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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2002–0302; FRL–8372–5]

Dichlorvos (DDVP); Order Denying NRDC's Objections and Requests for Hearing

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final Order.

SUMMARY: In this order, EPA denies objections to, and requests for hearing on, a prior order denying a petition requesting that EPA revoke all pesticide tolerances for dichlorvos under section 408(d) of the Federal Food, Drug, and Cosmetic Act. The objections and hearing requests were filed on February 1, 2008, by the Natural Resources Defense Council (''NRDC''). The Original petition was also filed by NRDC.

DATES: This order is effective July 23, 2008.

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2002–0302. To access the electronic docket, go to *http://www.regulations.gov*, and search for the docket number. Follow the instructions on the regulations.gov website 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.

FOR FURTHER INFORMATION CONTACT: Susan Bartow, Special Review and Reregistration Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: 703-603-0065; e-mail address: *bartow.susan@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

In this document EPA denies objections and hearing requests by the Natural Resources Defense Council (''NRDC'') concerning EPA's denial of NRDC's petition to revoke pesticide tolerances. 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 those engaged in the following activities:

- Crop production (North American Industrial Classification System (''NAICS'') code 111), e.g., agricultural workers; greenhouse, nursery, and floriculture workers; farmers.
- Animal production (NAICS code 112), e.g., cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS code 311), e.g., agricultural workers; farmers; greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.
- Pesticide manufacturing (NAICS code 32532), e.g., agricultural workers; commercial applicators; farmers; greenhouse, nursery, and floriculture workers; residential users.

This listing is not intended to be exhaustive, but rather to provide 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 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:

CSFII - Continuing Survey of Food Intakes by Individuals
CNS - Central Nervous System
DDVP - dichlorvos
EDSTAC - Endocrine Disruptor Screening and Testing Advisory Committee
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
IRED - Interim Reregistration Eligibility Decision
LOAEL - Lowest Observed Adverse Effect Level
MOE - Margin of Exposure
MRID - Master Record Identification
NOAEL - No Observed Adverse Effect Level
NRDC - Natural Resources Defense Council
OECD - Organisation for Economic Co-operation and Development
PAD - Population Adjusted Dose
ppm - parts per million
RBC - red blood cell
RED - Reregistration Eligibility Decision
RfD - Reference Dose
SDWA - Safe Drinking Water Act
SOP - Standard Operating Procedure
USDA - United Stated Department of Agriculture

II. Introduction

A. What Action Is the Agency Taking?

In this order, EPA denies objections, and requests for a hearing on those objections, to an earlier EPA order, (72 FR 68662 (December 5, 2007)), denying a petition to revoke all tolerances established for the pesticide dichlorvos (''DDVP'') under the Federal Food, Drug, and Cosmetic Act (''FFDCA''), 21 U.S.C. 346a. (Refs. 1 and 2). Both the objections and hearing requests, as well as the petition, were filed with EPA by NRDC.

NRDC's petition, filed on June 2, 2006, pursuant to FFDCA section 408(d)(1), asserted numerous grounds as to why the DDVP tolerances allegedly fail to meet the FFDCA's safety standard. This petition was filed as EPA was completing its reassessment of the safety of the DDVP tolerances pursuant to FFDCA section 408(q). (Ref. 3). In response to the petition, EPA undertook an extensive review of its DDVP safety evaluation in the tolerance reassessment decision. Based on certain concerns raised by NRDC, EPA determined it was necessary to incorporate updated data on numerous points and to adopt revised and more conservative assumptions, in its DDVP risk assessments. This led to complete revisions of both EPA's assessments of

dietary and residential risks from exposure to DDVP. (72 FR at 68678, 68687-68691). Nonetheless, EPA concluded that its revised risk assessments demonstrated that DDVP met the FFDCA safety standard and, therefore, denied the petition. (Id. at 68695). EPA's denial was issued in the form of an order under FFDCA section 408(d)(4)(iii). (21 U.S.C. 346a(d)(4)(iii)).

NRDC then filed objections with EPA to the petition denial order and requested a hearing on its objections. These objections and hearing requests were filed pursuant to the procedures in the FFDCA section 408(g)(2). (21 U.S.C. 346a(g)(2)). The objections narrowed NRDC's claims to two main topics - that, in assessing the risk to DDVP, EPA unlawfully reduced the statutory safety factor for the protection of infants and children and EPA unlawfully relied on a human toxicity study. As to these claims, NRDC largely repeats the arguments as presented in its petition without addressing EPA's substantial revisions to the DDVP risk assessment and proffers little to no evidence in support of its requests for a hearing. After carefully reviewing the objections and hearing requests, EPA has determined that NRDC's hearing requests do not satisfy the regulatory requirements for such requests and that its substantive objections are without merit. Therefore, EPA, in this final order, denies NRDC's objections and its requests for a hearing on those objections.

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

NRDC petitioned to revoke the DDVP tolerances pursuant to the petition procedures in FFDCA section 408(d)(1). (21 U.S.C. 346a(d)(1)). Under section 408(d), EPA may respond to such a petition by either issuing a final or proposed rule modifying or revoking the tolerances or issuing an order denying the petition. (21 U.S.C. 346a(d)(4)). Here, EPA responded by issuing an order under section 408(d)(4)(iii) denying the petition. (72 FR 68622 (December 5, 2007)).

Orders issued under section 408(d)(4)(iii) are subject to a statutorily-created administrative review process. (21 U.S.C. 346a(g)(2)). Any person may file objections to a section 408(d)(4)(iii) order with EPA and request a hearing on those objections. (Id.). EPA is required by section 408(g)(2)(C) to issue a final order resolving the objections to the section 408(d)(4)(iii) order. (21 U.S.C. 346a(g)(2)(C)).

III. Statutory and Regulatory Background

In this Unit, EPA provides background on the relevant statutes and regulations governing NRDC's objections and requests for hearing as well as on pertinent Agency policies and practices. As noted, NRDC's objections and requests for hearing raise two main claims: (1) that EPA has unlawfully failed to retain the full tenfold safety factor for the protection of infants and children; and (2) that it was unlawful for EPA to rely on a toxicity study for DDVP that was conducted with humans. The children's safety factor claim is based on assertions regarding DDVP's potential endocrine effects and the adequacy of EPA's data and risk assessments pertaining to exposure to DDVP in food as a result of the use of DDVP (and similar pesticides) in agriculture or food storage and through use of DDVP in residential settings. The human studies claim involves a challenge to the EPA regulation governing reliance on human studies as well as to EPA's application of that rule to a particular human study. The human study in question measured cholinesterase inhibition in humans resulting from administration of DDVP. Background information on each of these topics is included in this Unit.

Unit III.A. summarizes the requirements and procedures in section 408 of the FFDCA and applicable regulations pertaining to pesticide tolerances, including the procedures for petitioning for revocation of tolerances and challenging the denial of such petitions and the substantive standards for evaluating the safety of pesticide tolerances. This unit also discusses the closely-related statute under which EPA regulates the sale, distribution, and use of pesticides, the Federal Insecticide, Fungicide, and Rodenticide Act (''FIFRA''), (7 U.S.C. 136 *et seq.*).

Unit III.B. provides an overview of EPA's risk assessment process. It contains an explanation of how EPA identifies the hazards posed by pesticides, how EPA determines the level of exposure to pesticides that pose a concern (''level of concern''), how EPA measures human exposure to pesticides, and how hazard, level of concern conclusions, and human exposure estimates are combined to evaluate risk. Further, this unit presents background information on two Agency policies with particular relevance to this action, EPA's policy with regard to the statutory safety factor for the protection of infants and children and its policy with regard to cholinesterase inhibition.

Unit III.C. summarizes EPA's program for implementing the statutory requirement to screen pesticides for potential endocrine effects. Unit III.D. describes the EPA regulation on use of human studies.

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 estrogenic substances screening program. (Public Law 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 which 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*. A pesticide tolerance may only be promulgated by EPA if the tolerance is ''safe.'' (21 U.S.C. 346a(b)(2)(A)(i)). ''Safe'' is defined by the statute 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.'' (21 U.S.C. 346a(b)(2)(A)(ii)). Section 408(b)(2)(D) directs EPA, in making a safety determination, to:

consider, among other relevant factors- ...

(v) available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity;

(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;

(viii) such information as the Administrator may require on whether the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects. ...

(21 U.S.C. 346a(b)(2)(D)(v), (vi) and (viii)).

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; and

(III) available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity. ...

(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 established, amended, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, amend, or revoke a tolerance by means of filing a petition with EPA. (See 21 U.S.C. 346a(d)(1)). EPA publishes in the **Federal Register** a notice of the petition filing and requests public comment. (21 U.S.C. 346a(d)(3)). After reviewing the petition, and any comments received on it, EPA may issue a final rule establishing, amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition. (21 U.S.C. 346a(d)(4)).

Once EPA takes final action on the petition by either establishing, amending, or revoking the tolerance or denying the petition, any person may file objections with EPA and seek an evidentiary hearing on those objections. (21 U.S.C. 346a(g)(2)). 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, 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)). EPA's final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

4. *Tolerance reassessment and FIFRA reregistration.* 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'').

5. *Estrogenic substances screening program.* The FQPA also imposed requirements regarding creation of an estrogenic substances screening program. Section 408(p) gives EPA 2 years from enactment of the FQPA to ''develop a screening program ... to determine whether [pesticide chemicals and certain other substances] may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate.'' (21 U.S.C. 346a(p)(1)). This screening program must use ''appropriate validated test systems and scientifically relevant information.'' (Id.). Once the program is developed, EPA is required to take public comment and seek independent scientific review of it. Following the period for public comment and scientific review, and not later than 3 years following enactment of the FQPA, EPA is directed to ''implement the program.'' (21 U.S.C. 346a(p)(2)).

The scope of the estrogenic screening program was expanded by an amendment to the Safe Drinking Water Act (''SDWA'') passed contemporaneously with the FQPA. That amendment gave EPA the authority to provide for the testing, under the FQPA estrogenic screening program, ''of any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance.'' (42 U.S.C. 300j-17).

B. EPA Risk Assessment for Tolerances—Policy and Practice

1. *The safety determination - risk assessment.* To assess 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 ''level of concern'' with respect to human exposure to the pesticide; (3) estimation of human exposure to the pesticide; and (4) characterization of risk posed to humans by the pesticide based on comparison of human exposure to the level of concern.

a. *Hazard identification.* In evaluating toxicity or hazard, EPA reviews toxicity studies, primarily in laboratory animals,

to identify any adverse effects on the test subjects. Animal studies typically involve investigating a broad range of endpoints including gross and microscopic effects on organs and tissues, functional effects on bodily organs and systems, effects on blood parameters (such as red blood cell count, hemoglobin concentration, hematocrit, and a measure of clotting potential), effects on the concentrations of normal blood chemicals (including glucose, total cholesterol, urea nitrogen, creatinine, total protein, total bilirubin, albumin, hormones, and enzymes such as alkaline phosphatase, alanine aminotransfersase and cholinesterases), and behavioral or other gross effects identified through clinical observation and measurement. EPA examines whether adverse effects are caused by either short-term (e.g., ''acute'') or longer-term (e.g., ''chronic'') pesticide exposure and the effects of pre-natal and post-natal exposure in animals.

EPA also considers whether the adverse effect has a threshold - a level below which exposure has no appreciable chance of causing the adverse effect. For non-threshold effects, EPA assumes that any exposure to the substance increases the risk that the adverse effect may occur. At present, EPA only considers one adverse effect, the chronic effect of cancer, to potentially be a non-threshold effect. (Ref. 4 at 8-9). Not all carcinogens, however, pose a risk at any exposure level (i.e., ''a non-threshold effect or risk''). Advances in the understanding of the mode of action of carcinogenesis have increasingly led EPA to conclude that some pesticides that cause carcinogenic effects in animal studies only cause such effects above a certain threshold of exposure. EPA has traditionally considered non-cancer adverse effects on the endocrine system to be threshold effects; that determination is being reexamined in conjunction with the endocrine disruptor screening program.

b. *Level of concern/dose-response analysis*. 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). EPA follows differing approaches to identifying a level of concern for threshold and non-threshold hazards.

i. *Threshold effects*. In examining the dose-response relationship for a pesticide's threshold effects, EPA evaluates an array of toxicity studies on the pesticide. In each of these studies, EPA attempts to identify the lowest observed adverse effect level (''LOAEL'') and the next lower dose at which there are no observed adverse affect levels (''NOAEL''). Generally, EPA will use the lowest NOAEL from the available studies as a starting point (called ''the Point of Departure'') in estimating the level of concern for humans. (Ref. 4 at 9 (The Point of Departure ''is simply the toxic dose that serves as the 'starting point' in extrapolating a risk to the human population.'')). At times, however, EPA will use a LOAEL from a study as the Point of Departure when no NOAEL is identified in that study and the LOAEL is close to, or lower than, other relevant NOAELs. The Point of Departure is in turn used in choosing a level of concern. EPA will make separate determinations as to the Points of Departure, and correspondingly levels of concern, for both short and long exposure periods as well as for the different routes of exposure (oral, dermal, and inhalation).

In estimating and describing the level of concern, the Point of Departure is at times used differently depending on whether the risk assessment addresses dietary or non-dietary exposures. For dietary risks, EPA uses the Point of Departure to calculate an acceptable level of exposure or reference dose (''RfD''). The RfD is calculated by dividing the Point of Departure by all applicable safety or uncertainty factors. Typically, EPA uses a baseline safety/uncertainty factor equal to 100. That value includes a factor of ten (''10X'') where EPA is using data from laboratory animals to reflect potentially greater sensitivity in humans than animals and a factor of 10X to account for potential variations in sensitivity among members of the human population as well as other unknowns. Additional safety factors may be added to address data deficiencies or concerns raised by the existing data. Under the FQPA, an additional safety factor of 10X is presumptively applied to protect infants and children, unless reliable data support selection of a different factor. This FQPA additional safety factor largely replaces pre-FQPA EPA practice regarding additional safety factors. (Ref. 5 at 4-11).

In implementing FFDCA section 408, EPA's Office of Pesticide Programs, 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 FQPA safety factor that does not correspond to one of the traditional additional safety factors used in general Agency risk assessments. (Ref. 5 at 13-16). 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. Today, RfDs and PADs are generally calculated for both acute and chronic dietary risks although traditionally a RfD or PAD was only calculated for chronic dietary risks. Throughout this document general references to EPA's calculated safe dose are denoted as a RfD/PAD.

For non-dietary, and combined dietary and non-dietary, risk assessments of threshold effects, the toxicological level of concern is not expressed as a RfD/PAD but rather in terms of an acceptable (or ''target'') margin of exposure (''MOE'') between human exposure and the Point of Departure. The ''margin'' of interest is the ratio between human exposure and the Point of Departure which is calculated by dividing human exposure into the Point of Departure. An acceptable MOE is generally considered to be a margin at least as high as the product of all applicable safety factors for a pesticide. For example, if a pesticide needs a 10X factor to account for inter-species differences, 10X factor for intra-species differences, and 10X factor for the FQPA children's safety provision, the safe or target MOE would be a MOE of at least 1,000. What that means is that for the pesticide to meet the safety standard, human exposure to the pesticide would have to be at least 1,000 times smaller than the Point of Departure. Like RfD/PADs, specific target MOEs are selected for exposures of different durations. For non-dietary exposures, EPA typically examines short-term, intermediate-term, and long-term exposures. Additionally, target MOEs may be selected based on both the duration of exposure and the various routes of non-dietary exposure - dermal, inhalation, and oral.

ii. *Non-threshold effects*. For risk assessments for non-threshold effects, EPA does not use the RfD/PAD or MOE approach to choose a level of concern if quantification of the risk is deemed appropriate. Rather, EPA calculates the slope of the dose-response curve for the non-threshold effects from relevant studies using a linear, low-dose extrapolation model that assumes that any amount of exposure will lead to some degree of risk. This dose-response

analysis will be used in the risk characterization stage to estimate the risk to humans of the non-threshold effect. Linear, low-dose extrapolation is typically used as the default approach for estimating the risk to carcinogens, unless there are mode of action data indicating a threshold response (or nonlinearity).

c. *Estimating human exposure*. Risk is a function of both hazard and exposure. Thus, equally important to the risk assessment process as determining the hazards posed by a pesticide and the toxicological level of concern for those hazards is estimating human exposure. Under FFDCA section 408, EPA is concerned not only with exposure to pesticide residues in food but also exposure resulting from pesticide contamination of drinking water supplies and from use of pesticides in the home or other non-occupational settings. (See 21 U.S.C. 346a(b)(2)(D)(vi)).

i. *Exposure from food*. There are two critical variables in estimating exposure in food: (1) The types and amount of food that is consumed; and (2) the residue level in that food. Consumption is estimated by EPA based on scientific surveys of individuals' food consumption in the United States conducted by the USDA. (Ref. 4 at 12). Information on residue values comes from a range of sources including crop field trials, data on pesticide reduction (or concentration) due to processing, cooking, and other practices, information on the extent of usage of the pesticide, and monitoring of the food supply. (Id. at 17).

In assessing exposure from pesticide residues in food, EPA, for efficiency's sake, follows a tiered approach in which it, in the first instance, assesses exposure using the worst case assumptions that 100 percent of the crop in question is treated with the pesticide and 100 percent of the food from that crop contains pesticide residues at the tolerance level. (Id. at 11). When such an assessment shows no risks of concern, a more complex risk assessment is unnecessary. By avoiding a more complex risk assessment, EPA's resources are conserved and regulated parties are spared the cost of any additional studies that may be needed. If, however, a first tier assessment suggests there could be a risk of concern, EPA then attempts to refine its exposure assumptions to yield a more realistic picture of residue values through use of data on the percent of the crop actually treated with the pesticide and data on the level of residues that may be present on the treated crop. These latter data are used to estimate what has been traditionally referred to by EPA as ''anticipated residues.''

Use of percent crop treated data and anticipated residue information is appropriate because EPA's worst-case assumptions of 100 percent treatment and residues at tolerance value significantly overstate residue values. There are several reasons this is true. First, all growers of a particular crop would rarely choose to apply the same pesticide to that crop; generally, the proportion of the crop treated with a particular pesticide is significantly below 100 percent. (70 FR 46706, 46731 (August 10, 2005)). Second, the tolerance value represents a high end or worst case value. Tolerance values are chosen only after EPA has evaluated data from experimental crop field trials in which the pesticide has been used in a manner, consistent with the draft FIFRA label, that is likely to produce the highest residue in the crop in question (e.g., maximum application rate, maximum number of applications, minimum pre-harvest interval between last pesticide application and harvest). (Refs. 4 and 6). These crop field trials are generally conducted in several fields at several geographical locations. (Id. at 5, 7 and Tables 1 and 5). Several samples are then gathered from each field and analyzed. (Id. at 53). Generally, the results from such field trials show that the residue levels for a given pesticide use will vary from as low as non-detectable to measurable values in the parts per million (''ppm'') range with the majority of the values falling at the lower part of the range. (70 FR at 46731). EPA uses a statistical procedure to analyze the field trial results and identify the upper bound of expected residue values. This upper bound value is used as the tolerance value. (Ref. 7). There may be some commodities from a treated crop that approach the tolerance value where the maximum label rates are followed, but most generally fall significantly below the tolerance value. If less than the maximum legal rate is applied, residues will be even lower. Third, residue values in the field do not take into account the lowering of residue values that frequently occurs as a result of degradation over time and through food processing and cooking.

EPA uses several techniques to refine residue value estimates. (Ref. 4 at 17-28). First, where appropriate, EPA will take into account all the residue values reported in the crop field trials, either through use of an average or individually. Second, EPA will consider data showing what portion of the crop is not treated with the pesticide. Third, data can be produced showing pesticide degradation and decline over time, and the effect of commercial and consumer food handling and processing practices. Finally, EPA can consult monitoring data gathered by the FDA, the USDA, or pesticide registrants, on pesticide levels in food at points in the food distribution chain distant from the farm, including retail food establishments.

