this subissue consist of mere reiteration of the comments submitted in response to the proposed tolerance revocation. The final rule explained the reasons that Petitioners' arguments are flawed, and the objections are denied for the same reasons.

(vii) Subissue: Is EPA's approach to comparing brain and RBC AChE inhibition in juveniles due to carbofuran exposure scientifically valid? Petitioners allege that EPA's approach to calculating the relative sensitivity between AChE inhibition in brain and RBC in juveniles is not scientifically valid. EPA derived the ratio of RBC and brain AChE inhibition using the data on administered dose (measured in terms of BMD_{50}) for PND11 animals. In addition, the Petitioners criticize EPA for incorrectly assuming that the relationship of the dose response curve between BMD_{50}s and BMD_{10}s is linear, which they claim overstates the potential differences. In support of the claim that EPA's approach overstates the differences, Petitioners argue that data suggests that BMD_{50}s for brain and RBC AChE inhibition for the carbamates tend to diverge more than the dose levels that cause the low levels of AChE inhibition used to select the PoD (*i.e.,* the BMD_{10}s), which demonstrates that at levels causing lower levels of inhibition, no safety factor is necessary. Petitioners' argument is that the 4X ratio EPA calculated based on the BMD_{50} is unnecessarily protective, because the difference between brain and RBC at the doses causing lower levels of inhibition (*i.e.,* 10%), which are the levels at which EPA is regulating, would not be significant.

Petitioners' hearing request on this subissue is denied for two reasons. First, Petitioners proffered no evidence on any carbamate, much less carbofuran, in support of their claim that BMD_{50}s for the carbamates tend to diverge more than the BMD_{10}s or that the response curve between BMD_{50}s and BMD_{10}s is not linear. A hearing will not be granted on the basis of mere allegations. Second, Petitioners' claims are immaterial because unless Petitioners can show what the relationship is between the response curves for BMD_{50}s and BMD_{10}s (an assertion they have not even made), a showing that EPA's assumption of linearity is incorrect can only force EPA to abandon the 4X children's safety factor in favor of the default 10X value.

The objection that EPA's modeling is scientifically invalid is denied. EPA's modeling has been repeatedly reviewed and approved by the SAP, including most recently with respect to the modeling of carbofuran's dose-response curves. There is no indication in the modeling that EPA's assumption of parallel dose-response curves overstates the difference, and given the absence of data supplied by Petitioners in support of this objection, the objection is denied.

(viii) Subissue: Did EPA err by combining data from different toxicological studies in calculating the estimates of BMD_{50}s that serves as

quantitative support for derivation of the 4X childrens' safety factor? In its risk assessment, EPA relied on all of the valid data from the available studies to calculate the estimates that served as the PoD, and to calculate BMD_{50}s used in choosing the children's safety factor. In their comments on the proposed rule, Petitioners claimed that EPA's decision to combine data for different strains of rats, sexes, experiments, laboratories, dates, dose preparations, rat ages, and times between dosing and AChE measurement, is problematic, claiming that these differences in study design severely limit the validity of EPA's comparisons and caused EPA to overestimate the difference between brain and RBC AChE inhibition. EPA responded to these comments in full during the rulemaking (74 FR 23052–23053; Ref. 85). Petitioners referenced their earlier comments in their objections, but presented no further evidence on any of these points. Nor in their objections and request for hearing did Petitioners address EPA's explanation set forth in the final rule.

A hearing is not appropriate on this subissue because Petitioners have not challenged the basis EPA asserted in the final rule for rejecting their concerns nor have they proffered any evidence that calls the substance of EPA's conclusions into question. A hearing is not warranted on the basis of mere denials or contentions, nor when the commenter simply reiterates comments raised in response to the proposed rule (40 CFR 178.32(b)(1) and (2)). Additionally, this hearing request is rejected for lack of materiality. If EPA abandoned its sophisticated analysis of multiple studies and datasets and simply followed the general approach laid out in its BMD policy, EPA would have chosen a significantly lower BMD dramatically raising EPA's risk estimates.