Another critical component of the exposure assessment is how data on consumption patterns are combined with data on pesticide residue levels in food. Traditionally, EPA has calculated exposure by simply multiplying average consumption by average residue values for estimating chronic risks and high-end consumption by maximum residue values for estimating acute risks. Using average residues is a realistic approach for chronic risk assessment due to the fact that variations in residue levels and consumption amounts average out over time. Using average values is inappropriate for acute risk assessments, however, because in assessing acute exposure situations it matters how much of each treated food a given consumer eats and what the residue levels are in the particular foods consumed. Yet, using maximum residue values for acute risk assessment tends to greatly overstate exposure because it is unlikely that a person would consume at a single meal multiple food components bearing high-end residues. To take into account the variations in short-term consumption patterns and food residue values for acute risk assessments, EPA has more recently begun using probabilistic modeling techniques for estimating exposure when more simplistic models appear to show risks of concerns.

All of these refinements to the exposure assessment process, from use of food monitoring data through probabilistic modeling, can have dramatic effects on the level of exposure predicted, reducing worst case estimates by 1 or 2 orders of magnitude or more. (Ref. 8 at 16-17; 70 FR 46706, 46732 (August 10, 2005).

ii. *Exposure from water*. EPA may use either or both field monitoring data and mathematical water exposure models to generate pesticide exposure 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 specific agricultural or residential pesticide practices and under environmental conditions associated with a sampling design. Although monitoring data can provide a

direct measure of the concentration of a pesticide in water, it does not always provide a reliable estimate of exposure because sampling may not occur in areas with the highest pesticide use, and/or the sampling may not occur when the pesticides are being used.

In estimating pesticide exposure levels in drinking water, EPA most frequently uses mathematical water exposure models. EPA's models are based on extensive monitoring data and detailed information on soil properties, crop characteristics, and weather patterns. (69 FR 30042, 30058-30065 (May 26, 2004)). These models calculate estimated environmental concentrations of pesticides using laboratory data that describe how fast the pesticide breaks down to other chemicals and how it moves in the environment. These concentrations can be estimated continuously over long periods of time, and for places that are of most interest for any particular pesticide. Modeling is a useful tool for characterizing vulnerable sites, and can be used to estimate peak concentrations from infrequent, large storms.

iii. *Residential exposures*. Generally, in assessing residential exposure to pesticides EPA relies on its Residential Standard Operating Procedures (''SOPs''). (Ref. 9). The SOPs establish models for estimating application and post-application exposures in a residential setting where pesticide-specific monitoring data are not available. SOPs have been developed for many common exposure scenarios including pesticide treatment of lawns, garden plants, trees, swimming pools, pets, and indoor surfaces including crack and crevice treatments. The SOPs are based on existing monitoring and survey data including information on activity patterns, particularly for children. Where available, EPA relies on pesticide-specific data in estimating residential exposures.

d. *Risk characterization*. The final step in the risk assessment is risk characterization. In this step, EPA combines information from the first three steps (hazard identification, level of concern/dose-response analysis, and human exposure assessment) to quantitatively estimate the risks posed by a pesticide. Separate characterizations of risk are conducted for different durations of exposure. Additionally, separate and, where appropriate, aggregate characterizations or risk are conducted for the different routes of exposure (dietary and non-dietary).

For threshold risks, EPA estimates risk in one of two ways. Where EPA has calculated a RfD/PAD, risk is estimated by expressing human exposure as a percentage of the RfD/PAD. Exposures lower than 100 percent of the RfD/PAD are generally not of concern. Alternatively, EPA may express risk by comparing the MOE between estimated human exposure and the Point of Departure with the acceptable or target MOE. As described above, the acceptable or target MOE is the product of all applicable safety factors. To calculate the actual MOE for a pesticide, estimated human exposure to the pesticide is divided into the Point of Departure. In contrast to the RfD/PAD approach, the higher the MOE, the safer the pesticide. Accordingly, if the target MOE for a pesticide is 100, MOEs equal to or exceeding 100 would generally not be of concern.

As a conceptual matter, the RfD/PAD and MOE approaches are fundamentally equivalent. For a given risk and given exposure of a pesticide, if exposure to a pesticide were found to be acceptable under an RfD/PAD analysis it would also pass under the MOE approach, and vice-versa. However, for any specific pesticide, risk assessments for different exposure durations or routes may yield different results. This is a function not of the choice of the RfD/PAD or MOE approach but of the fact that the levels of concern and the levels of exposure may differ depending on the duration and route of exposure.

For non-threshold risks (generally, cancer risks), EPA uses the slope of the dose-response curve for a pesticide in conjunction with an estimation of human exposure to that pesticide to estimate the probability of occurrence of additional adverse effects. For non-threshold cancer risks, EPA generally considers cancer risk to be negligible if the probability of increased cancer cases falls within the range of 1 in 1 million. Risks exceeding values within that range would raise a risk concern.

2. *EPA policy on the children's safety factor*. As the above brief summary of EPA's risk assessment practice indicates, the use of safety factors plays a critical role in the process. This is true for traditional 10X safety factors to account for potential differences between animals and humans when relying on studies in animals (inter-species safety factor) and potential differences among humans (intra-species safety factor) as well as the FQPA's additional 10X children's safety factor.

In applying the children's safety factor provision, EPA has interpreted it as imposing a presumption in favor of applying an additional 10X safety factor. (Ref. 5 at 4, 11). Thus, EPA generally refers to the additional 10X factor as a presumptive or default 10X factor. EPA has also made clear, however, that this presumption or default in favor of the additional 10X is only a presumption. The presumption can be overcome if reliable data demonstrate that a different factor is safe for children. (Id.). 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. (Id. at 24-25, 35).

3. *EPA policy on cholinesterase inhibition as a regulatory endpoint*. Cholinesterase 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. 10 at 10).

Acetylcholinesterase is an enzyme that breaks down acetylcholine and terminates its stimulating action in the synapse between nerve cells and target cells. When acetylcholinesterase 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 cholinesterase-inhibiting pesticides such as DDVP. (Ref. 10). The policy focuses on three types of effects associated with cholinesterase-

inhibiting pesticides that may be assessed in animal and human toxicological studies: (1) Physiological and behavioral/functional effects; (2) cholinesterase inhibition in the central and peripheral nervous system; and (3) cholinesterase 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 cholinesterase-inhibiting pesticide.

Clinical signs or symptoms of cholinesterase inhibition in humans, the policy concludes, provide the most direct evidence of the adverse consequences of exposure to cholinesterase-inhibiting pesticides. Nonetheless, as the policy notes, due to strict ethical limitations, studies in humans are ''quite limited.'' (Id. at 19). Although animal studies can also provide direct evidence of cholinesterase inhibition effects, animal studies cannot easily measure cognitive effects of cholinesterase inhibition such as effects on perception, learning, and memory. For these reasons, the policy recommends that ''functional data obtained from human and animal studies should not be relied on solely, to the exclusion of other kinds of pertinent information, when weighing the evidence for selection of the critical effect(s) that will be used as the basis of the RfD or RfC.'' (Id. at 20).

After clinical signs or symptoms, cholinesterase inhibition in the nervous system provides the next most important endpoint for evaluating cholinesterase-inhibiting pesticides. Although cholinesterase 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 anticholinesterase pesticides.'' (Id.). Unfortunately, useful data measuring cholinesterase inhibition in the central and peripheral nervous systems has only been relatively rarely captured by standard toxicology testing, particularly as to peripheral nervous system effects. 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).

Cholinesterase inhibition in the blood is one step further removed from the direct harmful consequences of cholinesterase-inhibiting pesticides. According to the policy, inhibition of blood cholinesterases ''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 cholinesterase data are considered appropriate surrogate measures of potential effects on peripheral nervous system acetylcholinesterase activity in animals, for central nervous system (''CNS'') acetylcholinesterase activity in animals when CNS data are lacking and for both peripheral and central nervous system acetylcholinesterase in humans.'' (Id. at 29). The policy notes that ''there is often a direct relationship between a greater magnitude of exposure [to a cholinesterase-inhibiting pesticide] and an increase in incidence and severity of clinical signs and symptoms as well as blood cholinesterase inhibition.'' (Id. at 30). Thus, the policy regards blood cholinesterase 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 cholinesterase inhibition measured in red blood cell (''RBC'') or blood plasma, the policy states a preference for reliance on RBC acetylcholinesterase 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).

If a measure of cholinesterase inhibition (e.g., RBC cholinesterase) is being considered as a potential adverse effect or surrogate for an adverse effect, the policy advises that the level of inhibition must be critically evaluated ''in the context of both statistical *and* biological significance.'' (Id. at 37) (emphasis in Original). The policy notes that ''[n]o fixed percentage of change (e.g., 20% for cholinesterase enzyme inhibition) is predetermined to separate adverse from non-adverse effects.'' (Id.). Rather, the policy explains that ''OPP's experience with the review of toxicity studies with cholinesterase-inhibiting substances shows that differences between pre- and post-exposure of 20% or more in enzyme levels is nearly always statistically significant and would generally be viewed as biologically significant.'' (Id. at 37-38). The policy recommends that ''[t]he biological significance of statistically-significant changes of less than 20% would have to be judged on a case-by-case basis, noting, in particular the pattern of changes in the enzyme levels and the presence or absence of accompanying clinical signs and/or symptoms.'' (Id. at 38). The policy notes that similar or higher levels of cholinesterase inhibition are used ''in monitoring workers for occupational exposures (even in the absence of signs, symptoms, or other behavioral effects).'' (Id. at 31). For example, the policy points out that the California Department of Health Services requires that workers exposed to toxic chemicals such as organophosphate pesticides be removed from the workplace if ''red blood cell cholinesterase levels show 30% or greater inhibition,'' and that the World Health Organization ''has guidelines with the same RBC action levels (i.e., 30% or greater inhibition).'' (Id.).

C. Endocrine Disruptor Screening Program

The 1996 FQPA and SWDA amendments directed EPA to develop and implement an endocrine screening program. To aid in the design of this program called for in the FQPA and SDWA amendments, EPA created the Endocrine Disruptor Screening and Testing Advisory Committee (''EDSTAC''), which was comprised of members representing the commercial chemical and pesticides industries, federal and state agencies, worker protection and labor organizations, environmental and public health groups, and research scientists. (63 FR 71542, 71544, Dec. 28, 1998). The EDSTAC presented a comprehensive report in August 1998 addressing both the scope and elements of the endocrine screening program. (Ref. 11). The EDSTAC's recommendations were largely adopted by EPA.

As recommended by EDSTAC, EPA expanded the scope of the program from focusing only on estrogenic effects to include other effects on the endocrine system (i.e., androgenic and thyroid effects). (63 FR at 71545). Further, EPA, again on the EDSTAC's recommendation, chose to include both human and ecological effects in the program. (Id.). Finally, based on EDSTAC's recommendation, EPA established the universe of chemicals to be screened to include not just pesticides but also a wide range of other chemical substances. (Id.). As to the program elements, EPA adopted EDSTAC's recommended two-tier approach with the first tier involving screening ''to identify substances that have the potential to interact with the endocrine system'' and the second tier involving testing ''to determine whether the substance causes adverse effects,

identify the adverse effects caused by the substance, and establish a quantitative relationship between the dose and the adverse effect.'' (Id.). Tier 1 screening is limited to evaluating whether a substance is ''capable of interacting with'' the endocrine system, and is ''not sufficient to determine whether a chemical substance may have an effect in humans that is similar to an effect produced by naturally occurring hormones.'' (Id. at 71550). Based on the results of Tier 1 screening, EPA will decide whether Tier 2 testing is needed. Importantly, ''[t]he outcome of Tier 2 is designed to be conclusive in relation to the outcome of Tier 1 and any other prior information. Thus, a negative outcome in Tier 2 will supersede a positive outcome in Tier 1.'' (Id. at 71554-71555).

The EDSTAC provided detailed recommendations for Tier 1 screening and Tier 2 testing. The panel of the EDSTAC that devised these recommendations was comprised of distinguished scientists from academia, government, industry, and the environmental community. (Ref. 11 at Appendix B). As suggested by the EDSTAC, EPA has proposed a battery of short-term *in vitro* and *in vivo* assays for the Tier 1 screening exercise. (63 FR at 71550-71551). Validation of all but one of these assays is complete. As to Tier 2 testing, EPA, on the recommendation of the EDSTAC, has proposed using five longer-term reproduction studies that, with one exception, ''are routinely performed for pesticides with widespread outdoor exposures that are expected to affect reproduction.'' (Id. at 71555). EPA is examining, pursuant to the suggestion of the EDSTAC, modifications to these studies to enhance their ability to detect endocrine effects.

EPA has published a draft list of the first group of chemicals that will be tested under the Agency's endocrine disruptor screening program. (72 FR 33486 (June 18, 2007)). The draft list was produced based solely on the exposure potential of the chemicals and EPA has emphasized that ''[n]othing in the approach for generating the initial list provides a basis to infer that by simply being on this list these chemicals are suspected to interfere with the endocrine systems of humans or other species, and it would be inappropriate to do so.'' (Id.)

D. EPA's Human Research Rule

EPA decisions regarding the ethics of human studies 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 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. 12).

NRDC and other parties have challenged the legality of the Human Research rule. (NRDC v. U.S. EPA, No. 06-0820-ag (2d Cir.)). A decision on this challenge is presently pending before the United States Court of Appeals for the Second Circuit.

IV. Regulatory History of DDVP

A. In General

1. *DDVP use*. Dichlorvos (2, 2-dichlorovinyl dimethyl phosphate), also known as DDVP, is an insecticide used in controlling flies, mosquitoes, gnats, cockroaches, fleas, and other insect pests. (Ref. 3). DDVP is registered for use on agricultural sites; commercial, institutional, and industrial sites; and for domestic use in and around homes. Agricultural and other commercial uses include in greenhouses; mushroom houses; storage areas for bulk, packaged and bagged raw and processed agricultural commodities; food manufacturing/processing plants; animal premises; and non-food areas of food-handling establishments. It is also registered for treatment of cattle, poultry and swine. DDVP is not registered for direct use on any field grown commodities. Currently, there are 27 tolerances listed in 40 CFR 180.235 for DDVP on agricultural (food and feed) crops and animal commodities. DDVP is

applied with aerosols, fogging equipment, and spray equipment, and through use of impregnated materials such as resin strips which result in slow release of the pesticide. The current registrant for the technical active ingredient, DDVP, is Amvac Chemical Corporation (''Amvac'').

2. *DDVP risks*. The following information on the assessment of the risks posed by DDVP is drawn from EPA's decision on the reassessment of DDVP tolerances and its response to NRDC's petition.

DDVP is a chlorinated organophosphate pesticide which inhibits plasma, RBC, and brain cholinesterase in a variety of species. (Ref. 3 at 122-123). Subchronic and chronic oral DDVP exposures to rats and dogs as well as chronic inhalation DDVP exposure to rats resulted in significant decreases in plasma, RBC and/or brain cholinesterase activity. However, DDVP does not cause delayed neurotoxicity in the hen. Repeated, oral subchronic DDVP exposures in male humans were associated with statistically and biologically significant decreases in RBC cholinesterase inhibition. There was no evidence of increased susceptibility to young animals following in utero DDVP exposure to rat and rabbit fetuses as well as pre/post natal DDVP exposure to rats in developmental, reproduction, and comparative cholinesterase studies. Evidence of sensitivity in the young was seen in one parameter, auditory startle amplitude, in a developmental neurotoxicity study; however, the effects in the rat pups here was at levels well above levels which result in RBC cholinesterase inhibition. Cancer studies with DDVP provide suggestive evidence of DDVP's potential human carcinogenicity; however, following the advice of numerous independent scientific panels, EPA has determined that DDVP poses a negligible cancer risk to humans due to the lack of relevance to humans of the tumors identified in the DDVP cancer studies. (72 FR at 68671-68673).

Inhibition of cholinesterase activity was the toxicity endpoint selected to assess hazards for all acute and chronic dietary exposures, as well as short-, intermediate-, and long-term (chronic) dermal, inhalation, and incidental oral residential exposures. Doses selected for the Point of Departure in determining the level of concern - i.e., RfD/PADs and acceptable MOEs - were based on both human and animal studies. (Ref. 3 at 130-135). Animal studies were used in choosing levels of concern for evaluating risk from acute and chronic dietary exposure; acute dermal exposure; and acute and chronic inhalation exposure. A human study was used evaluating risk from short-term incidental oral exposure; short-, intermediate-, and long-term dermal exposure; and short- and intermediate-term inhalation exposure.

Safety factor determinations used in selecting the level of concern differed based on whether EPA relied on one of several different animal studies or a human study. For levels of concerns derived from a Point of Departure from an animal study, EPA generally applied a 100X safety factor (10X for inter-species variability and 10X for intra-human variability). EPA removed the 10X children's safety factor for risk assessments based on an animal study. For levels of concerns derived from a Point of Departure from the human study, EPA applied a 10X safety factor for intra-human variability and a 3X children's safety factor. (Id.).

EPA based its decision to remove the children's safety factor when relying on animal data on its conclusions that (1) the toxicity database was complete; (2) most of the data indicated no sensitivity in the young and the only evidence of sensitivity occurred at levels well above the Points of Departure used for establishing the levels of concern; and (3) its estimate of human exposure to DDVP was not understated. EPA retained a portion of the children's safety factor when relying on the human study because that study did not determine a NOAEL. EPA concluded, however, that reliable data supported reduction of the 10X factor because the effect seen at the LOAEL in that study was so marginal that a lower dose would have been unlikely to detect any adverse effect. (72 FR 68694-68695).

EPA has estimated exposure to DDVP taking into account the potential for DDVP residues in food, drinking water, and in the home as the result of the use of DDVP pest strips. DDVP exposure may result not only from use of DDVP but use of two closely-related pesticides, naled and trichlorfon, which metabolize or degrade to DDVP in food, water, or the environment. In assessing the risks of DDVP, EPA has taken into account exposure to DDVP resulting from use of all three of these pesticides. (Ref. 3 at 147-149). Additionally, DDVP, naled, and trichlorfon are within a family of pesticides known as the organophosphates. EPA has classified the organophosphate pesticides and their common cholinesterase-inhibiting degradates as having a common mechanism of toxicity. Thus, in addition to assessing the risks posed by exposure to organophosphate pesticides individually, EPA has assessed the potential cumulative effects from concurrent exposure to organophosphate pesticides. (Ref. 13).

As discussed in Unit IV.B.1. below, taking all of the above information into account, EPA concluded that the tolerances for DDVP were safe.

B. FFDCA Tolerance Reassessment and FIFRA Pesticide Reregistration

1. *In general*. As required by the FQPA of 1996, EPA reassessed the safety of the DDVP tolerances under the new safety standard established in the FQPA. EPA released for comment a preliminary risk assessment for DDVP in October, 2000. (65 FR 60430 (October 11, 2000)). Subsequently, after consideration of public comment, EPA, on June 30, 2006, issued an Interim Reregistration Eligibility Document (''IRED'') for DDVP. In that document, EPA determined that aggregate exposure to DDVP as a result of use of DDVP, naled, and trichlorfon, complied with the FQPA safety standard. (Ref. 3). Separately, on July 31, 2006, EPA determined that cumulative ffects from exposure to all organophosphate residues were safe. (Ref. 14). In combination, these findings satisfied EPA's obligation to review the DDVP tolerances under the new safety standard.