Petitioners' objection on this subissue is denied because Petitioners have not responded to the explanation EPA provided in the final rule supporting its meta-analysis of multiple studies. Consistent with Agency guidance, EPA believes that consideration of all available data is the scientifically more defensible approach, rather than the selective exclusion of reliable data. Petitioners' objection on this point is particularly weak given that their analysis also combines various data sets and only arrives at a higher estimate of the BMD by selectively excluding, without explanation, the data most pertinent to assessing carbofuran's acute affects.

b. Drinking Water Exposure Objection—In large part, Petitioners' objections to EPA's assessment of carbofuran levels in drinking water are inextricably intertwined with their recently-proposed registration amendments which attempt to create a scheme whereby carbofuran use would be limited in individual watersheds. As explained above (see Unit VI.F.2.a), objections based on these recently-proposed registration amendments are irrelevant to EPA's determination in the final tolerance revocation rule. Nonetheless, in Unit VI.F, EPA exhaustively evaluated all of the arguments put forward in Petitioners' drinking water objection and explained why a hearing was not appropriate on any of these arguments and why, on the merits, the arguments were without basis. Below EPA has summarized its reasoning.

The first four subissues below pertain to EPA's assessment of the carbofuran groundwater exposure assessment and the last eight address the surface water assessment. In this regard, it is important to note that, in order to determine that a tolerance for a particular use will be safe, EPA must be able to determine that anticipated concentrations in both surface water and ground water resulting from that use will be safe.

(i) Subissue: Did EPA err in relying on the results of the prospective ground water study (PGW) and historical monitoring to validate groundwater exposure estimate? The Petitioners object that EPA should not have relied for validation on their PGW study or historical monitoring data. They argue that these data no longer reflect current use patterns and that all areas like those seen in the PGW have now been removed from the carbofuran label.

A hearing is not appropriate on this subissue because the Petitioners have failed to proffer evidence, which would, if established, resolve a material issue in their favor. First, Petitioners fail to take into account the clear record evidence that EPA scaled the PGW modeling to reflect the lower current use rates. Second, Petitioners are simply incorrect to claim that EPA ''validated'' its quantitative groundwater assessment based on historic monitoring data that are not reflective of current application rates. The targeted monitoring data used for validation were based on application rates that are identical or lower than the current use rates. Third, the majority of Petitioners' evidence is untimely, and to the extent Petitioners' are claiming that the PGW and other targeted monitoring data are not reflective of FMC's June 29, 2009 proposed registration amendments, that claim is irrelevant to the current proceeding. Finally, Petitioners' evidentiary proffer on the PGW is internally contradictory given that Petitioners' own experts relied on the PGW to validate the modeling submitted in support of this objection.

The objection on this subissue is denied because timely evidence and reasoning submitted by Petitioners is contradictory, non-probative, or flatly contradicted by the record.

(ii) Subissue: Does EPA's assessment of carbofuran levels in ground water account for all of FMC's label mitigation measures and ''rely on unrealistic and overly conservative assumptions about potential concentrations''? In this objection, the Petitioners allege that maximum concentrations of carbofuran in groundwater are expected to be below 1.1 ppb, based on their proposed geographic restrictions and well setbacks. EPA believes Petitioners' objection and hearing request on this subissue is inextricably intertwined with FMC's recently-submitted FIFRA registration amendments and thus the objection is denied as irrelevant on that account.

Nonetheless, to the extent possible EPA has attempted to evaluate this objection based on the label mitigation measures submitted and adopted prior to issuance of the final tolerance revocation rule and ruled on it on that basis. EPA denies the objection and its associated hearing request because Petitioners have again failed to object to EPA's final rule. It is clear from the record that EPA's final rule and risk assessment did account for all of the risk mitigation measures submitted as part of the September 2008 comments. Petitioners have not raised any substantive challenge to the manner in which EPA's modeling addressed those measures. In addition, Petitioners' objections provide no further clarification as to what is meant by their claim that EPA's assessment relied on ''unrealistic and overly conservative assumptions.'' Therefore, this objection, and the attendant hearing request, is denied based on Petitioners' failure to state with ''particularity * * * the basis for the objection * * *.''(40 CFR 178.25(a)(2)). As Petitioners raised similar allegations in their comments, EPA has assumed that they intended to incorporate all of the issues raised in the comments on the proposed rule. However, EPA addressed these assertions in the final rule. Because Petitioners have once again ignored the explanations provided in the final rule, this objection and hearing request are denied as immaterial.