As a result of the FIFRA reregistration and FFDCA tolerance reassessment process there were numerous changes made to DDVP's registration that affect non-occupational exposure to DDVP. Specifically, on May 9, 2006, EPA received from Amvac, the only registrant of DDVP as a product for manufacturing end-use DDVP products, an irrevocable request to cancel certain uses and include additional pest strip label restrictions on the DDVP active ingredient product labels. Pursuant to section 6(f) of FIFRA, on June 30, 2006, the Agency published a notice in the **Federal Register** that it had received the request and sought comment on EPA's intention to grant the request and cancel the specified uses. (71 FR 37570 (June 30, 2006)). On October 20, 2006, EPA issued the final cancellation order. (71 FR 61968 (October 20, 2006)).

The added restrictions on the use of the pest strip products were approved on October 11, 2006, and provided, among other things, that large pest strips could no longer be used in homes except for garages, attics, crawl spaces, and sheds that are occupied for less than 4 hours per day. The only pest strips permitted for use in occupied areas inside the home were significantly smaller strips for use in closets, wardrobes, or cupboards. Additionally, in early March, 2007, Amvac requested the voluntary cancellation of all its pet

collar and bait registrations and deletion of those uses from its technical label. Pursuant to section 6(f) of FIFRA, Amvac's requests to cancel the pet collar and bait registrations as well as deleting such uses from the technical label were published in the **Federal Register** on March 23, 2007. (72 FR 13786 (March 23, 2007)). On June 27, 2007, EPA issued the final cancellation notice for the pet collar and bait registrations. (72 FR 35235 (June 27, 2007)).

Cancellation of uses and label restrictions imposed on Amvac's registration apply to all formulated DDVP end-use products because it is unlawful to use a pesticide in a manner inconsistent with its label. (7 U.S.C. 136(ee)). This bar on use inconsistent with the label applies to the formulation of end-use pesticide products from manufacturing use products. Accordingly, because Amvac holds the only registration for a DDVP manufacturing use product, the removal of uses and the addition of restrictions with respect to Amvac's manufacturing use product label has the effect of imposing those use cancellations and label restrictions on all DDVP end-use products.

2. *Review of human study.* Completion of the DDVP IRED was delayed, in part, by questions regarding whether it was appropriate for EPA to rely on several human toxicity studies conducted with DDVP which were submitted by Amvac. The study receiving principal attention was a study involving repeated dosing over several days conducted in 1997 by A.J. Gledhill. (Refs. 3 at 133; and 15). That study is identified by the Master Record Identification (''MRID'') number of 44248801. Amvac also cited approximately a dozen other human studies, several of which were also conducted by Gledhill. (Ref. 16).

Following promulgation of the Human Research rule, EPA evaluated whether the human data submitted by Amvac complied with the rule, and, pursuant to the rule's requirements, presented these data and its recommendations to the Human Studies Review Board (''HSRB'') for review. On March 9, 2006, the HSRB published a notice in the **Federal Register** announcing that a public meeting would be held to consider the DDVP studies as well as human studies for several other pesticides. (71 FR 12194 (March 9, 2006)). The meeting was scheduled for April 4-6, 2006. The notice alerted the public of the opportunity to file both written comments with the HSRB and to make oral comments at the April meeting. The members of the HSRB at the time of this meeting are listed in Appendix 1.

NRDC filed written comments with the HSRB concerning DDVP, (Ref. 17), and also presented oral testimony at the public meeting. (Ref. 18). NRDC's comments and oral remarks specifically focused on whether the Gledhill study had sufficient statistical power ''to detect an effect when it may occur'' and the fact that the Gledhill study only used healthy, male test subjects. (Ref. 7 at 13). Other subjects discussed at the meeting included the relative strengths and weaknesses of the Gledhill study such as its repeat dosing regime, the failure to test blood plasma cholinesterase, the failure to monitor subjects after testing, and the study's consent form. (Id.; Ref. 18 at 18, 20-23). On May 23, 2006, the HSRB published a notice in the **Federal Register** alerting the public that it had released a draft report (dated May 16, 2006) and would be holding a public teleconference meeting on June 6, 2006 to discuss its draft report. (71 FR 29624 (May 23, 2006)). The notice included instructions on how members of the public could participate in the teleconference and explained the procedure for providing oral and written comments. (Ref. 19). NRDC did not file comments on the draft report. (Ref. 20).

On June 26, 2006, the HSRB issued its finding that reliance on the Gledhill human study was appropriate given that the study had scientific value and there was no clear and convincing evidence that the study was fundamentally unethical. (Ref. 21). The HSRB concluded that the other DDVP human studies should not be used in the DDVP risk assessment. These findings were unchanged from its May 16, 2006 draft report.

EPA agreed with the findings of the HSRB and relied upon the HSRB's reasoning in using the Gledhill study in its DDVP risk assessment. (72 FR at 68675).

V. NRDC Petition Regarding DDVP

On June 2, 2006, the NRDC filed a petition with EPA which, among other things, requested that EPA: (1) Conclude the DDVP Special Review by August 3, 2006, with a finding that DDVP causes unreasonable adverse effects on the environment; (2) conclude the DDVP FIFRA reregistration process by August 3, 2006, with a finding that DDVP is not eligible for reregistration; (3) submit draft notices of intent to cancel all DDVP registrations to the FIFRA Scientific Advisory Panel and USDA by August 3, 2006, and issue those notices 60 days thereafter; (4) conclude the DDVP tolerance reassessment process by August 3, 2006, with a finding that the DDVP tolerances do not meet the FFDCA safety standard; and (5) issue a final rule by August 3, 2006, revoking all DDVP tolerances. (Ref. 2). Shortly after the petition was filed, on June 30, 2006, EPA released the IRED for DDVP which addressed DDVP's eligibility for reregistration under FIFRA and assessed, in part, whether DDVP's tolerances met the new safety standard enacted by the FQPA. NRDC submitted comments on the IRED and some of these comments bore on issues in its petition. (Ref. 3).

NRDC's petition contained dozens of claims as to why DDVP's registration under FIFRA should be canceled and its FFDCA tolerances revoked. These issues are not presented in detail here because many raised solely FIFRA concerns and NRDC has not pursued most of its tolerance-related claims in its objections and hearing requests.

EPA published notice of the petition for comment on October 11, 2006. (71 FR 59784 (October 11, 2006)). EPA received roughly 1,500 brief comments in support of the petition. These comments added no new information pertaining to whether the tolerances were in compliance with the FFDCA. Detailed comments in opposition to the petition were submitted by Amvac. (Ref. 22).

EPA responded to the petition in three separate documents: (1) It issued an order closing out the DDVP Special Review; (72 FR 72709 (December 21, 2007)); (2) it issued an order denying the request to cancel DDVP's FIFRA registration (72 FR 68581(December 5, 2007)); and (3) it issued an order pursuant to FFDCA section 408(d)(4)(iii) denying the request to revoke DDVP's FFDCA tolerances (78 FR 68662 (December 5, 2007). Today's final order only concerns the objections filed to the section 408(d)(4)(iii) order denying the request to revoke tolerances.

VI. EPA Response to the Petition to Revoke DDVP Tolerances

EPA issued a section 408(d)(4)(iii) order responding to the petition's request to revoke DDVP tolerances on December 5, 2007 (hereinafter referred to as EPA's ''petition response'' or ''petition denial order''). (72 FR 68662 (December 5, 2005). That order denied the petition finding that none of the grounds asserted by NRDC demonstrated that the DDVP tolerances should be revoked. Nonetheless, EPA did conclude that NRDC raised several pertinent concerns with EPA's assessment of the risks posed by DDVP.

To respond to NRDC's concerns, EPA completely revamped both its dietary

and residential risk assessments. In its new risk assessments, EPA included updated information on residue levels of DDVP in food, the amount of usage of DDVP and related pesticides in agriculture, and food consumption patterns of infants and children. EPA also adopted modified and more conservative assumptions regarding exposure patterns to DDVP in residential settings and exposure to DDVP from naled's use to control mosquitoes. Because, however, EPA concluded that the revised risk assessments still showed that the DDVP tolerances are safe, EPA denied NRDC's petition.

EPA's specific responses to the claims in the petition that are relevant to NRDC's objections are summarized in the portion of this order responding to the objections and hearing requests.

VII. NRDC's Objections and Requests for Hearing

On February 1, 2008, NRDC filed, pursuant to FFDCA section 408(g)(2), objections to EPA's denial of its tolerance revocation petition and requested a hearing on those objections. As indicated above, NRDC's objections and requests for hearing raise two main claims: (1) that EPA has unlawfully failed to retain the full 10X safety factor for the protection of infants and children; and (2) that it was unlawful for EPA to rely on a toxicity study for DDVP that was conducted with humans.

NRDC cites three grounds for its assertion that EPA unlawfully lowered the 10X children's safety factor: (1) that EPA lacked adequate data on DDVP's potential effects on the endocrine system; (2) that EPA lacked adequate data on several matters related to assessing dietary exposure to DDVP residues in food; and (3) that EPA has inadequate data on exposure to DDVP from its use in residential pest strips. As to the DDVP human study, NRDC claimed that EPA's regulation concerning use of human studies is unlawful and that the study is scientifically flawed and ethically compromised. In analyzing NRDC's claims, EPA has broken NRDC's two main claims down into 19 separate sub-issues. Each sub-issue is described in detail and responded to separately in Unit VIII.

In support of its request for hearing, NRDC proffered the following documents as evidence that a hearing would be appropriate:

(1) the Interim Reregistration Eligibility Determination for DDVP; (2) the entire record for the IRED and the documents referenced and cited therein; (3) NRDC's comments on the IRED; (4) EPA's petition denial and the references cited in that denial; (5) NRDC's petition and all references cited in the petition; and (6) the arguments, citations, and attachments contained in these objections.

(Ref. 1 at 3) (citations and references to attachments omitted).

VIII. Response to Objections and Requests for Hearing

A. Overview

EPA denies each of NRDC's objections as well as its hearing requests. NRDC's hearing requests fail to meet the statutory and regulatory requirements for holding a hearing. NRDC has failed to proffer evidence on its hearing requests which would, if established, resolve one or more issues in its favor. Rather, NRDC relies on mere allegations and general denials and contentions. Further, many of NRDC's claims do not present genuine and substantial issues of fact and/or are immaterial to the relief requested. On the merits, NRDC's objections are denied for substantially the same reasons given in EPA's petition denial order. NRDC's objections largely restate the claims in its petition. Significantly, NRDC does not acknowledge or respond to the substantial revisions to the DDVP dietary and residential risk assessments made in response to the NRDC petition. Similarly, NRDC does not acknowledge or respond to EPA's detailed summary of why it adopted the conclusion by the independent HSRB that the Gledhill human study complied with EPA's Human Research rule.

The remainder of this Unit is organized in the following manner. Unit VIII.B. describes in greater detail the requirements pertaining to when it is appropriate to grant a hearing request. Unit VIII.C. examines the evidence proffered by NRDC in support of its hearing requests. Units VIII.D. and E. provide EPA's response to the NRDC's objections and hearing requests. Unit VIII.D. addresses NRDC's claims regarding the children's safety factor and subunit E addresses NRDC's arguments concerning reliance on the Gledhill human study. EPA's conclusions on the hearing requests and objections are summarized in Units VIII.F. and G., respectively.

EPA has adopted a 4-part format in Units VIII.D. and E. for explaining its ruling on each of the 19 sub-issues EPA identified in the objections. First, NRDC's 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 NRDC's petition and, if it was presented, EPA's reasons for denying the claim in its earlier petition denial order. 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.
(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.

C. Evidentiary Proffer by NRDC

As noted above, the purpose for holding hearings is ''to receive factual evidence.'' (U.S.C. 346a(g)(2)(B); 53 FR 41126, 41129 (''Hearings are for the purpose of gathering evidence on disputed factual issues . . . .'')). A requestor must identify evidence relied upon to justify a hearing and either submit copies of that evidence or summarize it. (40 CFR 178.27). After reviewing the proffer, EPA must find that there is a reasonable possibility that the proffered evidence, if established, would resolve one or more genuinely-disputed, material factual issues in a requestor's favor. (40 CFR 178.32(b)). Because a substantial portion of NRDC's evidentiary proffer is deficient on its face, EPA finds it most efficient to preliminarily review the proffer before turning to the individual issues raised by NRDC.

As previously mentioned, NRDC proffered the following items as evidence supporting its requests for hearing:

> (1) the Interim Reregistration Eligibility Determination for DDVP; (2) the entire record for the IRED and the documents referenced and cited therein; (3) NRDC's comments on the IRED; (4) EPA's petition denial and the references cited in that denial; (5) NRDC's petition and all references cited in the petition; and (6) the arguments, citations, and attachments contained in these objections.

(Ref. 1 at 3). These items can be divided into two groups: (1) items produced or assembled by EPA (the IRED; the IRED record; and EPA's petition denial); and (2) items produced by NRDC (NRDC's comments on the IRED; NRDC's petition; and NRDC's objections).

The items in the first group - the EPA documents - clearly do not constitute a proper proffer. Essentially, this is a non-specific identification of every document and piece of data EPA has considered and relied upon in the multi-year process of conducting the FIFRA reregistration and FFDCA tolerance reassessment for DDVP and in responding to NRDC's DDVP petition. This could easily encompass hundreds, if not thousands of documents, and tens of thousands of pages of analysis and data. EPA's petition response alone cited 82 documents and those documents generally were EPA analytical papers and not the underlying data. EPA concludes that NRDC's citation to the thousands of pages in the IRED, the IRED record, and the petition denial is so vague a proffer as to not constitute a proffer at all. It would be as if a lawyer, in responding to a court's request for case law authority for a principle he or she was defending, cited the court to West's Federal Reporter, 3rd Series. While somewhere in those hundreds of volumes a case may exist that supports the asserted principle, the lawyer cannot be said to have identified it by a vague wave at a substantial portion of the law library. Further, given that the purpose of a hearing is to gather or receive evidence, proffering evidence already considered and relied upon by EPA would not seem to be grounds for holding a hearing. Finally, as a matter of law, EPA does not understand how it can be argued that a proffer consisting of a general reference to a record of decision which EPA has found supported one result could constitute evidence that if established, would justify the opposite conclusion. At bottom, the proffer of the items in the first group fails to ''identify'' evidence which would, if established, resolve an issue in NRDC's favor.

NRDC's second group of documents consists of NRDC's comments on the IRED; NRDC's petition; and NRDC's objections. In analyzing this proffer, EPA has focused on NRDC's objections because the objections appear to contain, almost word-for-word, the arguments and claims put forward in its petition and IRED comments with regard to the children's safety factor and reliance on human studies. The objections reference 16 documents. For the reasons explained below, 10 of these documents can be rejected on their face

as not justifying a hearing. Four of the documents, however, potentially include factual evidence supporting a hearing and are analyzed more thoroughly in connection with the specific issue in the hearing request to which they are tied. The other two documents that are referenced are NRDC's DDVP petition and NRDC's comments on the DDVP IRED. As described above, these documents do not add anything beyond what is in the objections.

1. *Documents that clearly do not proffer evidence of a genuinely-disputed, material issue of fact.* (10 items)

• Five Newspaper Stories. NRDC cites to an Associated Press story from 2002 and four Los Angeles Times stories from 2007. These news stories contain basic background information about DDVP; general contentions from Amvac, NRDC, and EPA regarding the safety of DDVP; and no more than a cursory, passing reference to any of the issues raised in the petition. There can be no serious contention that these articles present evidence justifying a hearing.

• NRDC comments to HSRB. NRDC references the comments it submitted to the HSRB with regard to the HSRB's review of the human studies conducted with DDVP. The comments - three pages of bulleted talking points and one graph - are a summary of the slightly more detailed arguments contained in NRDC's objections. This document adds no justification for a hearing not otherwise included in NRDC's objections.

2. *Legal Briefs in NRDC v. EPA, No. 06-0820-ag (2d Cir.).* NRDC cites to its opening and reply briefs in NRDC v. EPA, the case adjudicating NRDC's challenge to EPA's Human Research rule. These briefs contain legal arguments regarding the lawfulness of the Human Research rule. They contain no factual evidence justifying NRDC's DDVP hearing requests.

• Three Law Review Articles. NRDC references: (1) a short article by a NRDC attorney summarizing his legal objections to EPA's Human Research rule; (2) an article concerning EPA's implementation of the FQPA; and (3) an article focusing on how tort law might be used to supplement the FQPA to protect children. None of these articles mention DDVP and no serious contention can be made that they provide factual evidence justifying a hearing.

3. *Documents which may present evidence of a genuinely-disputed, material issue of fact.* (4 items)

• Lockwood Articles. NRDC cites two articles by Dr. Alan Lockwood which discuss science and ethical issues with regard to several human intentional dosing studies involving pesticides. Several of the human studies addressed were DDVP studies, one of which is the Gledhill human study that is the focus of this proceeding. Whether the information presented in these articles supports NRDC's hearing requests is examined in Unit VIII.E.3.a.

• Sass Letters. NRDC cites two letters published in the journal Environmental Health Perspectives co-authored by Dr. Jennifer Sass of NRDC. These letters discuss science and ethical issues with regard to two human studies, including the DDVP human study in question in this proceeding. Whether the information presented in these letters supports NRDC's hearing requests is examined in Unit VIII.E.3.a.

D. Response to Specific Issues Raised in Objections and Hearing Requests - Children's Safety Factor

1. *Failure to support children's safety factor decision with DDVP-specific data*— a. *Objection/hearing request sub-issue.* NRDC asserts that EPA, in choosing a 3X children's safety factor for DDVP, did not rely on reliable data showing that such a factor was safe for infants and children because EPA's choice of 3X ''is not based on any data specific to DDVP.'' (Ref. 1 at 5). NRDC's argument is that EPA erred by not deriving a precise safety factor for DDVP but instead used a value that EPA considered to be half of the 10X safety factor. NRDC claims that ''EPA could not have determined that 'such margin' [i.e., 3X] will be safe, when the replacement safety factor is simply a generic stand-in for EPA's conclusion that 'something less than 10X' is enough.'' (Id.). According to NRDC, EPA should have explained ''what reliable data supports a 3X safety factor in particular, as opposed to 4X or some other number, for DDVP specifically.'' (Id.).

b. *Background.* Similar assertions were made in NRDC's petition and its IRED comments. For example, the petition claimed that ''[t]he Agency did not explain why it chose 3X as opposed to 4X or any other factor,'' (Ref. 2 at 14), and the IRED comments asserted that there was a ''complete lack of explanation'' for EPA's safety factor decisions. (Ref. 23 at 5). Both documents also alleged there were inadequacies in the toxicity and exposure databases. (Refs. 2 at 15, and 38-41; and 23 at 8-9).

In response to these claims by NRDC, EPA, in the petition response, comprehensively restated its reasoning for its decisions on the children's safety factor for DDVP in the IRED. (72 FR at 68694-68695). EPA noted that it had a complete toxicity database for DDVP and it carefully reviewed the evidence regarding the sensitivity of the young to DDVP and explained why an additional safety factor was not needed to protect infants and children. Further, EPA detailed why it had concluded that its exposure assessments would not understate human exposure to DDVP.

For some DDVP risk assessments EPA chose to remove the children's safety factor entirely, and for others EPA reduced the safety factor to 3X. EPA explained that it retained a 3X children's safety for certain assessments because the toxicity study which was relied upon in conducting those risk assessments had not identified a ''no adverse effect level'' (''NOAEL'') in its subjects but rather only a ''lowest adverse effect level'' (''LOAEL''). Despite the failure to identify a NOAEL in the study, EPA concluded that ''a 3X factor'' would be more than adequate to identify a NOAEL based upon the slight adverse effect (marginal RBC cholinesterase inhibition in a human study) observed at the LOAEL.'' (72 FR at 68695). EPA noted that an independent science review board had confirmed that lower doses were unlikely to produce a measurable effect. Finally, EPA explained why it chose 3X instead of 4X or some other value. (Id.). The petition response noted that ''where the data does not warrant a full 10X, EPA generally does not attempt to mathematically derive a precise replacement safety factor because regulatory agencies' traditional use of 10X safety factors (upon which the FQPA safety factor was modeled) was based on rough estimates rather than detailed calculations. Instead, where a 10X factor would clearly overstate the uncertainty, EPA simply applies a factor valued at half of 10X.'' (Id.). EPA explained that it considers 3X to be half of 10X assuming a lognormal distribution of effects. (Id.).

c. *Denial of hearing request.* In analyzing whether a hearing would be appropriate on this sub-issue, it is helpful to break the sub-issue down into three separate, but related, questions: (1) Whether EPA, in selecting a children's safety factor lower than 10X, is required to justify with precision why it chose one factor over another; (2) whether EPA offered a justification for the children's safety factor it chose; and (3) whether EPA relied upon DDVP specific information in choosing a safety factor or instead relied upon ''generic assertions.'' When broken down in this way, it is clear that none of these questions meets the standard for a hearing.