(iii) Subissue: Is EPA's assessment of the levels of carbofuran in groundwater appropriate given the manner in which

EPA assessed groundwater exposures in the NMC CRA? Petitioners object that EPA's estimates in the final rule are inconsistent with the groundwater concentration estimates EPA developed for the NMC CRA. However, they do not identify any specific inconsistency, they simply make the general allegation. They allege that, by contrast, their assessment, which estimated maximum concentrations of 1.1 ppb, is consistent with the NMC CRA.

EPA denies the request for a hearing on this sub-issue because there is no disputed factual matter for resolution (*i.e.*, the manner in which EPA assessed groundwater exposure for carbofuran and for the NMCs is a matter of record); rather, the objection poses the legal question of whether it was appropriate for EPA to assess groundwater exposure for carbofuran and the NMCs in a different manner. Further, because Petitioners have not identified any specific inconsistency between the two groundwater exposure assessments, it constitutes nothing more than a mere allegation or denial. As EPA's regulations make clear, a mere ''denial'' of an EPA position is not sufficient to satisfy the standard for granting a hearing (40 CFR 178.32(b)(2)). Finally, the claim that their modeling is consistent with the NMC CRA does not justify a hearing on this question. As EPA explained in the final rule, the values estimated in the modeling conducted for the NMC CRA are greater than the 1.1 ppb level that FMC claims is the maximum expected 1-in-10-year peak concentration. A hearing is not warranted where the claim is clearly contradicted by the record (40 CFR 178.32(b)(2)).

On the merits, Petitioners' objection is denied because the results of Petitioners' groundwater assessment are not consistent with the estimates developed for the NMC CRA. The NMC CRA examined carbofuran at two sites, northeast Florida and the Delmarva Peninsula. In Florida, concentrations were found to be below levels of concern because of high pH, but in Delmarva, both in corn and in melon scenarios EPA estimated that 90% of daily concentrations could be as high as 20.5 and 25.6 ppb, respectively. These values are far greater than the 1.1 ppb that Petitioners claim is the maximum expected 1-in-10-year peak concentration.

(iv) Did EPA err in not using PCT data in assessing surface water exposure? The Petitioners object to the assumption in the surface water assessments in the final rule that 100% of the crops in a watershed will be treated with carbofuran. The Petitioners argue that actual carbofuran sales data on a county basis from 2002-present demonstrate that the current carbofuran PCT is less than 4.25%. Using this PCT, and taking into account the recently submitted ''no application buffers,'' the Petitioners allege that the modeling in Exhibit 15 demonstrates that carbofuran concentrations in surface water will not exceed 1.1 ppb, ''which is below the level of concern.'' In support of this objection, the Petitioners reference county level sales data that were submitted to the Agency after the close of the comment period. They also reference the use tracking system proposed in their recent registration amendments (Exhibit 2) and the modeling contained in Exhibit 15. Because this subissue is inextricably intertwined with Petitioners' recently-proposed FIFRA registration amendments, it is denied as irrelevant.

To the extent Petitioners' objection on this subissue is limited to EPA's refusal to use a 4% PCT in estimating drinking water concentrations in individual watersheds based on the information provided as part of their comments on the proposed rule, this objection and hearing request are also denied as immaterial. The Petitioners have failed to respond to EPA's explanation in the final rule that the information and methodology on which they relied to estimate a 4% PCT was fundamentally flawed, and to submit any evidence calling the basis of EPA's response into question (40 CFR 178.32(b)(3)). Additionally, the proffered evidence here is untimely. The sales data and methodology used to generate use estimates, as well as the modeling in Exhibit 15, were not submitted during the comment period on the proposed rule even though the information was clearly available to Petitioners (40 CFR 178.32(b)(2)).

Petitioners' objection on this subissue is denied because the proffered evidence is untimely and, even if considered, insufficient. Although EPA does use reliable data on pesticide usage in estimating exposure levels in food, this approach has limited applicability in drinking water assessments due to the differences in the sources of food and water for consumers. The food market in the United States is national in scope but the sources of drinking water are primarily local. Thus, while differences in the usage of pesticides across the country will average out in estimating pesticide exposure from food, such averaging is not applicable to estimating pesticide exposure in drinking water—*i.e.*, a person's drinking water exposure is generally always from the same watershed. Moreover, the information that Petitioners submitted on PCT was not usage data—the type of information normally used in estimating PCT for food—but sales data. The link between sales data and the location of use is tenuous. Given that EPA lacks the information to allow EPA to generally use PCT information in estimating drinking water exposure, and the poor quality of information Petitioners submitted on usage (*i.e.* county-level sales data), EPA concludes it could not make an exposure estimate on carbofuran in drinking water with sufficient confidence to meet the FFDCA's reasonable certainty of no harm standard.

(v) Subissue: Do the results of FMC surface water modeling establish that carbofuran levels will not exceed 1.1 ppb? The Petitioners claim that the prior surface water assessments submitted to the Agency and a new assessment incorporating FMC's newly-proposed FIFRA registration amendments demonstrate that carbofuran concentrations in surface water are not expected to exceed 1.1 ppb. Because this subissue is inextricably intertwined with Petitioners' recently-proposed FIFRA registration amendments, it is denied as irrelevant. Nonetheless, EPA has carefully evaluated all of Petitioners' allegation to determine if any of their claims meet the standard for a hearing or are otherwise meritorious.

A hearing is also denied on this sub-issue because Petitioners' objection on this subissue is irrelevant, and therefore immaterial, with regard to EPA's final tolerance revocation regulation. Petitioners have not responded to EPA's extensive analysis of these studies, which included an explanation for the Agency's conclusion that they were significantly flawed, presented in the final rule. The statute, however, requires that objections be filed on the final rule not the proposal. By ignoring EPA's final rule on this subissue, Petitioners have failed to lodge a relevant objection. Both EPA and FDA precedent make clear that when the agency substantively responds to comments on the proposal, the commenter may only keep that issue alive in its objections by addressing the agency's substantive response (40 CFR 178.32(b)(3)). Similarly, the Petitioners' new assessment directly relies on FMC's newly-proposed FIFRA registration amendments and is thus irrelevant to this proceeding. Their new assessment is also untimely in that it primarily appears to be a fuller description of Petitioners' National CWS Assessment, which was described, but not provided as part of their comments on the proposed rule (40 CFR 178.32(b)(2)).

EPA has outlined the substantial flaws in the previously-submitted assessments in the final tolerance revocation rule and in Unit VI.F, above. For the all the reasons cited therein, this objection is denied.

(vi) Did EPA inappropriately rely on NAWQA monitoring data in assessing carbofuran levels in surface water? The Petitioners object to EPA's discussion in the final rule of the high concentrations detected in Zollner Creek in Oregon and claim that EPA inappropriately relied on NAWQA monitoring data in estimating surface water exposure levels of carbofuran. A hearing on this issue is denied because there are no material factual issues in dispute. The extent to which EPA discussed the Zollner Creek data as part of its discussion of monitoring results from all other NAWQA sites, SDWA post-treatment monitoring, and the results of field studies is clear on the record. The record is also clear regarding the degree of reliance EPA placed on monitoring data in estimating carbofuran levels in surface water. The objection on this subissue is denied because it was reasonable for EPA to consider NAWQA data in assessing the likelihood that carbofuran residues may be present in surface water. Moreover, the record is clear that, even though EPA considered the NAWQA data, it placed primary emphasis on the carbofuran levels detected in post-treatment SDWA monitoring.

(vii) Should EPA consider FMC's newly-proposed terms of registration for carbofuran? The objection is denied because it is based on FMC's newly proposed revisions to its carbofuran registration that were submitted after publication of the final tolerance revocation rule and is thus irrelevant to this proceeding. An additional ground for denial of this objection and hearing request is that Petitioners proferred no evidence to support their allegation that these proposed requirements would be effective in limiting carbofuran exposure to the extent claimed

(viii) Should EPA have used the NMC CRA surface water estimates in assessing exposure to carbofuran in surface water? Petitioners object to EPA's surface water exposure estimates on the ground that they are inconsistent with the estimates EPA developed for purposes of the NMC CRA. This hearing request is denied because there are no factual matters in dispute; rather, the only question is a legal one of whether it was inappropriate for EPA to use different approaches to assessing surface water exposure for the carbofuran surface water assessment and the cumulative assessment of surface water exposure for NMCs (40 CFR 178.32(b)(1)). In addition, this issue was raised in Petitioners' comments on the proposed revocation. In the final revocation, EPA explained how the substantial differences between a cumulative risk assessment for a class of pesticides and a risk assessment for a single pesticide necessitate different approaches. Petitioners have not challenged the substance of EPA's response to their comments or submitted evidence that calls the substance of EPA's final rule conclusions into question, and the objection and associated hearing request is therefore immaterial (40 CFR 178.32(b)(3)). Finally, on multiple grounds, Petitioners' evidentiary proffer is insufficient to support a conclusion that there is a reasonable possibility that the issue could be resolved in their favor. Petitioners' objection on this subissue is denied for essentially the same reasons explained in the final tolerance revocation.