The first question is a pure question of law - does FFDCA section 408(c) require EPA to offer a reasoned explanation for its choice of a children's safety factor, including an explanation as to why a different factor is not needed. A question of fact, not of law, is required to justify a hearing. (40 CFR 178.32(b)(1)).The second and third questions fail to present a matter of genuinely-disputed facts because it is plain on the record that EPA did offer a reasoned justification for its decision and, in that justification, relied upon DDVP-specific facts. EPA's petition response to NRDC's 10X arguments laid out in careful detail information regarding the extent of the toxicity and exposure database on DDVP and the data bearing on DDVP's effects on young animals. (72 FR at 68694-68695 (discussing the completeness of the DDVP toxicity database, DDVP studies bearing on pre- and post-natal toxicity, and the basis for DDVP exposure estimates)). Further, NRDC proffers no evidence - because there is none to proffer - suggesting that EPA did not consider DDVP-specific information in making its children's safety factor decision. Therefore, this question does not meet the standard for a hearing both because there are no genuinely-disputed facts and NRDC has proffered no evidence which, if established, could resolve this issue in its favor. 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.'')

d. *Denial of objection.* EPA agrees with NRDC that general principles of administrative law require it to provide a reasoned explanation for its decision on selection of a children's safety factor. (Baltimore Gas & Electric Co. v. NRDC, 462 U.S. 87, 103 (1983)). EPA disagrees with NRDC, however, to the extent it is suggesting that as part of this reasoned explanation for its selection of a children's safety factor, EPA must show why it did not choose some other mathematical value. Rather, the statute imposes upon EPA, if it decides to vary from the presumptive 10X children's safety factor, the burden to show that any ''different'' safety factor is safe. Once EPA has made that showing, its obligation to offer a reasoned explanation is complete. Because EPA offered a reasoned explanation as to why the children's safety factors it chose protect the safety of infants and children, (72 FR 68694-68695), EPA denies NRDC's objection on this point.

As to the substance of EPA's explanation of why it chose a 3X safety factor for certain DDVP risk assessments, NRDC claims that EPA erred because its choice of 3X is based on ''a generic assertion not [] on any data specific to DDVP.'' (Ref. 1 at 5). NRDC is wrong. The generic assertion NRDC mentions is EPA's explanation of why 3X is half of 10X. EPA's choice of 3X, however, is not based on its conclusion that 3X is half of 10X but on the data in the DDVP human study at issue. As noted above, the petition response explained in detail that a full 10X safety factor was not needed to address the uncertainty raised by the failure of the DDVP human study to identify a NOAEL. The effects seen in that study at the LOAEL were only marginally adverse at best, and therefore, EPA concluded that applying the full 10X safety factor (i.e., dividing the LOAEL by another factor of 10X in addition to the 10X factor for intra-human variability) was more than was needed to address the lack of a NOAEL. The HSRB confirmed as much when it wrote: ''because the decreased activity in RBC cholinesterase activity observed in this study was at or near the limit of what could be distinguished from baseline values, it was unlikely that a lower dose would produce a measurable effect in RBC cholinesterase activity.'' (Ref. 21 at 41).

EPA chose a safety factor of 3X for DDVP based on its conclusion that not only was 10X overprotective but that 3X would be protective given the results seen in the relevant DDVP study. (72 FR at 68695). As EPA concluded in the petition denial order: ''a 3X safety factor would be more than adequate to identify a NOAEL based upon the slight adverse effect (marginal RBC cholinesterase inhibition in a human study) observed at the LOAEL.'' (Id.). Generally, EPA uses a 3X safety factor as the default value when reducing a 10X safety factor. (Refs. 5 at 9-10, 26; and 24 at 4-40 - 4-41;). A safety factor of 3X is deemed to be approximately half the value of a safety factor of an order of magnitude (10X). As EPA explained in the petition denial order:

> In choosing a safety factor in circumstances where the data does not warrant a full 10X, EPA generally does not attempt to mathematically derive a precise replacement safety factor because regulatory agencies' traditional use of 10X safety factors (upon which the FQPA safety factor was modeled) was based on rough estimates rather than detailed calculations. Instead, where a 10X factor would clearly overstate the uncertainty, EPA simply applies a factor valued at half of 10X. In determining half of a 10X factor, EPA assumes that the distribution of effects within the range of a safety factor is distributed lognormally (which is generally the case for biological effects), and reduction of a lognormal distribution by half is equal to half a log (10^{-5}) or approximately 3X. A lognormal distribution is a distribution which if plotted based on the logarithm of each of its values would yield a bell-shaped (normal) distribution but if plotted according to actual values would be skewed having a clumping of values along the vertical axis of the plot.

(72 FR at 68695) (citations omitted).

NRDC does not challenge EPA's reasoning regarding whether the choice of 3X is justified based on the results of a DDVP-specific study and thus, the merits of EPA's DDVP-specific reasoning is not here at issue. Rather, NRDC denies that EPA engaged in DDVP-specific reasoning in choosing 3X. Because NRDC's argument is contradicted on the face of the petition response, it is denied.

2. *Endocrine effects.* As described below, NRDC claims that EPA cannot remove the children's safety factor because it has not completed the endocrine screening program for DDVP under section 408(p) and because EPA has inadequate endocrine data for DDVP. Although NRDC did argue in its petition that EPA cannot make a safety finding without completing the endocrine screening program, it did not assert claims regarding endocrine data and the children's safety factor. EPA has previously ruled that a petitioner may not raise new issues in filing objections to EPA's denial of its Original petition. (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.'')). Accordingly, NRDC's objections and hearing requests as to the children's safety factor and endocrine data are denied.

Even if these claims were properly presented in these objections, for the reasons set forth below they neither entitle NRDC to a hearing nor justify the relief sought.

a. *Endocrine disruptor screening program*—i. *Objection/hearing request sub-issue.* NRDC argues that EPA must retain the 10X children's safety factor because EPA has not fulfilled its obligations under FFDCA section 408(p) to screen pesticides, including DDVP, for endocrine disruption potential. (Ref. 1 at 5). Essentially, NRDC argues that EPA must retain the children's safety factor for any pesticide until testing under the endocrine screening program is completed for that pesticide.

ii. *Background.* In its petition, NRDC claimed that failure to conduct the

endocrine screening program for DDVP under section 408(p) made it impossible for EPA to conclude that the DDVP tolerances are safe. (Ref. 2 at 49). EPA responded to this argument by citing its denial of a petition to revoke various pesticide tolerances in which the claim was made that EPA could not remove the children's safety factor if endocrine screening under section 408(p) had not been conducted. (72 FR at 68676). There, EPA concluded that the statute did not impose a mandatory bar upon removal of the children's safety factor until completion of the endocrine screening program. (71 FR 43906, 43920 (August 2, 2006)). EPA also found in responding to the prior petition that it had sufficient data on endocrine screening for the pesticide in question to make a safety finding. (71 FR at 43920-43921). After analyzing the endocrine data for DDVP, EPA concluded that it had sufficient data to make a safety finding as to DDVP. (72 FR at 68676 - 68677).

iii. *Denial of hearing request.* The question of whether completion of the endocrine screening program under FFDCA section 408(p) is a mandatory prerequisite to removal of the children's safety factor is a legal issue. A question of fact, not of law, is required to justify a hearing. (40 CFR 178.32(b)(1)).

iv. *Denial of objection.* In response to a prior pesticide tolerance revocation petition, and objections filed as to EPA's denial of that petition, EPA has already rejected the legal claim presented in this objection. (71 FR at 43920; 72 FR 39318, 39327-39328 (July 18, 2007). After analyzing the statutory language, structure, and legislative history, EPA concluded that section 408(p) does not override the ''clear and unmistakable language[] [in section 408(b)(2)(C)] grant[ing] EPA discretion to make a fact-based determination of whether a safety factor different than the 10X default value is safe for children.'' (71 FR at 43920). EPA summarized its reasoning as follows:

> under section 408(b)(2)(C) EPA clearly has the discretion to determine, in any given case, whether it has reliable data to choose a factor different than the 10X default value. Not only is there no statutory language supporting the [petitioners'] argument in favor of automatic retention of the 10X until completion of the endocrine screening program but the legislative history is in no way supportive of construing the enactment of the program as intended to have such a dramatic impact. Further, since the enactment of the FQPA, EPA's contemporaneous and consistent approach to the endocrine screening program has been to treat that information-gathering exercise as not imposing some type of statutorily-prescribed, automatic injunction barring removal of the children's safety factor until completion of information-gathering under the program.

(Id.). EPA also catalogued the extensive data requirements already in place for pesticides that produced information on a pesticide's potential endocrine effects. (71 FR at 43920-43921). EPA concluded that ''in many instances the totality of the information gleaned from current data required for pesticides used on food will make it possible to develop a meaningful weight-of-the-evidence determination on the potential of the pesticide to adversely affect the endocrine system.'' (Id.).

NRDC has done nothing more than state in a conclusory fashion that completion of endocrine screening under section 408(p) is necessary to a decision to remove the children's safety factor. Accordingly, EPA denies this objection for the reasons stated in its previous two orders addressing this claim. (71 FR at 43920 - 43921; 72 FR at 39327-39328).

b. *DDVP endocrine data*—i. *Objection/hearing request sub-issue.* In its objections, NRDC argues that EPA has inadequate data on endocrine effects to remove the children's safety factor. As support for this argument NRDC asserts: (1) that the studies relied upon by EPA ''were not designed to detect endocrine disruption . . . ;'' and (2) that the two-generation rat reproduction study does not meet EPA's 1998 guideline for such studies and, given that the reproduction study did show endocrine effects, a ''[p]roper histopathology in the two generation rat reproduction study could have revealed adverse effects at lower levels than'' the levels at which cholinesterase inhibition was seen in DDVP studies. (Ref. 1 at 6).

ii. *Background.* As noted above, NRDC's petition argued that EPA could not make a safety finding for DDVP in the absence of data collected under the section 408(p) screening program. EPA responded to this claim by examining the data on DDVP bearing on its potential endocrine effects. EPA concluded that it could make a safety finding for DDVP in absence of further endocrine data given that: ''(1) data bearing on potential endocrine effects from a two-generation reproduction study as well as other chronic data in which effects on reproductive organs were examined; (2) EPA well understands DDVP's most sensitive mechanism of toxicity (cholinesterase inhibition); and (3) the potential endocrine-related effects seen for DDVP appeared in the presence of significant cholinesterase inhibition and at levels nearly two orders of magnitude above the most sensitive cholinesterase effects. . . .'' (72 FR at 68677).

iii. *Denial of hearing request.* A hearing on this sub-issue is not appropriate because NRDC's request is based on mere allegations, general contentions, and speculation. NRDC claims that the studies EPA relied upon were not ''designed'' to investigate endocrine effects; however, NRDC proffers no evidence to support such an allegation. Further, such a claim has little, if any, materiality, given that the important question is not whether the studies were ''designed'' to measure endocrine effects but whether they actually measure such effects. Notably, NRDC does not, and cannot upon this record, make the latter contention. (See 72 FR at 68676 (discussing the numerous endocrine-related endpoints assessed in the DDVP database)). Further, 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 is nothing more than speculation. In applying its hearing regulations, FDA has routinely denied hearings on speculation about what redoing a study might show. For example, in a proceeding establishing a food additive regulation for acesulfame potassium, FDA denied a hearing to an objector who challenged FDA's rejection of a study for only containing partial histopathological data. (57 FR 6667 (February 27, 1992)). The objector had argued that full histopathological data might have altered FDA's conclusion. FDA found such an argument unconvincing: ''Because complete histopathological examination of tissues from all animals in the first rat study was not done and cannot be done now, any prediction of the results of such an examination is simply speculation. Speculation regarding data that do not exist cannot serve as the basis for a hearing.'' (Id. at 6671). For all of the above reasons, the hearing request on this sub-issue is denied.

iv. *Denial of objection.* EPA denies NRDC's objection that EPA does not have adequate endocrine data on DDVP to remove the children's safety factor. First, NRDC is wrong to imply that existing, required toxicity studies do not provide valuable information on potential endocrine effects. EPA discussed this issue in detail in an earlier order involving similar claims concerning a different pesticide. There, EPA pointed out that:

> The primary proposed Tier 2 study [for the Endocrine Disruptor Screening Program]

relevant to endocrine effects on humans is the 2-generation reproductive toxicity study in rats. This is one of the core studies required for all food-use pesticides since 1984. In this reproduction study, potential hormonal effects can be detected through behavioral changes, ability to become pregnant, duration of gestation, signs of difficult or prolonged parturition, apparent sex ratio (as ascertained by anogenital distances) of the offspring, feminization or masculinization of offspring, number of pups, stillbirths, gross pathology and histopathology of the vagina, uterus, ovaries, testis, epididymis, seminal vesicles, prostate, and any other identified target organs. In fact, EPA, in 1998, in discussing this study's use in Tier 2, identified 39 endpoints examined in this study relevant to estrogenic, androgenic, or thyroid effects. At that time, EPA noted that it was evaluating whether to add another 10 endocrine-related endpoints to the study protocol to enhance the utility of the study to detect endocrine effects. Despite the ongoing evaluation of additional endpoints, EPA has concluded that the existing 2-generation mammalian assay is valid for the identification and characterization of reproductive and developmental effects, including those due to endocrine disruption, based on the long history of its use, the endorsement of the 1998 test guideline by the FIFRA Scientific Advisory Panel, and acceptance by member countries of the Organizations for Economic Cooperation and Development (OECD).

(71 FR 43906, 43921 (August 2, 2006) (citations omitted)). That order also catalogued the numerous endocrine-related endpoints in other chronic toxicities routinely-required for pesticides used on agricultural commodities. (Id.).

Specifically as to DDVP, in its response to NRDC's petition, EPA detailed four long-term DDVP toxicity studies, submitted under EPA data requirements that provided data on numerous effects that are relevant to potential endocrine disruption. EPA wrote:

EPA has adequate data on DDVP's potential endocrine effects to evaluate DDVP's safety. In the 1989 NTP cancer studies with rats and mice, male and female reproductive organs (prostate, testes, epididymis, ovaries, uterus) were examined and no changes attributable to DDVP were found. The 52–week dog study with DDVP also was without effect in the reproductive organs (testes, prostate, epididymides, cervix, ovaries, uterus, vagina). EPA also has a 1992 two-generation rat reproduction study with DDVP (via drinking water) that is similar to the most recent guidelines (1998) for conduct of such a study with respect to endocrine-related endpoints. Although that study did not include certain evaluations that the 1998 guidelines recommended related to endocrine-related effects (age of vaginal opening and preputial separation), it did incorporate other aspects of the 1998 guidelines such as an examination of esterous cycling in females and sperm number, motility, and morphology in males. The study did identify an adverse effect on esterous cycling in females but only at the high dose (8.3 mg/kg/day). All doses in the study showed significant cholinesterase inhibition. Further, the NOAEL and LOAEL from the esterous cycling endpoint in the reproduction study are nearly two orders of magnitude higher than the NOAEL and LOAEL used as a Point of Departure in setting the chronic RfD/PAD for DDVP.

(72 FR at 68676 (citations omitted). Further, the petition response additionally discussed a DDVP study from the scientific literature examining endocrine-related effects. (Id.).

NRDC's speculation - that further testing of DDVP might reveal endocrine effects at levels below those at which cholinesterase inhibition has been measured - does not convince EPA that there is not a reliable basis for removing the children's safety factor as regards endocrine effects. As EPA indicated in its denial of the NRDC petition, it has several studies addressing numerous endpoints bearing on DDVP's potential endocrine effects, DDVP's cholinesterase inhibition effects are well-defined by existing data, and the only endocrine effect seen in the DDVP data occurred in the presence of significant cholinesterase inhibition and at a level two orders of magnitude (i.e., 100X) greater than the level at which the most sensitive cholinesterase effects were seen. As a pesticide, DDVP is subject to testing under the endocrine disruptor screening program; however, EPA expects that that data will confirm its conclusion regarding DDVP's potential endocrine effects. NRDC's objection on this point is denied.

3. *Dietary exposure—a. Objection/hearing request sub-issue.* NRDC claims that there are numerous uncertainties in EPA's estimate of dietary exposure to DDVP from food and that these uncertainties preclude EPA from departing from the 10X children's safety factor. (Ref. 1 at 6). Specifically, NRDC cites to a list of uncertainties noted by EPA in a preliminary risk assessment for DDVP released in 2000. Those uncertainties involve the number of infants surveyed for the food consumption database; foods consumed from farm stands; use of data on residue decline from cooking studies; reliance on the residue sampling from the FDA Total Diet Study; and lack of monitoring data, and extensive use of data translation, for fumigated commodities. With the exception of the infant consumption issue, NRDC makes no claim other than to allege that ''[e]ach of these shortcomings poses a serious risk of understating the risks posed by DDVP contamination of food.'' (Id.). As to the infant consumption data, NRDC offers various challenges to the size and representativeness of the group of infants sampled in conjunction to the 2000 preliminary risk assessment. NRDC acknowledges that EPA, in its response to the NRDC petition, states that it used updated infant consumption data but NRDC objects that ''EPA does not assert that these data represent a statistically adequate or representative sample.'' (Id.). Finally, NRDC implies that EPA thinks the data are not reliable by citing an EPA statement regarding the reliability of monitoring data.

b. *Background.* NRDC made almost identical claims in its petition to revoke DDVP tolerances. EPA responded with a detailed examination of each of the factors cited by NRDC as well as several additional factors. (72 FR at 68684-68686). Where EPA identified weaknesses in the exposure database it either incorporated new, updated data in its risk assessment (for example, replacing data from the FDA Total Diet Study with data from USDA's Pesticide Data Program) or explained how that weakness had been addressed by conservative assumptions. (72 FR at 68684). This led to an entirely revised dietary exposure and risk assessment for DDVP. As to this revised assessment, EPA concluded that ''its assessment of exposure to DDVP from food will not under-estimate but rather over-estimate, and in all likelihood substantially over-estimate, DDVP exposure.'' (72 FR at 68686). EPA also noted that the largest ''driver'' or contributor to dietary exposure of DDVP was DDVP in drinking water and not DDVP in food. (Id.). Specifically, as to food consumption data for infants, EPA stated that it had incorporated the most recent consumption data for infants that is used in all EPA pesticide risk assessments currently in its revised risk assessment for DDVP. This most recent data was collected at the direction of Congress in the FQPA. (Public Law 104-170, sec. 301; 110 Stat. 1489, 1511).

c. *Denial of hearing request.* NRDC's objection and request for a hearing on this sub-issue suffers from several infirmities. First, NRDC has objected to an outdated document, EPA's preliminary risk assessment for DDVP. With the exception of the issue concerning food consumption data for infants, NRDC has made no effort to object to EPA's current assessment of the reliability of various factors cited by NRDC in EPA's petition response issued under FFDCA section 408(d)(4)(iii). 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. (See 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)). In fact, in these circumstances, it is questionable whether EPA has jurisdiction to consider the objection and hearing request because objections may only be filed as to a section 408(d)(4)(iii) order or other statutorily-specified action. (21 U.S.C. 346a(g)(2)(A)).