(ix) Has EPA taken natural surface water pH conditions into account? The Petitioners contend that the PCT levels guaranteed by the recently proposed use tracking system, along with natural surface water pH conditions in the areas included under the revised label will ensure that potential exposures are *de minimis*. Because this objection is inextricably intertwined with FMC's newly-proposed FIFRA registration amendments, it is denied as irrelevant to this proceeding.

Even assuming Petitioners' allegation concerning soil pH can be separated from the proposed registration amendments, Petitioners' claims are insufficient to justify the action urged (40 CFR 178.32(b)(3)). Petitioners admit that their pH analyses explicitly only capture 95% of surface waters. Because EPA cannot ignore the other 5% of surface water, this information, even if established, would provide an insufficient basis on which EPA could reasonably conclude that the drinking water exposures would be ''safe.'' Additionally, the proffered evidence for this objection is untimely because although the effects of pH were clearly discussed in the proposed rule, Petitioners' claim and the analyses supporting it were not submitted during the comment period.

For the same reasons, the Petitioners' objection is denied.

(x) Has EPA taken the effect of existing drinking water treatment systems into account? The Petitioners contend that, in the areas where carbofuran use is allowed under revised labels, the majority of the total population is protected from carbofuran by water treatment systems and that the rest of the population is protected by Petitioners' newly-proposed FIFRA registration amendments. Because this objection is inextricably intertwined with FMC's newly-proposed FIFRA registration amendments, it is denied as irrelevant to this proceeding.

Separating out the allegations that are independent from the new registration amendments, EPA denies this hearing request on the grounds that Petitioners' claims are insufficient to justify the action urged (40 CFR 178.32(b)(3)) in that they would fail to justify a conclusion that the carbofuran tolerances are safe. The fact that the majority of people are protected is irrelevant if major identifiable subpopulations are not. Further, both the objection and the proffered evidence are untimely because Petitioners' claims and analyses supporting them were not submitted during the comment period. For the same reasons, this objection is denied.

c. Recovery Time Objection—(i) Subissue: Has EPA overstated risk through its approach to considering recovery time to the effects of carbofuran? For carbofuran, EPA estimated acute dietary exposure for the acute risk assessment by summing exposure over a 24-hour period. Because humans are likely to recover in a relatively short time period from any single carbofuran exposure, EPA also undertook a more sophisticated exposure assessment that took recovery time into effect. This more sophisticated analysis was not substituted for the 24-hour assessment approach but rather was used to evaluate whether the 24-hour approach substantially overstated risk. The reason for not simply adopting the assessment incorporating recovery time was based on concerns that other aspects of its exposure model tend to understate exposure. If the assessment using recovery time had suggested that carbofuran risks may be acceptable, EPA would have further examined how exposure should be assessed. However, because both the assessment based on 24-hour exposure and the one incorporating recovery time showed carbofuran exposures significantly exceed the safe level, EPA concluded that its exposure assessment was reasonable. Further supporting this conclusion was the fact that various other analyses showed that a single eating occasion could result in excessive risk to infants. Petitioners have objected to this approach claiming that recovery time should be included in EPA's ''primary'' risk assessment.

EPA is denying this hearing request on two grounds. First, the objection fails

to present a disputed issue of material fact because EPA did incorporate recovery time into its analysis. Rather, Petitioners' only challenge is to whether EPA should have only presented risk estimates that accounted for recovery. This is a policy issue, and hearings are not appropriate on such (40 CFR 178.32(b)(1)).

Second, the fact that EPA relied on 24-hour aggregate exposures in addition to analyses that accounted for recovery is not material, because even though accounting for recovery resulted in a 2–3X reduction in exposure estimates, many of EPA's estimates for aggregate exposures ranged between 2700% aPAD and 9400% aPAD for infants. Accounting for recovery does not, therefore, demonstrate that aggregate exposures will be safe for infants. Of greater significance in this regard is EPA's finding that infants are at risk from a single exposure. Recovery is only relevant, by definition, where the risk is derived from multiple exposures over time.

Petitioners' objection to EPA's policy decision to present acute risks in terms of 24 hours of exposure is denied because EPA's policy approach here is reasonable. For the reasons explained in Unit VI.G, there are several factors that may cause EPA's exposure/risk model to either understate or overstate exposure/risk. It is unreasonable to present risks only incorporating factors that tend to reduce exposure/risk estimates (*e.g.,* recovery time), as Petitioners suggest. EPA's approach of evaluating the impact that these factors may have on the risk assessment is an appropriate method of taking all relevant factors into account.

(ii) Subissue: Did EPA err in calculating carbofuran half-lives? In the proposed rule, EPA used half-lives of 150 minutes and 300 minutes, based on calculations derived for the NMC CRA. In the final rule, EPA calculated half-lives specific to carbofuran to ensure that its analyses accurately reflected carbofuran's risk. Petitioners contend that EPA's calculation of carbofuran half-lives of 186 minutes and 426 minutes were flawed, and that the data instead support the use of a 150-minute half-life.

Petitioners' hearing requests on this subissue are denied for two reasons. First, Petitioners have not provided the underlying analyses conducted in support of their claims that the appropriate half-life for carbofuran is 150 minutes, rather than the 186 or 426 minutes that EPA calculated. Petitioners' evidentiary proffer thus consists of no more than mere allegations and denials. Hearings will not be granted on this basis (40 CFR 178.32(b)(2)).

Further, the issue of the appropriate half-lives for carbofuran is not material. Petitioners have proffered no evidence to show that reliance on a 150-minute half-life rather than a 186-minute half-life would make a significant difference to their estimates. By contrast, in the risk assessment supporting the final rule, EPA's estimates show that the use of a 150-minute or 186-minute half-life makes little or no difference. In addition, EPA's final risk assessment found that infants are at risk from a single exposure. Recovery is only relevant, by definition, where the risk is derived from multiple exposures over time.

EPA denies Petitioners' objection on this subissue because the evidence submitted fails to establish their allegations, or to rebut the data and analyses discussed in the final rule.

d. Human Study Objection—Issue: Did EPA reasonably conclude that a human toxicity study with carbofuran was barred from EPA consideration by the Human Research Rule? In conducting its dietary risk assessment for carbofuran, EPA relied on toxicity data conducted with rats, and applied the default 10X interspecies factor to account for the potential uncertainty in extrapolating from animal data to humans. Petitioners object to the decision to use a 10X interspecies factor claiming that data from a human toxicity study (Arnold) provides a basis for reducing this factor to 3X. However, EPA has previously determined that the Arnold study lacks scientific validity and thus may not be considered by the Agency under EPA's Human Research rule. That decision was based on the advice of the HSRB, which found the Arnold study to constitute ''poor science'' (Ref. 38 at 11).

Although Petitioners have made a number of arguments in support of adopting a 3X interspecies factor, all of the arguments rely on consideration of the Arnold study. Thus, as a preliminary matter, Petitioners must show that a hearing is appropriate based exclusively on whether EPA erred in determining that the Arnold study cannot be considered under the Human Research rule or, that even if a hearing is not warranted, that EPA's decision under the Human Research rule was incorrect.

Petitioners have proffered no evidence that merits a hearing on EPA's application of the Human Research rule to the Arnold study. As an evidentiary proffer, Petitioners claim (1) that review of the Arnold study under the Human Research rule was too narrow in that it did not consider the Arnold study in light of the animal data; (2) that insufficient weight was given prior independent reports on the value of the Arnold study; (3) that the ''technical'' concerns raised by the HSRB are addressed by ''the data within the study'' and that these ''technical'' deficiencies do not render the Arnold study unreliable. The first proffer is not material because the availability of animal data does not address the validity of the Arnold human study. At bottom, this issue involves a challenge to the policy underlying the Human Research rule that allows only limited consideration of human toxicity studies. A hearing is not appropriate on such a policy issue, nor on the Human Research rule itself. Petitioners' second proffer is a legal/policy question regarding the weight to be accorded to existing peer review reports. No hearing is required on such issues. To the extent the third proffer even constitutes a proffer of ''evidence,'' it fails because it is nothing more than a mere allegation. Petitioners have supplied no information as to how the HSRB's ''technical'' concerns are resolved by the study itself.