Second, NRDC has made no proffer of evidence supporting its claim that each of the factors cited from EPA's preliminary risk assessment ''poses a serious risk of understating the risks posed by DDVP contamination of food.'' (Ref. 1 at 6). NRDC's entire argument concerning the effect these factors (other than the infant food consumption data issue) would have on the DDVP exposure assessment is a single conclusory sentence. A hearing will not be granted on ''mere allegations'' or ''general contentions.'' (40 CFR 178.32(b)(2)). Although NRDC discusses the infant food consumption data issue at greater length, this discussion provides no support for granting a hearing. NRDC's discussion is limited to: (1) a presentation of a short analysis of the adequacy of the superseded consumption data as opposed to the data upon which EPA relied in denying NRDC's objection; and (2) a claim that EPA has not made a finding that the more recent infant food consumption data ''represent a statistically adequate or representative sample.'' (Ref. 1 at 6-7). However, the superseded data is irrelevant to the present proceeding and the allegation about an absent finding is framed as a procedural/legal challenge, not an identification of evidence supporting factual contentions. (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.'').

Third, ignoring for a moment the other serious flaws identified above, a hearing is inappropriate on this issue because NRDC has not shown a disputed factual issue. Rather, NRDC is essentially arguing about the correct conclusion that should be drawn from the factual findings made by EPA in its preliminary risk assessment. (47 FR 55471, 55474 (December 10, 1982) (''[Objectors] assertion about this evidence is, at best, an argument that a different inference (i.e., that the pieces are not 'reasonably uniform' and 'cube shaped') should be drawn from established fact (the dimensions of the pieces) than the agency has drawn. No hearing is required in such circumstances.'').

Finally, this entire issue suffers a materiality problem because dietary exposure to DDVP in food is so small relative to other DDVP exposures. As EPA noted in its petition denial, the ''latest dietary assessment shows that, by a large margin, the biggest driver in the DDVP dietary risk assessment are DDVP residues in water not food.'' (72 FR at 68686). Moreover, in evaluating aggregate exposure to DDVP from all sources EPA found that dietary exposure from food and water was ''insignificant'' compared to exposures from pest strips. NRDC has made no showing that its concerns regarding dietary exposure to DDVP in food are material to the overall exposure assessment. (See 53 FR 53176, 53202 (December 30, 1998) (The objector claims that radiation causes nutrient loss but ''to justify a hearing on this point, it is not enough for [the objector] to simply assert that some nutrient loss can occur. [The objector] must present evidence that suggests that nutrient losses in food irradiated at doses permitted by the regulation are sufficiently large and would so affect the diet that such food would be nutritionally unwholesome or unsafe.'').

For all of the above reasons, NRDC's hearing request on the adequacy of the DDVP dietary exposure assessment are denied.

d. *Denial of objections*. EPA questions whether NRDC's repetition of EPA's statements from a preliminary risk assessment constitute an objection to a superseding risk assessment in a section 408(d) petition denial. In any event, EPA has already explained in great detail in its petition denial why the factors cited in its preliminary risk assessment do not raise a concern that EPA in its latest assessment has understated DDVP dietary exposure. To the contrary, EPA concluded that its dietary assessment will ''over-estimate, and in all likelihood substantially over-estimate, DDVP exposure.'' (72 FR at 68686). Accordingly, NRDC's objections, to the extent they merely repeat the claims in the petition, are denied for the same reasons stated in the petition denial. (72 FR at 68684-68686).

EPA also denies NRDC's apparent objection that the updated infant food consumption data is unreliable and thus EPA may not depart from the 10X children's safety factor. The only two grounds NRDC cited for this objection were: (1) EPA's alleged failure to confirm that these data are ''statistically adequate or [a] representative sample;'' and (2) a reference EPA made to monitoring data. NRDC's arguments here are without merit.

EPA has traditionally relied upon large scale surveys of food consumption conducted by the USDA in assessing dietary exposure and risk from pesticides. USDA generally conducts these surveys roughly every 10 years. EPA currently relies primarily on the Continuing Survey of Food Intakes by Individuals (''CSFII'') which was conducted in 1994-96. Prior surveys were performed by USDA in 1977-78 and 1989-91. The 1994-96 CSFII was supplemented in 1998 to expand the number of data points for infants and children. As EPA has explained: ''These surveys were designed to monitor food use and food consumption patterns in the U.S. population. The data were collected as a multistage, stratified, probability sample that was representative of the U.S. population. [] The most recent survey (CSFII 1994-1996/1998) was designed to obtain a sample that would provide equal precision over all sex-age domains. The data are used by a number of federal and state agencies to improve understanding of factors that affect food intake and the nutritional status of the U.S. population. [EPA's Office of Pesticide Programs] considers the CSFII data adequate to model the daily variability in the U.S. diet.'' (Ref. 5 at 39).

The 1998 supplemental survey was collected in response to the mandate in the FQPA specifying that USDA, in consultation with EPA, was to ''coordinate the development and implementation of survey procedures to ensure that adequate data on food consumption patterns of infants and children are collected.'' (Public Law 104-170, sec. 301; 110 Stat. 1489, 1511). Congress specified that ''[t]o the extent practicable, [these] procedures [] shall include the collection of data on food consumption patterns of a statistically valid sample of infants and children.'' (Id.). Working together, EPA and USDA adopted a survey plan designed to be statistically reliable and representative. (Refs. 25 and 26). The 1998 survey involved sampling of 5,559 infants and children. When combined with the 4,253 infants and children from the 1994-96 survey, the total sample size for infants and children in the two surveys is near 10,000. EPA and USDA concluded that that ''the sample sizes for each sex-age group [from the combined surveys] provide a sufficient level of precision to ensure statistical reliability of the estimates'' except as to

certain low consumption items for individual age groups (e.g., infant consumption of lettuce). (Ref. 25 at 1). Comparison of the 1994-96 and 1998 surveys indicated few statistical differences in nutrient consumption for the different age groups with the exception of 3-5 year olds. Even so, ''[t]he differences seen, although statistically significant, were relatively small and likely to be of little practical or biological significance.'' (Ref. 26 at 2-3).

Because EPA, in conjunction with USDA, has taken care to insure that its surveys of food consumption constitute a statistically valid and representative sample of infants and children, NRDC's unsupported objection suggesting that this data is somehow inadequate is rejected.

NRDC's reference to an EPA statement about monitoring data does not in any way undermine this conclusion. EPA began a section of the petition denial which discusses, among other things, monitoring data of residues in food, infant food consumption data, and fumigant monitoring data, with the broad statement that ''[i]n general, EPA disagrees that the monitoring data are unreliable.'' (72 FR at 68684). While NRDC highlights the qualifying language ''in general,'' it ignores the critical following sentence that provides: ''To the contrary, EPA believes that the monitoring data provide for an appropriately conservative risk assessment.'' (Id.). The first sentence was qualified by the phrase ''[i]n general,'' because in two instances the EPA's residue monitoring data were less than optimal; however, as noted in the second sentence, EPA concluded that the risk assessment was appropriately conservative because either the data in question were insignificant or other factors compensated for any uncertainty in the data. The first instance involved residue monitoring data for one minor commodity (berries not including strawberries) out of dozens of commodities where EPA relied on FDA enforcement monitoring data rather than its preferred source, data from USDA's Pesticide Data Program. EPA prefers using the USDA data because it is collected using a sampling plan designed to capture a representative sample of food in the United States, whereas sampling for FDA enforcement data is targeted at food where violations are more likely to occur. Such targeted enforcement data generally overstates, in comparison to a more representative sample, both the frequency of finding pesticide residues in commodities and the level of the residues detected. In the second instance, fumigant monitoring data was not available for all bagged and packaged commodities so EPA translated data across commodities. Although noting that this translation introduced some uncertainty, EPA concluded that ''this uncertainty was more than offset by other factors,'' including a testing procedure that utilized maximum application rates and sampling within six hours of treatment and the assumption that all bagged and packaged commodities would be treated. Finally, the mention of ''monitoring data'' is a reference to studies that ''monitor'' residues in food not surveys of people's food consumption patterns. The latter topic was inadvertently included in a section of the order devoted to ''[f]ood monitoring data.'' (72 FR at 68683). Thus, the sentence cited by NRDC does not even refer to food consumption survey data.

4. *Pest strip exposure*. NRDC claims that EPA's assessment of exposure to DDVP from residential pest strips ''is based on unsupported assumptions and inadequate data.'' (Ref. 1 at 8). Accordingly, NRDC concludes the EPA lacks reliable data on DDVP exposure from pest strips and cannot reduce or remove the 10X children's safety factor. EPA has identified seven separate allegations made by NRDC and they are analyzed individually below.

a. *Representativeness of Collins and DeVries study*—i. *Objection/hearing request sub-issue*. NRDC argues that the Collins and DeVries study which EPA used to estimate DDVP exposure from pest strips had an inadequate sample size (15 houses). According to NRDC, 15 houses is not adequate to represent the diversity of housing in the United States given the variations in housing design and ventilation characteristics. (Ref. 1 at 7). Additionally, NRDC claims that, because the study was conducted in a single geographic area and for a period no longer than 91 days, it does not account for the varying weather conditions which can have differential effects on the movement and degradation of airborne residues.

ii. *Background*. NRDC made the identical claim in its petition. EPA's response in its petition denial order was two-fold. First, EPA pointed out that the Collins and DeVries study was not the only study considered by EPA in assessing DDVP exposure from pest strips. EPA reviewed several other studies involving over 100 homes in the United States and Europe. The results in the Collins and DeVries study were consistent with the results in the other studies and, thus, EPA concluded that it was reasonable to use the data from the Collins and DeVries study in assessing DDVP risk. (72 FR at 68692). Second, in response to this claim (as well as several of NRDC's other claims), EPA substantially revised the DDVP exposure and risk assessment. (72 FR at 68687-68691). Additional conservative assumptions were adopted and these conservative assumptions further offset any theoretical unrepresentativeness of the Collins and DeVries study. These assumptions were that exposed individuals spent 24 hours per day in a treated home, that a person spent all of the 24 hours per day in a room in the house with a pest strip, and that inclusion of a pest strip in a closet resulted in the same exposure as hanging the strip in the room itself. Further, EPA no longer averaged the exposure results from the houses in the study but evaluated each house individually.

iii. *Denial of hearing request*. NRDC's request for hearing on this issue is flawed for two reasons. First, as in its petition, NRDC proffers no evidence to support its claim that the Collins and DeVries study is inadequate due to the diversity of housing stock and geographic conditions in the United States. NRDC merely asserts that to be the case. However, hearings will not be granted on the basis of mere allegations or general contentions. (40 CFR 178.32(b)(2); see also 68 FR 46403, 46406-46407 (8/5/2003) (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 (D.C. 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, NRDC's hearing request is inadequate because NRDC does not object to the basis EPA asserted in its petition denial for concluding that the Collins and DeVries study does provide a sufficient basis for estimating residential exposure. Specifically, NRDC does not challenge EPA's conclusion that the Collins and DeVries study is consistent with several other pest strip studies and proffer evidence in support of that challenge. Neither does NRDC challenge and proffer evidence regarding EPA's conservative use of the Collins and DeVries study in assessing exposure. Rather, NRDC just repeats its assertions regarding the unrepresentativeness of the Collins and DeVries study from its petition. This

failure to challenge the basis of EPA's petition denial affects the materiality of the objection and hearing request. Even if NRDC could demonstrate in a hearing that the ventilation design of a house, for example, can affect the rate at which airborne contaminants are dissipated, that evidence would not contradict the fact that the Collins and DeVries study is consistent with DDVP pest strip studies in over 100 other homes in varying locations.

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 at 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 objection by proffering some information that called into question the agency's conclusion on this matter.'')). Similarly, here, NRDC has not challenged the basis EPA asserted for rejecting NRDC's challenge to EPA's reliance on the Collins and DeVries study and NRDC has not proffered any information calling into question EPA's conclusion.

iv. *Denial of objection*. Because NRDC offers no basis for its objection to EPA's denial of the challenge in its petition to EPA's reliance on the Collins and DeVries study—other than the claims made in its petition, itself—EPA denies the objections for the reasons in the petition denial order (i.e., the consistency of the Collins and DeVries study with other DDVP pest strip studies and the conservativeness of the DDVP pest strip exposure assessment).

b. *Sampling location in the Collins and DeVries study*—i. *Objection/hearing request sub-issue*. NRDC argues that the Collins and DeVries study is flawed because air concentration levels of DDVP were sampled in only one location in the house. According to NRDC, this sampling regime was inadequate because it ''provides no information about the movement of residues from room-to-room and therefore exposure in other rooms in the homes.'' (Ref. 1 at 7).

ii. *Background*. NRDC repeats this claim verbatim from its petition. The petition denial order rejected this challenge to the Collins and DeVries study and the manner of EPA's use of the study in its exposure assessment noting that ''the sample location in each instance was in a room with a pest strip, pest strips were used in other rooms of the house, and EPA assumed, for its calculation of the MOE, that the air concentration for all areas of a house is the same as at the sampled location.'' (72 FR at 68692).

iii. *Denial of hearing request*. This objection and hearing request does not involve a genuine and substantial issue of disputed fact. There is no dispute concerning how or where sampling was done in the Collins and DeVries study or how EPA used that data in estimating DDVP exposure from pest strips. NRDC's objection attacks EPA's conclusion that it is reasonable to assess residential DDVP exposure from pest strips using air concentrations of DDVP from rooms which contained a pest strip. A challenge to an EPA inference drawn from undisputed facts does not qualify as a disputed factual question. (47 FR 55471, 55474 (December 10, 1982) (''[Objectors] assertion about this evidence is, at best, an argument that a different inference (i.e., that the pieces are not 'reasonably uniform' and 'cube shaped') should be drawn from established fact (the dimensions of the pieces) than the agency has drawn. No hearing is required in such circumstances.'')). Moreover, NRDC does not explain why knowledge of the amount of room-to-room DDVP movement is relevant given that EPA based its exposure assumption on the level of DDVP found in a room with a pest strip, much less proffer any evidence to suggest why this issue is material and should be resolved in its favor. For all of these reasons, NRDC's hearing request on this issue is denied.

iv. *Denial of objection*. This objection is denied for the same reason stated in the petition denial order: knowledge of the amount of room-to-room movement of DDVP is irrelevant if EPA bases its exposure assessment on a room that contains a pest strip. In both its petition and its objections, NRDC cites the following statement from EPA's preliminary risk assessment as supporting its conclusion regarding the inadequacy of use of a single air monitor in the Collins and DeVries study: ''A more accurate exposure would be possible if air measurements were available from different rooms in the house.'' (Ref. 1 at 7). NRDC, however, misunderstands the thrust of this sentence. EPA was simply pointing out that monitoring in rooms without pest strips would have provided a more accurate and realistic - i.e., lower - estimate of exposure than using values from a room containing a pest strip. The sentences immediately following the language quoted by NRDC make this clear. EPA stated: ''Limited data suggest that the level of Dichlorvos in the air declines with distance from the resin pest strip. There are data from the Dichlorvos Flea Collar Study that show Dichlorvos levels are lower some distance away from the pet flea collar.'' (Ref. 27 at 53).

c. *Averaging DDVP concentrations over 120 days*—i. *Objection/hearing request sub-issue*. NRDC objects to EPA's assessment of exposure to pest strips challenging EPA's alleged use of a 120–day average of DDVP concentration levels. NRDC argues that ''[r]ather than using averages, the Agency should have presented the range of risks displayed over time, peak measurements, and the daily monitoring data so that trends over time could be determined.'' (Ref. 1 at 7).

ii. *Background*. NRDC repeats this claim verbatim from its petition. In its petition denial order, EPA agreed with NRDC and revised its residential exposure assessment to examine exposure and risk based on the first day of exposure after hanging the pest strip, the first 2 weeks of exposure, and exposure over a 91 day period. (72 FR at 68687).

iii. *Denial of hearing* 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. (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.'').

iv. *Denial of objection*. NRDC's objection is directed at a prior,

superseded risk assessment, not the risk assessment relied upon in the petition denial order. Thus, this objection is not material to this proceeding and is denied. (See Unit VIII.D.3.c.).

d. *Replacement cycle for pest strips*—i. Objection/hearing request sub-issue. NRDC objects to EPA's assumption that pest strips are replaced no more frequently than 120 days even though the pest strip label does not prohibit more frequent replacement. (Ref.1 at 8). NRDC argues that EPA has no data to substantiate this assumption and claims that homeowners may decide ''to replace strips sooner 'for good measure.''' (Id.). Recognizing that EPA decreased its assumption concerning the replacement cycle to 91 days in the revised risk assessment in the petition denial order, NRDC asserts that this value is equally arbitrary.

ii. *Background*. The challenge to the 120–day replacement assumption was included in NRDC's petition. EPA responded to NRDC's argument in the petition denial order by decreasing its assumption as on the replacement cycle of pest strips to 91 days. (72 FR at 68692).

iii. *Denial of hearing*. This sub-issue does not meet the standard for a hearing. NRDC disputes the reasonableness of EPA's choice of a replacement cycle for pest strips in the absence of a restriction on the pesticide label or data documenting consumer usage. NRDC proffers no evidence challenging EPA's use of a 91–day replacement cycle. Rather, NRDC asserts a legal argument that in the absence of specific data on consumer usage, EPA may not make an assumption about consumer practices. Hearings are not appropriate on legal questions. (40 CFR 178.32(b)(1)). Similarly, NRDC's speculation about how often homeowners may replace pest strips does not constitute an evidentiary proffer justifying a hearing. (See 57 FR 33244, 33248 (July 27, 1992) (NRDC claimed that the removal of premix batch analysis would lead to misformulation of selenium in feeds. A hearing was denied because NRDC ''provided no factual information to support its claim . . . . [A] hearing will not be granted on the basis of mere allegations.'')).

iv. *Denial of objection*. In its preliminary risk assessment and in the IRED, EPA assumed that pest strips would be replaced no more frequently than 120 days because the pest strip label specifies: ''Drafts, weather, and other conditions may affect the performance, but treatment usually last for 4 months. Record the date of installation and replace with a new, fresh, full-strength strip at the end of 4 months or when effectiveness diminishes.'' (Ref. 28). Given that the manufacturer was essentially designating 120 days as the likely effective period and that consumers might leave the pest strips up for either longer or shorter periods, EPA assumed that 120 days was a reasonable estimate of the average replacement cycle for pest strips. EPA generally uses average values for chronic exposure scenarios because over time high and low values tend to average out. (Ref. 5 at 42). Nonetheless, in recognition of NRDC's contention that homeowners might replace strips more frequently, EPA amended its pest strip exposure to assume a 91–day replacement cycle (the length of the Collins and DeVries study) rather than extrapolate the data from the Collins and DeVries study over 120 days as was done previously. EPA believes 91 days is a reasonable estimate of the replacement cycle especially given the label language and the numerous conservative assumptions in the risk assessment such as, for example, the assumption of 24 hours per day exposure in a room containing a pest strip. Accordingly, NRDC's objection on this sub-issue is denied.

e. *Number of pest strips*—i. Objection/hearing request sub-issue. NRDC claims that EPA's assessment of DDVP exposure from pest strips is not based on adequate data because EPA does not have any data on how many strips people use in their homes. EPA assessed residential DDVP exposure based on the Collins and DeVries study which used 3-4 strips per house in each of the studied houses. NRDC argues that some homeowners may use more than 3-4 strips because there is no limitation on the label as to the number of strips per house.

ii. *Background*. NRDC repeats this claim verbatim from its petition. EPA rejected NRDC's concern in the petition denial order reasoning that its assessment was based on data on the air concentration of DDVP in a room containing a pest strip. (72 FR at 68692). EPA also noted that the only strips allowed in occupied areas of the home under the current registration are for closets, wardrobes, or cupboards and given that they treat a relatively small space, compared to the bigger strips used in the Collins and DeVries study, they are unlikely to result in significant DDVP air concentrations in rooms other than in the room containing the treated area. (Id.).

iii. *Denial of hearing*. NRDC has not alleged and proffered evidence on a genuine and substantial issue of disputed fact. NRDC speculates that use of pest strips in every, or almost every, room in a house may lead to higher residues in a room containing a pest strip than a room containing a pest strip in a house which has a pest strip in 3-4 rooms. Based on this speculation, NRDC claims that EPA's exposure assessment is inadequate because EPA has not documented how many strips people use in their houses. A hearing will not be granted on the basis of mere allegations or speculation about what other studies might show. (See 57 FR 33244, 33248 (July 27, 1992) (NRDC claimed that the removal of premix batch analysis would lead to misformulation of selenimum in feeds. A hearing was denied because NRDC ''provided no factual information to support its claim . . . . [A] hearing will not be granted on the basis of mere allegations.'')).

iv. *Denial of objection*. For several reasons, NRDC's speculation that a house containing strips in nearly every room might lead to greater DDVP exposures than estimated by EPA must be rejected. First, EPA based its DDVP pest strip exposure assessment on a study (Collins and DeVries) which measured DDVP concentrations in a room containing a pest strip. Second, the Collins and DeVries study did not involve a house with a single strip but used pest strips in 3-4 rooms of the studied houses. Third, the results of the Collins and DeVries study were consistent with the results of several other pest strip studies. Fourth, although corrected for the smaller size of current pest strips compared to the pest strips used in the Collins and DeVries study, EPA did not adjust its assessment for the fact that current strips may not be used for general space treatment but must be put in closets, wardrobes, or cupboards. Taking into account these factors, EPA's assessment of exposure from DDVP pest strips was reasonable and based upon adequate, reliable data to reduce or remove the children's safety factor.

f. *Exposure time per day*—i. Objection/hearing request sub-issue. NRDC objects that it was unreasonable for EPA to assume that the high end exposure period in the home is 16 hours and that a low end exposure period is 2 hours. NRDC argues that some groups of people may spend significantly greater amounts of time in their homes. NRDC asserts that EPA does not adequately justify these assumptions in its petition denial order.

ii. *Background*. NRDC repeats this claim verbatim from its petition. In response to NRDC's petition, EPA substantially revised its pest strip exposure assessment. As to exposure

periods, EPA completely dropped its prior approach and assessed exposure assuming a person spent 24 hours per day in their home in a room containing a pest strip. (72 FR at 68687).

iii. *Denial of hearing*. 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. (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.'').

iv. *Denial of objection*. NRDC's objection is directed at a prior, superseded risk assessment, not the risk assessment relied upon in the petition denial order. Thus, this objection is not material to this proceeding and is denied. (See Unit VIII.D.3.c.).

g. *Movement of DDVP from unoccupied areas of the home to occupied areas*—i. *Objection/hearing request sub-issue*. NRDC claims that EPA does not have a sufficient basis for its conclusion that pest strips used in unoccupied places in a house (garages, attics, crawl spaces, sheds) will not migrate to occupied portions of the house. Thus, NRDC argues EPA does not have reliable data to reduce or remove the children's safety factor.

ii. *Background*. NRDC made the same argument in its petition. Additionally, in the petition, NRDC cited a study with another pesticide which NRDC claimed showed that pesticides could migrate into the house. EPA disagreed with NRDC's assertion, pointing out that migration was unlikely unless the unoccupied portion was connected to the air exchange system for the house. EPA also explained in detail why the study cited by NRDC was not relevant to DDVP. NRDC did not renew its arguments based on this study.

iii. *Denial of hearing*. NRDC has not alleged and proffered evidence on a genuine and substantial issue of disputed fact. NRDC speculates that use of pest strips in unoccupied areas of a house may lead to migration of DDVP residues to occupied portions of the house. Based on this speculation, NRDC claims that EPA's exposure assessment is inadequate because EPA has not documented that such migration does not occur. A hearing will not be granted on the basis of mere allegations or speculation about what other studies might show. (See 57 FR 33244, 33248 (July 27, 1992) (NRDC claimed that the removal of premix batch analysis would lead to misformulation of selenium in feeds. A hearing was denied because NRDC ''provided no factual information to support its claim . . . . [A] hearing will not be granted on the basis of mere allegations.'')).

iv. *Denial of objection*. NRDC's objection is denied. Given EPA's knowledge of the chemical properties of DDVP, it was reasonable to assume that DDVP would not migrate from unoccupied portions of the home to occupied portions absent some type of air exchange connection between the two areas. DDVP is a highly volatile chemical that quickly degrades once released to the environment. EPA reasonably concluded that the low concentration of airborne DDVP produced from a DDVP pest strip would not penetrate the walls of a home in meaningful amounts.

E. Response to Specific Issues Raised in Objections and Hearing Requests - Reliance on Human Study

1. *Background*. In making its FFDCA tolerance reassessment decision and FIFRA reregistration decision for DDVP, EPA relied upon one human toxicity study in deriving an acceptable level of exposure for several exposure scenarios. The study in question was conducted in 1997 by A.J. Gledhill. In this study, six male volunteers were administered 7 mg of DDVP in corn oil (equivalent to approximately 0.1 mg/kg/day) via capsule daily for 21 days. Three control subjects received corn oil as a placebo. Baseline values for RBC cholinesterase activity for each study participant were determined based upon repeated measurements prior to the administration of DDVP. After dosing started, RBC cholinesterase activity was monitored on days 2, 4, 7, 9, 11, 14, 16, and 18, and then on day 25 or 28 post-dosing. Although no toxicity attributable to administration of DDVP was reported by the test subjects, mean RBC cholinesterase activity was statistically significantly reduced in treated subjects on days 7, 11, 14, 16, and 18. These values were 8, 10, 14, 14, and 16 percent below the pre-dose mean. (Refs. 15 and 16).

EPA's decision to rely on the Gledhill study was made pursuant to its Human Research rule. As explained in Unit III.D, 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 Gledhill study, 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, 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 Gledhill 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 Gledhill study.

Previously, NRDC has challenged the lawfulness of the Human Research rule. Following promulgation of the Human Research Rule, NRDC filed a petition for judicial review of the rule in the United States Court of Appeals for the Second Circuit. (NRDC v. U.S. EPA, No. 06-0820-ag (2d Cir.)). That case has been briefed and argued and is awaiting decision.

NRDC also previously challenged the scientific merit and ethics of the Gledhill study in comments to EPA and to the HSRB. Specifically as to the HSRB, NRDC filed written comments prior to the HSRB's review of EPA's determination regarding the appropriateness of relying on the Gledhill study and also presented oral testimony at the public hearing the HSRB held with regard to that study. Subsequently, the HSRB, after taking into account the comments of NRDC and others, advised EPA that reliance on the Gledhill study was consistent with the Human Research rule. EPA relied heavily on the analysis of the HSRB in denying NRDC's petition to revoke DDVP tolerances. (72 FR at 68675).

In its petition to revoke DDVP tolerances, NRDC repeated its arguments made to the HSRB as to why the Gledhill study does not comply with the Human Research rule. As support, NRDC cited to a draft HSRB report on the Gledhill study, released shortly before NRDC filed its petition, which noted scientific and ethical deficiencies in the study. (Ref. 2 at 26). NRDC did not acknowledge, however, that despite identifying deficiencies in the Gledhill study, the HSRB, in its draft report, stated its agreement with EPA's determination that it would be acceptable to rely on the Gledhill study.

In its objections, NRDC once again makes the same arguments on the Gledhill study it made to the HSRB and in its petition to EPA (including the misleading reference to a portion of the draft report of the HSRB). Similar to the approach taken in the petition, NRDC does not even acknowledge the

recommendations made by the HSRB in its draft and final decisions despite EPA's explicit reliance on the HSRB's reasoning in EPA's petition denial order.

NRDC's objections also include a challenge to the legality of the Human Research rule paralleling the case pending in the Second Circuit.

2. *Challenge to the human research rule*—a. *Objection/hearing request sub-issue.* NRDC argues that ''to the extent [its] facial challenge to the [Human Research] rule is not proper,'' it is renewing its arguments regarding the legality of the rule in its objections. (Ref. 1 at 9-10). The objections incorporate by reference NRDC's legal briefs filed in the Second Circuit and its comments filed on the Human Research rule as support for this objection. In its legal briefs, NRDC argues that EPA's rule is inconsistent with a congressional funding moratorium in an Appropriations Act. (Ref. 29). That Act prohibited EPA from ''accept[ing], consider[ing] or rely[ing] on third-party intentional dosing human toxicity studies for pesticides . . . until [EPA] issues a final rulemaking on this subject.'' (Public Law 109-54, sec. 201, 119 Stat. 499, 531 (August 2, 2005)). According to NRDC, EPA did not comply with this legislation's requirement that the EPA human testing rule bar testing on pregnant women, infants and children and be consistent with the principles in a 2004 National Academy of Sciences Report and the Nuremburg Code on human experimentation. (Ref. 29 at 23). NRDC did not specifically lay out the arguments in its legal briefs in its objections other than to include a summary of some of the principles of the Nuremberg Code. (Ref. 1 at 11-12). Similar arguments are made in NRDC's comments on EPA's proposed Human Research rule. (Ref. 30).

b. *Background.* Arguments concerning the legality of the Human Research Rule were not contained in the petition.

c. *Denial of hearing request.* In this sub-issue, NRDC presents, by reference, various arguments that the Human Research rule is not consistent with congressional legislation bearing on the rule. These arguments raise questions regarding the proper interpretation of statutory language and hearings are not appropriate on such issues. (40 CFR 178.32(b)(1)).

d. *Denial of objection.* To the extent this matter is not resolved by the Second Circuit and NRDC has standing to challenge a rule whose ''primary concern'' is the ''[p]rotection of the health and safety of human test subjects,'' (Ref. 1 at 15), EPA denies NRDC's objections to the legality of the Human Research rule. EPA believes the Human Research rule is fully consistent with the Appropriations Act and EPA has fully explained the basis for this conclusion in the rulemaking record (EPA–HQ–OPP–2003–0132) and its legal brief filed in the Second Circuit proceeding. (Ref. 31).

3. *Challenge to reliance on the Gledhill Study*—a. *Statistical power - too few subjects to detect an effect*—i. *Objection/hearing request sub-issue.* NRDC objects that the number of test subjects in the Gledhill study was low and thus there are statistical issues with extrapolating from the results of the Gledhill study to the general human population. (Ref. 1 at 13). In part, NRDC frames this argument as the Gledhill study lacks ''statistical power'' and NRDC references four published letters or articles in support of this claim. (Ref. 1 at 15). Further, NRDC claims that the statistical power issue is particularly important for studies such as the Gledhill study which measure cholinesterase inhibition because of the variability among individuals of cholinesterase inhibition over time. According to NRDC, the ''range of variability both between and for the individual test subjects means that even greater than the customary number of test subjects would be required to permit adequate statistical power to detect effects caused by the test substance above background variations.'' (Ref. 1 at 13). As evidence of this cholinesterase inhibition variability in humans, NRDC cites to another human study by Gledhill (MRID # 4428802 rather than MRID # 44248801).

NRDC's objection here appears to be confusing two separate issues: (1) did the Gledhill study have sufficient statistical power to detect an effect caused by DDVP; and (2) does the Gledhill study contain sufficient data to reliably estimate a safe dose for humans. The first issue is addressed in this Unit and the second in Unit VIII.E.3.b.

ii. *Background.* NRDC's objection repeats assertions made in its petition to revoke DDVP tolerances and its comments on the DDVP IRED. (Ref. 2 at 26-27; Ref. 23 at 14-17). EPA rejected NRDC's claims about statistical power, explaining that ''[a]lthough as a general matter more subjects would provide greater 'statistical power,' in this case the use of 6 to 9 subjects with the appropriate statistical methodology is acceptable to EPA because a positive response was seen.'' (72 FR at 68675). EPA also noted that the variability within the cholinesterase inhibition of the tested subjects ''is not large, particularly since the percentage inhibition in all instances was at the marginal end of the range.'' (Id.).

iii. *Denial of hearing.* A hearing is not required on NRDC's statistical power claim because the concept of statistical power is simply not applicable to the conclusions EPA drew with regard to the Gledhill study and thus this issue is not material to NRDC's requested relief. Further, the evidence proffered by NRDC would not, if established, resolve this issue in NRDC's favor.

To understand EPA's ruling here, some basic definitional information on the concept of ''statistical power'' and how it applies in the context of toxicity studies may be helpful. Toxicity testing is designed to test the veracity of the hypothesis that there will be no differences in health outcomes between treated and untreated (control) subjects. Statisticians refer to this hypothesis as the ''null hypothesis.'' The ''alternative hypothesis'' is that there will be a difference between treated and control subjects. In general terms, statistical power measures the probability that a toxicological study will find a treatment-related adverse health outcome when there is a treatment-related adverse effect to be found. (Ref. 32 at 125 and n.144). In the language of a statistician, statistical power measures the ''probability of rejecting the null hypothesis when the alternative hypothesis is right.'' (Id.). A study with a statistical power value of near one (1) would have a very high chance of (properly) rejecting the null hypothesis if the alternative hypothesis is true, whereas a power value close to zero (0) would indicate that there is little chance that the study will identify any true adverse health outcomes occurring as a result of treatment.

Statistical power can also be used to calculate the probability that the study will falsely find that there is no difference in the health outcomes between treated and control subjects, that is, whether the study will falsely affirm the null hypothesis. The probability of such a false negative, is determined by subtracting the statistical power of a study from one (1). (Id.). Thus, the chance that a study will result in a false negative is directly related to the chance that the study will identify any effects present. For example, if a study has low statistical power, there will be a low probability that the study will find an effect if there is one and a high probability that the study will falsely affirm that there is no effect. Statistical power, therefore, is a important tool in designing studies to ensure that effects from treatment are not missed and may play a role in

evaluating completed studies that confirm the null hypothesis to determine the probability that the null hypothesis was not falsely affirmed (i.e., a false negative).

If analysis of a toxicological study shows that there are treatment-related effects (i.e., the null hypothesis of no treatment-related effect is rejected), then the question of the statistical power of the study becomes largely irrelevant. Put another way, if a study shows a positive outcome, the probability that the study might have produced a false negative becomes a moot point. Importantly, with the Gledhill study, the null hypothesis of no treatment-related effect was rejected: that is, the HSRB and EPA concluded that there was a significant difference in cholinesterase inhibition both between controls and DDVP-treated subjects and between the inhibition levels pre- and post-treatment of the DDVP-treated subjects.

With that background, the scientific papers cited by NRDC can be more easily followed. First, NRDC cites a one-page letter to the Environmental Health Perspectives journal which was co-authored by Jennifer Sass, a NRDC senior scientist, and a subsequent letter, again co-authored by Sass, that responded to various letters expressing a different viewpoint. (Ref. 1 at 15, and Refs. 33 and 34). The topic of both Sass letters is nicely captured by the title attached to the first letter: ''Industry Testing of Toxic Pesticide on Human Subjects Concluded 'No Effect,' Despite the Evidence.'' (Ref. 33).

The first letter discusses the DDVP Gledhill study and a second human study involving a different pesticide. With regard to the DDVP Gledhill study, Sass criticizes Amvac's analysis of that study. Amvac had concluded that the Gledhill study demonstrated a NOAEL arguing that the cholinesterase inhibition effects seen at the single dose in that study were not biologically significant. Sass counters that ''the only biological end point measured in the study was cholinesterase inhibition, and this was significantly inhibited.'' (Ref. 33 at A150). As to statistical power, Sass claims that studies involving only a few human subjects ''often lack enough subjects to provide adequate statistical power to detect an effect if it is present.'' (Id.).

The second letter repeats this latter assertion and claims that the statistical power of human studies then available have such low statistical power that they ''practically guarantee[d] a finding of no effect.'' (Ref. 34 at A340). Sass then returns to the Gledhill study and notes with approval EPA's conclusion that that study demonstrated a LOAEL: ''the U.S. Environmental Protection Agency (EPA) rejected AMVAC's interpretation of the results, instead concluding that 'the reduction in RBC cholinesterase activity was considered by the Hazard ID [identification] Committee to be biologically significant, and the dose tested was considered to be a lowest observed effect level (LOEL).''' (Id.). EPA's reversal of the Amvac conclusion is cited by the letter as illustrative of bias by chemical manufacturers in the design and interpretation of studies.

For at least two reasons, these letters neither demonstrate the materiality of NRDC's statistical power claims nor constitute a sufficient evidentiary proffer. First, although they do contain allegations about low statistical power of human studies with low numbers of subjects, they only address the question of whether such studies can detect an effect even if an effect is present (i.e., are they likely to falsely affirm the null hypothesis that there are no treatment-related adverse effects). In the DDVP Gledhill study, however, EPA and the HSRB concluded that the study did identify an adverse effect. Accordingly, the letters have little relevance to EPA's ultimate finding with regard to the Gledhill study. Second, these letters do not challenge EPA's analysis of the Gledhill study - rather, they ratify it. Thus, the letters do not proffer evidence, which would, if established, resolve a material issue in NRDC's favor. (See 57 FR 33244, 33246 (July 7, 1992) (Studies cited by NRDC do not provide a basis for the hearing because they ''support the [FDA] conclusion in question.'')).

NRDC also cites two articles by Alan Lockwood. One is an article in the American Journal of Public Health discussing ethical and scientific considerations with regard to six human toxicology studies, including the Gledhill study at issue in this proceeding. (Refs. 1 at 15; and 35). The second is a one-page summary of the earlier article that was published in The Environmental Forum. (Ref. 36). The first article contains the following paragraph discussing statistical power:

> A power analysis to define the proper size of study group(s) is an essential part of the design. If too many participants are enrolled, the excess will be subjected to unnecessary risk. If too few are enrolled, the investigator risks erroneous acceptance of the null hypothesis. Underpowered studies are inconclusive, and all participants in an underpowered study will have been exposed to risk unnecessarily. All of these studies were underpowered.

(Ref. 35 at 1912). There is little to no explanation provided in the article for the ''underpowered'' conclusion other than the notation that the six studies involved young healthy adults. There is little, if any, discussion of the Gledhill DDVP study at issue in this proceeding. The summary article adds nothing new to the longer article.

Like the Sass letters, therefore, the Lockwood articles do not constitute a proffer of evidence that if established would resolve a material issue in favor of NRDC. Not only do they not proffer any evidence, they focus on an issue not involved here - do human studies, such as the Gledhill study, have sufficient statistical power to avoid ''erroneous acceptance of the null hypothesis.'' Both EPA and the HSRB rejected the null hypothesis as to the Gledhill study (i.e., an adverse effect on the treated subjects was identified). Additionally, these articles do not advance specific evidence, or even arguments, concerning the Gledhill study itself. (See 53 FR 53176, 53179-53180 (December 30, 1998) (a general assertion in a letter to Science magazine is not basis for a hearing); 68 FR 46403, 46405-46406 (August 5, 2003) (a hearing was denied because the cited studies only contained equivocal statements supporting the objector's position)).

NRDC also cites the variable level of cholinesterase inhibition within individuals as supporting its statistical power argument. NRDC references a different DDVP human study by Gledhill (MRID # 44248802) to show variability in cholinesterase inhibition. This argument and these data also do not justify a hearing.

Initially, it must be noted that EPA cannot consider this other Gledhill study because both EPA and the HSRB concluded it was without scientific merit and therefore does not qualify for EPA consideration under the Human Research rule. (Ref. 21 at 42-43). Whether or not the aspect of the study cited by NRDC is implicated by this conclusion has not been evaluated; nonetheless, EPA does not disagree with NRDC's assertion that individual humans have variable levels of cholinesterase inhibition and thus this is not a disputed issue of fact. Neither does EPA dispute that variability of cholinesterase inhibition should be taken into account in considering statistical power and in analyzing the results of a human study.