Viewed on their merits, these claims do not convince EPA that it erred in determining that the Arnold study did not meet the Human Research rule because it lacked scientific validity. EPA concluded, based on the advice of the HSRB, that, because the Arnold study had an extremely small sample size (2 persons per dose) and highly variable measurement of RBC and plasma AChE, it had no scientific value. The claim by Petitioners that somehow the Arnold study could be rehabilitated by considering it in the context of carbofuran animal data misunderstands the issue. The question under the Human Research rule is whether the human study at issue is scientifically valid. Here, EPA found the Arnold study to be flawed at its core. Animal data on carbofuran are simply irrelevant to the problems with sample size and AChE measurement in the Arnold study. As to the earlier reports on the Arnold study, Petitioners have provided no reason as to why these should outweigh the HSRB's conclusion concerning whether the Arnold study met the Human Research rule standard. The earlier reports were completed well before the Human Research rule was promulgated and thus could not have addressed the rule's requirements. Further, the earlier reports identified the same defects, but concluded that the Arnold's study's flaws could be addressed by the use of additional safety

factors—an option not available under the Human Research rule. In such circumstances, it was reasonable for EPA to give primary weight to the HSRB findings. Petitioners' claim that the HSRB only identified ''technical'' problems with the Arnold study and that the study itself addresses the HSRB's concerns is without basis. The flaws in the Arnold study are not technical but fundamental, and cannot be explained away. Finally, Petitioners' allegations that EPA hampered the HSRB's consideration of the prior peer review reports and that EPA's recusal decision was somehow improper are contradicted by the record. Accordingly, the objection is denied.

e. Import Tolerance Objection—Issue: Did EPA err by failing to retain the carbofuran tolerances that apply solely to imported food. Whether EPA had some type of independent duty to retain carbofuran tolerances for the imported foods bananas, rice, coffee, and sugarcane despite its finding that aggregate exposure to carbofuran is unsafe, is a legal question. Hearings are not held on legal issues. Having found that aggregate exposure to carbofuran is unsafe, EPA was clearly warranted, if not required, to revoke all tolerances. For the policy reasons identified above, (see Unit VI.I), when aggregate risk to a pesticide is unsafe, EPA defers to interested parties to decide in the first instance what tolerances, if any, they wish to retain. Although explicitly invited to do so, no person submitted a comment on the proposed revocation that identified the import tolerances as a subset of tolerances that were asserted to be safe, and that the commenter wished to retain. Accordingly, this objection is denied.

K. Conclusion

For all of the reasons set forth above, EPA denies the Petitioners' objections and their requests for a hearing on those objections.

VII. Regulatory Assessment Requirements

As indicated previously, this action announces the Agency's final order regarding objections filed under section 408 of FFDCA. As such, this action is an adjudication and not a rule. The regulatory assessment requirements imposed on rulemaking do not, therefore, apply to this action.

VIII. Submission to Congress and the Comptroller General

The Congressional Review Act, (5 U.S.C. 801 *et seq.*), as added by the Small Business Regulatory Enforcement Fairness Act of 1996, does not apply because this action is not a rule for purposes of 5 U.S.C. 804(3).

IX. References

EPA has established an official record for this rulemaking. The official record includes all information considered by EPA in developing this proposed rule including documents specifically referenced in this action and listed below, any public comments received during an applicable comment period, and any other information related to this action, including any information claimed as CBI. This official record includes all information physically located in docket ID number EPA–HQ–OPP–2005–0162, as well as any documents that are referenced in the documents listed below or in the docket. The public version of the official record does not include any information claimed as CBI.

Objections to the Final Order Revoking Tolerances for Carbofuran, and Request for Public Evidentiary Hearing, submitted by National Potato Council, National Corn Growers Association, National Cotton Council, National Sunflower Association, and FMC Corporation. June 30, 2009. EPA–HQ–OPP–2005–0162–0578.

Exhibit 1

- FMC's letter of 9–29–08 and accompanying label amendments.

Exhibit 2

- FMC's letter of 12–24–08 and accompanying label amendments.

Exhibit 3

- FMC's letter of 6–30–09 and accompanying label amendments.

Exhibit 4

- Expert Report: Carbofuran's FQPA Safety Factor and Interspecies Uncertainty Factor by K. Wallace (6 p.)
- 13 published articles on pesticide effect on cholinesterase activity.