However, as discussed above, statistical power is no longer a relevant concept once EPA has concluded that a toxicity study shows that the pesticide has an adverse effect on treated subjects. Statistical power is a tool used to evaluate the possibility of accepting false negatives. Moreover, the variability

of cholinesterase inhibition in subjects is also a factor relating to a concern with false negatives. Normal variation in the responses of individual test subjects may mask treatment-related effects leading to a false conclusion that there were no treatment-related effects. Finally, NRDC's claims on variability amount to no more than a mere allegation that the existence of variable rates of cholinesterase inhibition indicate a flaw in the Gledhill study and EPA's reliance on it. Without an evidentiary proffer, however, a hearing is not appropriate.

iv. *Denial of objection*. NRDC has misconstrued the concept of statistical power. It has little relevance in circumstances where a positive effect is found in a toxicological study. NRDC's objection that EPA should not have relied upon the Gledhill study because it lacked statistical power is denied.

b. *Too few test subjects to establish a NOAEL*—i. *Objection/hearing request*. NRDC objects to reliance on the Gledhill study claiming that because it only involved six treated test subjects it cannot ''support the establishment of a reliable NOAEL or dose response curve . . . .'' (Ref. 1 at 13).

ii. *Background*. NRDC's claim was contained in both its petition and its comments on the IRED. (Refs. 1 at 26; and 23 at 15). In its petition denial order, EPA responded to these claims by concurring with the HSRB's conclusion that the Gledhill study was ''sufficiently robust for developing a Point of Departure for estimating dermal, incidental oral, and inhalation risk from exposure to DDVP in a single chemical assessment.'' (72 FR at 68675 (quoting HSRB Report)). The HSRB found the study to be ''robust'' based on the following attributes: ''the repeated dose approach which allowed examination of the sustained nature of RBC cholinesterase inhibition; robust analysis of RBC cholinesterase inhibition both in terms of identifying pre-treatment levels and consistency of response within and between subjects; and the observation of a low, but statistically significant RBC cholinesterase inhibition response.'' (Id.; Ref. 21 at 39-41).

iii. *Denial of hearing*. NRDC has not met the requirements for a hearing on this sub-issue. First, NRDC has proffered no evidence that the six treated subjects in the Gledhill subject were too few for EPA to use data from that study as a Point of Departure. Rather, NRDC does no more than state ''[w]e are aware of no statistical test'' which would support EPA's use of the Gledhill data. (Ref. 1 at 13). 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)). Second, NRDC does not confront the reasoning of the HSRB, which was adopted by EPA, for why the data from the Gledhill study are sufficiently robust to justify their use as a Point of Departure. This failure to challenge the basis of EPA's petition denial affects the materiality of the objection and hearing request. Even if NRDC could demonstrate in a hearing that generally more test subjects are needed to derive a Point of Departure for a RfD/PAD, that evidence would not address the specific factors in the Gledhill study that EPA and the HSRB found convincing on this question. (See Unit VIII.D.4.a.iii).

iv. *Denial of objections*. EPA does not agree with NRDC's undocumented assertion that the Gledhill study does not provide an appropriate Point of Departure for assessing DDVP risk. EPA, and the HSRB, found that there were several features of the study and the statistical analysis of the study that made it ''sufficiently robust for developing a Point of Departure . . . .'' (72 FR at 68675). Important factors cited by the HSRB, and adopted by EPA, included: (1) the study design which involved repeated dosing and repeated measurement of cholinesterase effects in individuals; (2) extensive pre-dosing measurement of the test subjects' cholinesterase inhibition levels which showed consistency both within and between individual test subjects; and (3) the clear study results which showed a statistically significant effect on cholinesterase inhibition was found (both between controls and treated subjects and between the tested subjects' pre- and post-dosing levels) that was at or near the lowest level that could be distinguished from baseline values. (72 FR at 68675). Further, as EPA noted in its petition denial order, a similar number of test subjects (four per sex) are recommended for a toxicology study in non-rodents (usually the dog) routinely required for pesticide risk assessment. (72 FR at 68675).

In response to EPA's and the HSRB's conclusions as to the Gledhill study, NRDC does little more than repeat its allegation that the Gledhill study was underpowered. NRDC does respond to EPA's reference to the chronic dog study, alleging without providing any basis that that study is underpowered, and claiming that ''EPA rarely relies upon that study.'' (Ref. 1 at 13). NRDC is incorrect. The chronic dog study was added to EPA's testing requirement regulations in 1984 and was included in the revised regulations re-promulgated just last year, although the length of the study was shortened from 1 year to 13 weeks. (72 FR 60934, 60940-60941 (October 26, 2007); 49 FR 42881 (October 24, 1984)). As a standard study required in evaluating pesticides used on food, the chronic dog study would have been considered and relied upon in virtually every one of the roughly 10,000 FFDCA tolerance reassessments conducted in the 10 years following enactment of the FQPA. (Ref. 37). If, by ''rarely relied upon,'' NRDC means the results from chronic dog are rarely used as a Point of Departure, NRDC is still incorrect. For example, a cursory review of rules establishing new tolerances in 2005 showed at least eight instances in which the Point of Departure for assessment of a pesticide's risk was based on the chronic dog study. (70 FR 77363, 77366 (December 30, 2005) (hexythiazox); 70 FR 74688, 74690 (December 16, 2005) (bifenazate); 70 FR 55740, 55743 (September 23, 2005) (fenpropathrin); 70 FR 55752, 55757 (September 23, 2005) (amicarbazone); 70 FR 55761, 55764 (September 23, 2005) (pyridaben); 70 FR 54640, 54644 (September 16, 2005) (fluoxastrobin); 70 FR 53944, 53946 (September 13, 2005); 70 FR 51615, 51617 (August 31, 2005) (halosulfuron-methyl). A retrospective analysis performed by EPA in 2005 also showed that 116 out of 304 chronic RfDs for pesticides was based on the chronic dog study. (Ref. 38). Finally, another example somewhat closer to home would be DDVP, where the NOAEL from the chronic dog study is used as the Point of Departure in assessing chronic dietary risk. (Ref. 3 at 132).

Further, EPA's recommendation for four test subjects per sex per dose in the sub-chronic and chronic non-rodent (dog) study is widely followed. The FDA has a similar recommendation for conducting non-rodent studies of sub-chronic and chronic duration as does the Organisation for Economic Co-operation and Development (''OECD''), Canada which has accepted the OECD guideline on the sub-chronic and chronic non-rodent (dog) study, and the European Commission's Joint Research Centre of the European Union. (Refs. 39, 40, 41, 42, and 43).

c. *Adult males only*—i. *Objection/hearing request sub-issue*. NRDC objects to the Gledhill study because it included as test subjects only adult males. (Ref. 1 at 14). NRDC claims that adult males are ''biologically unrepresentative'' of the human population.

ii. *Background*. NRDC's objection is drawn verbatim from its comments on the DDVP IRED. EPA responded to this argument by pointing out that ''no sex differences were observed in the

comparative cholinesterase studies.'' (72 FR at 68675). EPA also found no age-related differences in cholinesterase inhibition. (72 FR at 68694).

iii. *Denial of hearing*. A hearing is denied on this sub-issue because there is no disputed factual matter for resolution at a hearing. There is no dispute concerning the subjects in the Gledhill study - they were adult males. Thus, the only question is whether a human study using only adult males meets the regulatory requirement of ''scientifically valid and relevant data.'' (40 CFR 26.1701). Because NRDC has proffered no evidence regarding the representativeness of adult males to the general population, 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)). 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)).

NRDC's hearing request is also flawed because NRDC does not object to the basis EPA asserted in its petition denial for concluding that the Gledhill study provided scientifically valid data despite its use of only adult male subjects. As noted above, EPA thought representativeness concerns were addressed by the fact that animal studies with DDVP showed no differences in sensitivities between males and females and adults and the young. NRDC, however, has not challenged and proffered evidence to rebut this conclusion nor has NRDC challenged or proffered evidence to rebut EPA's analysis of the underlying data. Rather, NRDC just repeats its assertions regarding the unrepresentativeness of adult males generally. This failure to challenge the basis of EPA's petition denial affects the materiality of the objection and hearing request. Even if NRDC offers evidence to show sex- and age-related sensitivities in the population to some toxicants, such evidence would not rebut the DDVP-specific data on sensitivity. (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.'')).

iv. *Denial of objection*. EPA concludes that it was reasonable to use the Gledhill study despite that fact that it only examined adult males given that the animal toxicology data on DDVP's cholinesterase effects consistently showed no differences between males and females and adults and the young. Multiple studies involving adult animals yielded consistent cholinesterase inhibition results in males and females. (Ref. 3 at 124-126). Similarly, Benchmark Dose Method analysis of the developmental neurotoxicity data ''did not demonstrate any substantial numerical differences in [Benchmark Dose Method Level] values for either RBC or brain cholinesterase between young and adult animals.'' (72 FR at 68694).

d. *Plasma*—i. *Objection/hearing request*. NRDC objects that the Gledhill study is unreliable because it measured only RBC cholinesterase inhibition and not plasma cholinesterase inhibition. NRDC claims that measuring plasma cholinesterase might have reduced the variability measured in RBC cholinesterase.

ii. *Background*. In its petition, NRDC argued that plasma cholinesterase should have been measured because it might be a more sensitive indicator of DDVP's cholinesterase effects. EPA responded to the petition by noting that RBC cholinesterase is the Agency's preferred cholinesterase inhibition endpoint as compared to plasma cholinesterase. (72 FR at 68676). EPA explained that ''[s]ince the red blood cell contains only acetylcholinesterase, the potential for exerting effects on neural or neuroeffector acetylcholinesterase may be better reflected by changes in red blood cell acetylcholinesterase than by changes in plasma cholinesterases which contain both butyrylcholinesterase and acetylcholinesterase in varying ratios depending upon the species.'' (Id.). EPA concluded that information on a less preferred endpoint ''adds little meaningful information.'' (Id.).

iii. *Denial of hearing*. NRDC proffers no evidence in support of its allegation that collection of plasma cholinesterase inhibition data would be useful in limiting the variability seen in the RBC cholinesterase inhibition data. Hearings will not be granted on mere allegations. (40 CFR 178.32(b)(2)). Further, given EPA's conclusion that the variability in RBC cholinesterase inhibition in the test subjects was accounted for by pre- and post-treatment measurement, this issue is not material to resolution of NRDC's claim. Finally, to the extent NRDC is advocating reliance on plasma cholinesterase inhibition data over RBC cholinesterase inhibition data that is a policy issue and hearings will not be held as to policy issues. (40 CFR 178.32(b)(1)).

iv. *Denial of objection*. EPA's well-established policy when evaluating blood cholinesterase inhibition is to use RBC cholinesterase data in preference to plasma cholinesterase. (Ref. 10 at 32). EPA's reasoning here is straightforward. Blood cholinesterase data is used as an indicator of possible effects on acetylcholinesterase in the peripheral nervous system. RBC cholinesterase is composed entirely of acetylcholinesterase, whereas plasma cholinesterase is a mixture of acetylcholinesterase and butyrylcholinesterase, a compound somewhat similar to acetylcholinesterase in structure that nonetheless is ''different in important ways which often result in it having binding affinities to anticholinesterase agents as well as other characteristics that are quite different from those of acetylcholinesterase.'' (Id. at 32). The ratio of acetylcholinesterase to butyrylcholinesterase in plasma differs by species; in humans, plasma ''is overwhelmingly butyrylcholinesterase with a ratio of butyrylcholinesterase to acetyl cholinesterase of 1,000:1.'' (Id.)

It is preferable to have both RBC and plasma cholinesterase data from a study because effects in the RBC may be non-existent, equivocal, or fail to establish a clear-dose response pattern. In those circumstances, plasma cholinesterase inhibition data may serve as a Point of Departure or may aid in the interpretation of the RBC data, particularly when extrapolating animal data to humans. In the Gledhill study, however, the robust RBC cholinesterase sampling approach in humans (multiple pre- and post-dosing samples and sampling after repeat dosing) as well as the clear pattern on RBC cholinesterase inhibition means the absence of plasma cholinesterase inhibition data is of little to no consequence.

In its objections NRDC claims that plasma cholinesterase inhibition data ''might have reduced somewhat'' the variability in the RBC cholinesterase data. EPA disagrees both because plasma cholinesterase in humans is overwhelmingly composed of butyrylcholinesterase not acetylcholinesterase, and because the robust sampling plan in the Gledhill study well-characterized the RBC cholinesterase variability. For all of these reasons, NRDC's objection on this issue are denied.

e. *Controls over environment*—i. *Objection/hearing request sub-issue*. NRDC argues that because there were

not controls over the Gledhill test subjects' exposure to environmental factors which might affect cholinesterase inhibition (e.g., ingestion of pharmaceuticals), the results of Gledhill study might be caused environmental factors and are thus invalid.

ii. *Background*. This claim is contained in NRDC's petition and was not specifically addressed by EPA in the petition denial order other than through its acceptance of the HSRB's analysis.

iii. *Denial of hearing request*. The control measures used in the Gledhill study are set forth in the study report and are not in dispute. The only question is whether these control measures make the Gledhill study scientifically invalid and thus not in compliance with EPA regulations. Legal questions such as this are not appropriate for a hearing. (40 CFR 178.32(b)(1); 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 and thus is not a hearing issue; whether a particular effect is a ''harm'' is a question of law not of fact and a hearing will not be held on issues of law)). Additionally, NRDC proffers no evidence regarding the effect of the study's control measures other than speculation about how environmental factors might have affected the study. A hearing will not be granted on the basis of mere allegations or speculation. (40 CFR 178.32(b)(2); (57 FR 6667, 6671 (February 27, 1992)). Finally, NRDC's argument here is immaterial to its claim. As EPA explains below in denying this objection, the lack of control measures would only be an issue if NRDC is arguing that EPA has wrongfully concluded that the Gledhill study has not shown a measurable effect in the treated subjects.

iv. *Denial of objection*. NRDC's objection here might warrant some consideration if the study results had shown no pattern and EPA had concluded that the study established a NOAEL for DDVP. In those circumstances, it could be argued that any effects from DDVP exposure may have been masked by other factors. However, the study results here showed a clear and consistent pattern of marginal effects on RBC cholinesterase inhibition in connection with DDVP dosing. Given these results and the fact that the test subjects were pre-screened for environmental factors that might affect study results (e.g., regular use of pharmaceuticals; excessive alcohol consumption; exposure to organophosphurus compounds), NRDC's speculation that environmental factors might have affected the study results is without merit.

f. *Consent*—i. *Objection/hearing request sub-issue*. NRDC asserts that informed consent was not obtained from the Gledhill test subjects because the consent form for the experiment identified DDVP as a ''drug.'' (Ref. 1 at 14). NRDC claims that EPA has ignored this issue. NRDC cites an EPA memorandum dated March 16, 2006, examining the ethics of the Gledhill study and asserts that it ''fails to mention [the informed consent] issue when it concludes that the study was not fundamentally unethical.'' (Id. at 15). NRDC argues that describing DDVP as a drug ''constitute[s] 'fundamentally unethical' actions by any reasonable understanding of that term.'' (Id.).

ii. *Background*. This objection comes verbatim from NRDC's comments on the DDVP IRED. EPA responded to this issue in its denial of NRDC's petition by adopting the HSRB's conclusion that informed consent was obtained. EPA explained that ''[t]he HSRB reasoned that references to DDVP as a drug did not vitiate informed consent because 'the consent materials clearly advised subjects that this was a study involving consuming an insecticide.''' (72 FR at 68675).

iii. *Denial of hearing*. It is not clear from NRDC's objections whether NRDC is challenging EPA's conclusion on the ethics of consent issue based on (1) an alleged failure of EPA to address this question; or (2) the legal proposition that identification of a pesticide as a drug ''constitute[s] 'fundamentally unethical' actions by any reasonable understanding of that term.'' In either case, a hearing is not appropriate on NRDC's objection.

First, NRDC's allegation that EPA did not address the consent issue does not present a genuinely-disputed issue of fact. It is plain on the face of EPA's petition denial order, that EPA adopted the reasoning of the HSRB on why references on the consent form to DDVP as a drug do not constitute clear and convincing evidence that the Gledhill study is fundamentally unethical. (72 FR at 68675). After summarizing the decision of the HSRB on the consent issue (see quoted language in Unit VIII.E.3.f.ii. above), EPA stated: ''EPA adopts the HSRB's reasoning and finds it persuasive in rejecting NRDC's arguments concerning why the Gledhill study should not be relied upon.'' (Id.). NRDC's argument that EPA offered no explanation is based on a memorandum that predates and is superseded by EPA's denial of NRDC's petition. The March 16, 2006 memorandum was finalized more than 20 months before issuance of the DDVP petition denial order and the order contains EPA's rationale on the consent issue. As noted earlier in Unit VIII.D.3.c., when an objector to a section 408(d)(4)(iii) order challenges an EPA conclusion that has been superseded by the section 408(d)(4)(iii) order, the objector has not raised a live controversy as to a material issue. (See 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)). Moreover, objections, and hearing requests on objections, may only be filed as to a section 408(d)(4)(iii) order or other statutorily-specified action. (21 U.S.C. 346a(g)(2)(A)).

Second, the informed consent question as to the Gledhill study is a legal/policy issue not a factual one. There are no disputed facts regarding the consent form. The consent form used in the Gledhill study is set forth in the study report and NRDC has not proffered any other evidence bearing on consent. Accordingly, the only question is the legal/policy one of whether use of the Gledhill study consent form is ''clear and convincing evidence'' that the Gledhill study was ''fundamentally unethical'' and thus not in compliance with EPA regulations. (40 CFR 26.1704). In fact, NRDC has framed the consent issue as a legal question, arguing that the undisputed reference to DDVP as a drug in the consent form for the Gledhill study ''constitute[s] [a] 'fundamentally unethical' action[] by any reasonable understanding of that [regulatory] term.'' (Ref. 1 at 15). Further, to support this legal argument, NRDC turns to other legal authorities arguing that ''[t]he requirement for obtaining informed consent is at the core of the [40 CFR] Part 26 regulations and FIFRA section 12(a)(2)(P),'' and ''[v]iolation of these regulations, laws and international standards in the design and conduct of human studies is fundamentally unethical.'' (Id.). Hearings are not appropriate on questions of law or policy. (40 CFR 178.32(b)(1)).

Finally, a hearing is not appropriate on this sub-issue because NRDC's objection does not respond to EPA's conclusion, based on the HSRB's reasoning, as to why there was not a problem with consent in the Gledhill study. As such, NRDC's objection on this point is nothing more than a general denial of EPA's conclusion and a hearing cannot be justified on this basis. (40 CFR 178.32(b)(2)).

iv. *Denial of objection*. NRDC has offered no response to EPA's petition

denial order which incorporated the HSRB's reasoning as to why the references to DDVP as a drug did not constitute clear and convincing evidence that the Gledhill study was fundamentally unethical. Specifically, NRDC does not address the HSRB's conclusion, adopted by EPA, that the test subjects' consent was informed because ''the consent materials clearly advised subjects that this was a study involving consuming an insecticide.'' (Ref. 21 at 46). Thus, EPA denies the objection.

g. *Protection of health of the test subjects*—i. *Objection/hearing request sub-issue*. NRDC differs with EPA's conclusion that there was not clear and convincing evidence that the Gledhill study was rendered fundamentally unethical by the failure of the test conductors to retest the subjects until their cholinesterase inhibition levels returned to baseline levels. (Ref. 1 at 14-15). According to NRDC, EPA acknowledged, in a March 16, 2006, memorandum, that the failure to retest was inconsistent with the standards in the Declaration of Helskinki by showing a lack of concern for the safety of the test subjects. (Id.). NRDC claims that EPA has offered no explanation for why it concluded that the Gledhill study was not fundamentally unethical despite this inconsistency with the Declaration of Helsinki. (Id. at 15).

ii. *Background*. This objection is adopted verbatim from the comments that NRDC filed on the IRED. (Ref. 23 at 16-17). In responding to this claim, EPA adopted the reasoning of the HSRB that ''[d]eficiencies in monitoring of subjects were found not to provide clear and convincing evidence that the study was ethically deficient by subjecting the test subjects to the threat of serious harm because prior studies by this researcher involving higher doses had only invoked minimal responses.'' (72 FR at 68675).

iii. *Denial of hearing*. As with the consent issue, it is not clear from NRDC's objections whether NRDC is challenging EPA's conclusion on the ethics of not retesting based on (1) an alleged failure of EPA to offer an explanation for its conclusion; or (2) the legal proposition that a study that is inconsistent with the Declaration of Helsinki is necessarily ''fundamentally unethical'' under the Human Research rule. In either case, a hearing is not appropriate on NRDC's objections.

If NRDC is challenging EPA's alleged lack of an explanation, then NRDC has failed to identify a genuinely-disputed issue of fact. As with the consent issue, EPA, in its petition denial order, summarized and then adopted the reasoning of the HSRB on why the failure to retest does not constitute clear and convincing evidence that the Gledhill study is fundamentally unethical. (72 FR at 68675) (see quoted language in Unit VIII.E.3.g.ii. above). NRDC's argument that EPA offered no explanation is based on a memorandum that predates and is superseded by EPA's denial of NRDC's petition. For the reasons set forth in Unit VIII.D.3.c and Unit VIII.E.3.f.iii., an objection and hearing request as to a section 408(d)(4)(iii) order based on a memorandum superseded by the section 408(d)(4)(iii) order does not constitute a live controversy on an issue material to the section 408(d)(4)(iii) order and, arguably, not even a valid objection under section 408(g)(2)(A). (21 U.S.C. 346a(g)(2)(A); see 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)).

If NRDC is challenging the substance of EPA's conclusion on the ethics of the Gledhill study, this objection also does not warrant a hearing because NRDC is making no more than a legal or policy argument. There is no dispute with regard to what post-testing was performed as to the Gledhill subjects. NRDC admits as much. (Ref. 1 at 15 (''There is nothing in the [EPA] memo that suggests that there is any uncertainty or controversy about what the various study documents said or what was done in the study in relation to this ethical 'inconsistency' with the Helsinki Declaration. . . . Notwithstanding the clear facts of the case [regarding retesting] . . . .''). The only question is whether the failure to test subjects until cholinesterase inhibition levels returned to baseline is ''clear and convincing evidence'' that the Gledhill study was ''fundamentally unethical.'' (40 CFR 26.1704). Like the consent issue, NRDC, itself, has framed the issue as involving a legal question as to which there is only one answer. According to NRDC, ''these failings [as to retesting subjects and consent] both constitute 'fundamentally unethical' actions by any reasonable understanding of that term.'' (Ref. 1 at 15). Further, NRDC argues categorically that ''[v]iolation of . . . international standards in the design and conduct of human studies is fundamentally unethical.'' (Id.). This is a legal/policy determination regarding application of an EPA regulatory standard and the standards of the Declaration of Helsinki to undisputed facts. Certainly, NRDC has proffered no genuine factual issue to be resolved at a hearing. Hearings are not appropriate on questions of law or policy. (40 CFR 178.32(b)(1)).

Finally, a hearing is not appropriate on this sub-issue because NRDC's objection does not respond to EPA's conclusion, based on the HSRB's reasoning, as to why the failures in monitoring of subjects following the conclusion of dosing did not amount to clear and convincing evidence that the study was fundamentally unethical. As such, NRDC's objection on this point is nothing more than a general denial of EPA's conclusion and a hearing cannot be justified on this basis. (40 CFR 178.32(b)(2)).

iv. *Denial of objection*. NRDC has offered no response to EPA's petition denial order which incorporated the HSRB's reasoning as to why the failure to retest subjects did not constitute clear and convincing evidence that the Gledhill study was fundamentally unethical. Specifically, NRDC does not address the HSRB's conclusion, adopted by EPA, that the lack of retesting was not fundamentally unethical because ''prior studies by this researcher involving higher doses had only invoked minimal responses.'' (72 FR at 68675). Thus, NRDC's objection on this point is denied.

F. Summary of Reasons for Denial of NRDC's Hearing Requests

EPA denies NRDC's request for a hearing on whether reliable data support EPA's reduction of the children's safety factor and on whether EPA properly relied on the Gledhill human study. EPA's close examination of each of the 19 sub-issues involved in these two hearing requests demonstrates that none of the issues satisfies the standard for granting a hearing in 40 CFR 178.32. Most fail for multiple reasons.

Several sub-issues do not present an issue of genuinely-disputed fact. Instead, NRDC raises issues presenting purely legal or policy questions or questions involving the application of legal standards to undisputed facts. For example, with regard to its children's safety factor objection, NRDC makes the legal argument that failure to complete the mandatory endocrine screening program compels EPA to retain the children's safety factor for DDVP and all other pesticides. (See Unit VIII.D.2.a.). In other cases, NRDC's description of a factual dispute is clearly contradicted by the record. An example here is NRDC's assertion that EPA failed to consider acute residential exposure even though EPA, in response to

NRDC's petition, amended its risk assessment to include examination of exposure for 1–day and 14–day periods. (See Unit VIII.D.4.c.)

Many of NRDC's sub-issues lack materiality. In some instances that is due to NRDC's misunderstanding of a scientific concept - as when NRDC raises questions about the statistical power of the Gledhill study or seeks to invalidate the Gledhill study based on a alleged inadequacy to control for environmental factors. Both of these concepts have little relevance given the positive results found in that study. (See Units VIII.E.3.a. and VIII.E.3.e.). In other instances, the sub-issues presented by NRDC lack materiality either because (1) NRDC objects to aspects of EPA's risk assessments that were changed in response to the petition; (2) NRDC fails to address the reasons given by EPA for denying NRDC's petition; or (3) NRDC objects to prior conclusions of EPA that were superseded by the petition denial order. (See Units VIII.D.3., VIII.E.3.b., and VIII.E.3.g.)

Most importantly, as to all of the sub-issues, NRDC fails to identify and proffer evidence which, if established, would resolve one or more questions in NRDC's favor. As EPA's analysis shows, NRDC essentially proffered no evidence in support of its hearing requests and objections and instead relies upon legal and policy arguments and unsupported or speculative factual assertions. NRDC's attempted evidentiary proffers are either: (1) so broad as to be meaningless (e.g., the complete EPA docket for DDVP); (2) too general to define a factual issue as to DDVP (e.g., newspaper and law review articles); (3) supportive of scientifically irrelevant claims (e.g., Sass and Lockwood articles); or (4) mere allegations or general denials (e.g., NRDC's claim that dietary risk assessment ''poses a serious risk of understating risks posed by DDVP;'' NRDC's speculation about how many DDVP pest strips a homeowner may use). (See Units VIII.C., VIII.D.3., and VIII.D.4.e.).

NRDC's failure to offer evidence in support of its contentions is a consistent pattern in this proceeding. NRDC offered no greater support for its arguments in its petition, in its comments on the IRED, or, for that matter, in its written or oral comments to the HSRB. In these circumstances, EPA questions whether granting a hearing would have been appropriate even if NRDC had, at this last stage of the administrative process, suddenly produced factual evidence in support of its claims. Presumably, Congress created a multi-stage administrative process for resolution of tolerance petitions to give EPA the opportunity in the first stage of the proceeding 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. While EPA has not held any pesticide tolerance hearings under the FFDCA, its experience with pesticide hearings under FIFRA in the 1970s indicates the process can be quite lengthy. (See were e.g., Environmental Defense Fund v. EPA, 548 F.2d 998, 1002 (D.C. Cir. 1976) (4 months were needed for testimony in an expedited FIFRA suspension proceeding); Environmental Defense Fund, Inc. v. EPA, 510 F.2d 1292, 1297 (D.C. Cir. 1975) (13 months of testimony in a FIFRA cancellation proceeding); Environmental Defense Fund v. Ruckelshaus, 489 F.2d 1247, 1251 n. 24 (D.C. Cir. 1973) (''During seven months of hearings [in the DDT cancellation proceeding], 125 witnesses appeared to testify and 365 exhibits were placed in evidence. The transcript of the hearings was over 9,000 pages long.''); Ref. 44 at 246 (referring to FIFRA cancellation proceedings in the 1970s as the '''100–years' pesticide wars''). Given that in the ensuing 30 years the pesticide risk assessment process has become exponentially more complex, FFDCA pesticide hearings have the potential for being even more resource intensive. 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 process (if, consideration of information that was previously available is appropriate at all).

Finally, EPA notes that it is denying NRDC's hearing requests under 40 CFR 178.32 and does not here rely on the even broader discretionary authority to deny hearing requests in FFDCA section 408(g)(2)(B). As recounted previously, 40 CFR 178.32 predates the explicit addition to the statute by the FQPA of the grant of authority to EPA to deny hearings. That language 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 does not interpret this language as requiring it to hold a hearing in any instance where factual evidence relevant to a material issue of fact is proffered (essentially the standard set forth in 40 CFR 178.32); rather, EPA construes the statutory language as requiring it to hold a hearing only where it determines a hearing is *necessary* to receive such proffered evidence. In other words, a party wishing to obtain a hearing must not only satisfy the requirements of 40 CFR 178.32, it must also show that an evidentiary hearing is necessary to presentation of proffered evidence to the Agency. Because, however, NRDC has not satisfied the standard set forth in 40 CFR 178.32, EPA does not need to address whether a hearing is necessary to receive NRDC's ''evidentiary'' proffer.

G. Summary of Reasons for Denial of NRDC's Objections

EPA denies NRDC's objections to EPA's petition denial that EPA lacked sufficient data to reduce the children's safety factor for DDVP, and EPA unlawfully relied on the Gledhill intentional human dosing study in assessing the risk of DDVP exposure.

1. *Children's safety factor objection.* In support of its children's safety factor objection, NRDC claims that EPA has inadequate data on endocrine effects, dietary exposure to DDVP residues in food, and exposure from residential pest strips. On endocrine effects, NRDC argues that EPA lacks adequate data, as a legal matter, because it has not completed the section 408(p) endocrine screening program, and, as a factual matter, because DDVP has not been tested under the most recent two-generation rat reproduction study. EPA has previously rejected NRDC's legal argument as not consistent with the statutory language, structure, or history, and NRDC has offered no arguments as to why EPA's previous conclusion was incorrect. On the factual question of whether EPA has adequate endocrine data on DDVP, EPA concluded in the petition denial that, given the existing data bearing on DDVP's potential to cause endocrine effects and large difference in sensitivity between DDVP's cholinesterase inhibition effects and potential endocrine effects, EPA had sufficient reliable data on DDVP's potential endocrine effects to vary from the default children's safety factor. In its objections, NRDC offers nothing other than speculation about what another two-generation rat reproduction study might show. NRDC's speculation does not convince EPA that its analysis was incorrect.

As to dietary exposure to DDVP residues in food, NRDC argues that EPA's dietary exposure assessment has

many shortcomings that may lead to underestimation of dietary exposure to DDVP. In support of this claim, NRDC relies on statements EPA made in 2000 in a preliminary risk assessment of DDVP. NRDC places particular emphasis on its claim that EPA's database on food consumption by infants is inadequate. These allegations by NRDC lack merit because NRDC has ignored the many revisions to the DDVP risk assessment since the 2000 preliminary risk assessment. First, EPA completely revised the dietary exposure and risk assessment in response to NRDC's petition. One of the specific reasons for revising the risk assessment was so that EPA's latest information on infant food consumption could be incorporated. Second, also in response to NRDC's petition, EPA comprehensively analyzed its dietary exposure assessment to evaluate whether that assessment potentially underestimated dietary exposure to DDVP. EPA concluded that ''its assessment of exposure to DDVP from food will not under-estimate but rather over-estimate, and in all likelihood substantially over-estimate, DDVP exposure.'' (72 FR at 68686). NRDC neither acknowledges nor challenges the revised dietary exposure assessment or EPA's detailed analysis of whether that assessment under- or over-estimates DDVP exposure. Finally, EPA questions the materiality of NRDC's argument with regard to DDVP exposure from food given that DDVP exposure from this source is trivial compared with other sources. For all of these reasons, EPA rejects NRDC's arguments on the alleged inadequacy of EPA's assessment of human dietary exposure to DDVP in food.

With regard to DDVP exposure from residential pest strips, NRDC claims that the data relied upon by EPA (the Collins and DeVries study) was inadequate and EPA's risk assessment based on that study was based on inadequately-supported assumptions. These arguments, however, are without merit because not only does NRDC offer nothing other than general, undocumented contentions in support but once again NRDC has ignored clear evidence and analysis in the record that contradict its allegations. First, NRDC ignores the other DDVP pest strip exposure studies relied upon by EPA to support the findings in the Collins and DeVries study. EPA concluded that these studies confirmed that the findings in Collins and DeVries were representative of DDVP concentration levels from pest strips that could be expected in houses in other locations. Second, NRDC ignores EPA's complete revision to the DDVP residential exposure assessment that was conducted in response to its petition. That revision modified numerous assumptions in the assessment to ensure that the data from the Collins and DeVries study were analyzed in a conservative fashion. NRDC does not acknowledge the new assessment much less offer a rebuttal to EPA's revised analysis. Most surprisingly, NRDC repeats challenges to several assumptions (only examining DDVP exposure as averaged over a 120–day period; considering 16 hours per day a maximum exposure in a home) that were explicitly modified (adding consideration of 1–day and 14–day exposure periods; assuming 24 hours exposure per day) in the revised risk assessment in response to NRDC's petition. Accordingly, EPA disagrees with NRDC's allegations concerning the inadequacy of the data and assumptions underlying its residential pest strip risk assessment.

2. *Human study objection.* NRDC challenged EPA's reliance on the Gledhill human study arguing that EPA's Human Research rule is unlawful and the study was both scientifically flawed and unethically conducted.

NRDC relies on its legal briefs filed in a separate challenge to the Human Research rule and its comments on that rule in support of its legal attack on the rule. Similarly, to the extent NRDC has standing to challenge a rule whose ''primary concern'' is the ''[p]rotection of the health and safety of human test subjects,'' (Ref. 1 at 15), EPA relies on its legal brief in the 2nd Circuit proceeding and the administrative record for the rule, in denying NRDC's challenge to Human Research Rule.

As to the Gledhill study, itself, NRDC makes various claims regarding its scientific validity and ethicality. NRDC has previously presented these claims in writing and orally to EPA's HSRB. The HSRB is an independent scientific panel, consisting of experts in bioethics, biostatistics, human health risk assessment, and human toxicology, created specifically for the purpose of advising EPA on whether human studies have scientific value and conform to ethical standards. Although NRDC's concerns as to the Gledhill study were presented to the HSRB, the HSRB concluded that the Gledhill study complied with the Human Research rule and could be considered by EPA in assessing the risk of DDVP. EPA relied heavily on the advice by the HSRB in denying NRDC's petition. Remarkably, NRDC, in its objections, proceeds as if the HSRB review never occurred. NRDC neither acknowledges the existence of the HSRB report nor attempts to refute its reasoning. In Unit VIII.E. above, EPA repeats the findings of the HSRB and EPA's reasons for accepting the HSRB's conclusions with regard to the specific contentions of NRDC. Based on both the findings of the HSRB and EPA in its petition denial, as described above, as well as NRDC's failure to meaningfully dispute those findings, EPA rejects NRDC's challenge to EPA's reliance on the Gledhill study.

H. Conclusion

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

IX. References

1. Natural Resources Defense Council, ''Objection to the Order Denying NRDC's Petition to Revoke All Tolerances for Dichlorvos (DDVP), and Request for Public Evidentiary Hearing'' (February 1, 2008).

2. Natural Resources Defense Council, Petition of Natural Resources Defense Council To Conclude Special Review, Reregistration and Tolerance Reassessment Processes and To Revoke All Tolerances and Cancel All Registrations for the Pesticide DDVP (June 2, 2006).

3. Office of Prevention, Pesticides and Toxic Substances, EPA, ''Interim Reregistration Eligibility Decision for Dichlorvos (DDVP)'' (June 2006).

4. U.S. EPA, ''A User's Guide to Available EPA Information on Assessing Exposure to Pesticides in Food'' (June 21, 2000).

5. Office of Pesticide Programs, US EPA, ''Office of Pesticide Programs' Policy on the Determination of the Appropriate FQPA Safety Factor(s) For Use in the Tolerance Setting Process'' (February 28, 2002).

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X. 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.

XI. 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).

Appendix 1—United States Environmental Protection Agency Human Studies Review Board

Chair

Celia B. Fisher, Ph.D. Marie Ward Doty Professor of Psychology, Director, Center for Ethics Education, Fordham University, Department of Psychology, Bronx, NY

Vice Chair

William S. Brimijoin, Ph.D., Chair and Professor, Molecular Pharmacology and Experimental Therapeutics, Mayo Foundation, Rochester, MN

Members

David C. Bellinger, Ph.D., Professor of Neurology, Harvard Medical School Professor in the Department of Environmental Health, Harvard School of Public Health Children's Hospital, Boston, MA

Alicia Carriquiry, Ph.D., Professor, Department of Statistics, Iowa State University Snedecor Hall, Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP, Associate Provost, Director, Office for Human Subjects Protection, University of Rochester, Rochester, NY

Janice Chambers, Ph.D., D.A.B.T., William L. Giles Distinguished Professor, Director, Center for Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University, Wise Center, Mississippi State, MS

Richard Fenske, Ph.D., MPH, Professor, Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA

Susan S. Fish, PharmD, MPH, Professor, Biostatistics and Epidemiology, Boston University School of Public Health, Co-Director, MA in Clinical Investigation Boston University School of Medicine, Boston, MA

Suzanne C. Fitzpatrick, Ph.D., DABT, Senior Science Policy Analyst, Office of the Commissioner, Office of Science and Health Coordination, U.S. Food and Drug Administration, Rockville, MD

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KyungMann Kim, Ph.D., CCRP, Professor and Associate Chair, Department of Biostatistics and Medical Informatics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI

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Jerry A. Menikoff, M.D., Associate Professor of Law, Ethics and Medicine, Director of the Institute for Bioethics, Law and Public Policy, University of Kansas Medical Center, Kansas City, KS

Robert Nelson, M.D., Ph.D., Associate Professor of Anesthesiology and Critical Care, Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA

Sean M. Philpott, Ph.D., Research Scientist, David Axelrod Institute, Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, NY

List of Subjects in 40 CFR Part 180

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

Dated: July 11, 2008.

Debra Edwards,

Director, Office of Pesticide Programs.

[FR Doc. E8–16617 Filed 7–22–08; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2008–0302; FRL–8369–5]

Fludioxonil; Pesticide Tolerance for Emergency Exemption

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes a time-limited tolerance for residues of fludioxonil in or on carambola (starfruit). This action is in response to EPA's granting of an emergency exemption under section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizing use of the pesticide on carambola. This regulation establishes a maximum permissible level for residues of fludioxonil in starfruit. The time-limited tolerance expires and is revoked on December 31, 2010.

DATES: This regulation is effective July 23, 2008. Objections and requests for hearings must be received on or before September 22, 2008, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**.

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2008–0302. To access the electronic docket, go to *http://www.regulations.gov*, select ''Advanced Search,'' then ''Docket Search.'' Insert the docket ID number where indicated and select the ''Submit'' button. Follow the instructions on the regulations.gov website 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 either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the Office of Pesticide Programs (OPP) Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Andrea Conrath, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 308–9356; e-mail address: conrath.andrea@*epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. 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