Exhibit 5

- Central Nervous System as the Primary Target for Carbofuran's Effects on Lip Smacking by Neal, Williams, & Lamb (3 p.)
- 10 published articles on effects of cholinergic stimulation.

Exhibit 6

- Expert Report: Carbofuran FQPA Safety Factor by K. Wallace (8 p.)
- 9 published articles on HBC versus brain cholinesterase inhibition.

Exhibit 7

- Dose Response Modeling Issue in Carbofuran by Sielken: AChE and BMD Ratios

Exhibit 8

- Dose Response Modeling Issue in Carbofuran by Sielken: Statistical Comparison of AChE Inhibition in RBC and Brain in Rats Exposed to Carbofuran.

Exhibit 9

- Dose Response Modeling Issue in Carbofuran by Sielken: OPP's Estimates of the Half-Life of AChE Recovery.

Exhibit 10

- Reiner, 1971. Spontaneous Reactivation of Phosphorylated and Carbamylated Cholinesterases Bulletin WHO 44, 109–112.

Exhibit 11

- Carbofuran Dietary Risk Assessment. 2009. (Exponent Inc., for FMC)

Exhibit 12

- Williams, Cheplick, Engle, Fawcett and Hoogeweg. 2009. National Carbofuran Leaching Assessment. Vol 1. Waterborne Environmental Inc., Engel Consulting, and Fawcett Consulting for FMC.

Exhibit 13

- Williams, Cheplick, Engle, Fawcett and Hoogeweg. 2009. National Carbofuran Leaching Assessment. Vol 2. Setback Analysis. Waterborne Environmental Inc., Engel Consulting, and Fawcett Consulting for FMC.

Exhibit 14

- Memorandum. From: Hoogeweg and Williams, Waterborne, Inc., To: Fuge, Latham and Watkins, LLP. June 30, 2009. Subject: Groundwater pH in selected states.

Exhibit 15

- Williams, Fawcett and Engle. 2009. The Development and Evaluation of a Carbofuran Management Plan to Protect Drinking Water Derived from Surface Water Sources. Waterborne Environmental Inc., for FMC.

Exhibit 16

- Memorandum. From: Hoogeweg and Williams, Waterborne, Inc., To: Fuge, Latham and Watkins, LLP. June 30, 2009. Subject: Surface water pH in selected states.

Exhibit 17

- Memorandum. From: Williams, Waterborne, Inc., To: Fuge, Latham and Watkins, LLP. June 30, 2009. Subject: Water Treatment Assessment in Carbofuran Use States.

Exhibit 18

• Petition of the National Corn Grower's Association, the National Sunflower Association, the National Potato Council, and FMC Corporation to Defer the Effective Date of Certain Tolerance Revocations for Carbofuran.

References

1. Acute oral (gavage) dose range-finding study of cholinesterase depression from carbofuran technical in juvenile (day 11) rats. Hoberman, 2007. MRID 47143703 (unpublished FMC study) EPA–HQ–OPP–2007–1088–0062.

2. Acute oral (gavage) time course study and final report of cholinesterase depression from carbofuran technical in adult and juvenile (day 11 postpartum) rats. Hoberman, 2007. MRID 47143704, 05 (unpublished FMC studies) EPA–HQ–OPP–2007–1088–0063 and –0066.

3. Acute time-course study of carbofuran technical administered by gavage to adult and postnatal day 11 male and female CD (Sprague-Dawley) rats: Tyl, Marr, and Myers. 2005. (Unpublished study received Nov. 14, 2005; prepared by RTI International, RTP, NC; submitted by FMC Corp., Philadelphia, Pa.; FMC Study No: A2005–5982. MRID 46688913. EPA–HQ–OPP–2005–0162–0058.

4. Acute dose-response study of carbofuran technical administered by gavage to adult and postnatal day 11 male and female CD (Sprague-Dawley) rats: Tyl and Myers. 2005. MRID 46688914. EPA–HQ–OPP–2005–0162–0078.

5. Anderson, S. A. (2002). The Toxicokinetics of Peripheral Cholinesterase Inhibition from Orally Administered Carbofuran in Adult Male and Female CD Rats. (Unpublished study received May 15, 2002; prepared by Toxicokinetics Laboratory, RTP, NC; submitted by FMC Corp., Philadelphia, Pa.; FMC Study No: A2001–5379. MRID 456757–01.

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List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

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