ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2002–0302; FRL–8341–9]

Dichlorvos (DDVP); Order Denying NRDC's Petition to Revoke All Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: In this Order, EPA denies a petition requesting that EPA revoke all pesticide tolerances for dichlorvos (DDVP) under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The petition was filed on June 2, 2006, by the Natural Resources Defense Council (NRDC).

DATES: This order is effective December 5, 2007. Objections and requests for hearings must be received on or before February 4, 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–2002-0302. 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 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 a petition by the Natural Resources Defense Council (''NRDC'') 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. Can I File an Objection or Hearing Request?

Under section 408(g) of FFDCA, any person may file an objection to any aspect of this order and may also request a hearing on those objections. You must file your objection or request a hearing on this order in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA–HQ–OPP–2002-0302 in the subject line on the first page of your submission. All requests must be in writing, and must be mailed or delivered to the Hearing Clerk as required by 40 CFR part 178 on or before February 4, 2008.

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing that does not contain any CBI for inclusion in the public docket that is described in **ADDRESSES**. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit this copy, identified by docket ID number EPA–HQ–OPP–2002-0302, by one of the following methods:

- *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.
- *Mail*: Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001.
- *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305–5805.

II. Introduction

A. What Action Is the Agency Taking?

On June 2, 2006, the Natural Resources Defense Council (NRDC) filed a petition with EPA which, among other things, requested that EPA revoke all tolerances for the pesticide dichlorvos (DDVP) established under section 408 of the Federal Food, Drug, and Cosmetic Act (''FFDCA''), 21 U.S.C. 346a. (Ref. 1). NRDC's petition asserts that the DDVP tolerances are unsafe and should be revoked for numerous reasons, including: EPA has improperly assessed the toxicity of DDVP; EPA has erred in

estimating dietary and residential exposure to DDVP; and EPA has unlawfully removed the additional safety factor for the protection of infants and children. This order finds NRDC's claims regarding the DDVP tolerances to be without merit and, accordingly, denies that aspect of NRDC petition. The other aspects of NRDC's petition are addressed in another EPA action.

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

Under section 408(d)(4) of the FFDCA, EPA is authorized to respond to a section 408(d) petition to revoke tolerances either by issuing a final rule revoking the tolerances, issuing a proposed rule, or issuing an order denying the petition. (21 U.S.C. 346a(d)(4)).

III. Statutory and Regulatory Background

A. Statutory Background

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 and the U. S. Department of Agriculture. 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.

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)).

Section 408(b)(2)(C) requires EPA to give special consideration to risks posed to infants and children. Specifically, this provision 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 further 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, the 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 affected party has 60 days to file objections with EPA and seek an evidentiary hearing on those objections. (21 U.S.C. 346a(g)(2)). 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 requires, among other things, that EPA reassess the safety of all pesticide tolerances existing at the time of its enactment. (21 U.S.C. 346a(q)). In this reassessment, EPA is 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 is generally handled in conjunction with a similar program involving reregistration of pesticides under FIFRA. (7 U.S.C. 136a-1). Reassessment and reregistration decisions are generally combined in a document labeled a Reregistration Eligibility Decision (''RED'').

5. *Estrogenic Substances Screening Program*. Section 408(p) of the FFDCA creates the estrogenic substances screening program. This provision gives EPA 2 years from enactment of the FQPA to ''develop a screening program ... to determine whether certain 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.'' This screening program must use ''appropriate validated test systems and scientifically relevant information.'' (21 U.S.C. 346a(p)(1)). 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 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. Setting and Reassessing Pesticide Tolerances Under the FFDCA

1. *In general*. The process EPA follows in setting and reassessing tolerances under the FFDCA includes two steps. First, EPA determines an appropriate residue level value for the tolerance taking into account data on levels that can be expected in food. Second, EPA evaluates the safety of the tolerance relying on toxicity and exposure data and guided by the statutory definition of ''safety'' and requirements concerning risk assessment. Only on completion of the second step can a tolerance be established or reassessed. Both stages of this process are relevant to EPA's analysis of petitions to revoke tolerances based on risk concerns because both stages bear on the assessment of risk.

2. *Choosing a tolerance value*. In the first step of the tolerance setting or reassessment process (choosing a tolerance value), EPA evaluates 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. 2 and 3). 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. 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. 4). (As discussed below, the safety of the tolerance value chosen is separately evaluated.).

There are three main reasons for closely linking tolerance values to the maximum value that could be present from maximum label usage of the pesticide. First, EPA believes it is important to coordinate its actions under the two statutory frameworks governing pesticides. (See 61 FR 2378, 2379 (January 25, 1996)). It would be illogical for EPA to set a pesticide tolerance under the FFDCA without considering what action is being taken under FIFRA with regard to registration of that pesticide use. (Cf. 40 CFR 152.112(g) (requiring all necessary tolerances to be in place before a FIFRA registration may be granted)). In coordinating its actions, one basic tenet that EPA follows is that a grower who applies a pesticide consistent with the FIFRA label directions should not run the risk that his or her crops will be adulterated under the FFDCA because the residues from that legal application exceed the tolerance associated with that use. Crop field trials require application of the pesticide in the manner most likely to produce maximum residues to further this goal. Second, choosing tolerance values based on FIFRA label rates helps to ensure that tolerance levels are established no higher than necessary. If tolerance values were selected solely in consideration of health risks, in some circumstances, tolerance values might be set so as to allow much greater application rates than necessary for effective use of the pesticide. This could encourage misuse of the pesticide. Finally, closely linking tolerance values to FIFRA labels helps EPA to police compliance with label directions by growers because detection of an over-tolerance residue is indicative of use of a pesticide at levels, or in a manner, not permitted on the label.

3. *The safety determination - risk assessment*. Once a tolerance value is chosen, EPA then evaluates the safety of the pesticide tolerance using the process of risk assessment. To assess risk of a pesticide, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide.

In evaluating toxicity or hazard, EPA examines both short-term (e.g., ''acute'') and longer-term (e.g., ''chronic'') adverse effects from pesticide exposure. (Ref. 2 at 8-10). EPA also considers whether the ''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. 2 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 carcinogenesis have increasingly led EPA to conclude that some pesticides that cause carcinogenic effects only cause such effects above a certain threshold of exposure. EPA has traditionally considered adverse effects on the endocrine system to be a threshold effect; that determination is being reexamined in conjunction with the endocrine disruptor screening program.

Once the hazard for a durational scenario is identified, EPA must determine the toxicological level of concern and then compare estimated human exposure to this level of concern. This comparison is done through either calculating a safe dose in humans (incorporating all appropriate safety factors) and expressing exposure as a percentage of this safe dose (the reference dose (''RfD'') approach) or dividing estimated human exposure into an appropriate dose from the relevant studies at which no adverse effects from the pesticide are seen (the margin of exposure (''MOE'') approach). How EPA determines the level of concern and assesses risk under these two approaches is explained in more detail below. EPA's general approach to estimating exposure is also briefly discussed.

a. *Levels of concern and risk assessment*—i. *Threshold effects*. In assessing the risk from a pesticide's threshold effects, EPA evaluates an array of toxicological 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 in estimating the level of concern for humans. In estimating and describing the level of

concern, however, the chosen NOAEL is at times manipulated differently depending on whether the risk assessment addresses dietary or non-dietary exposures.

For dietary risks, EPA uses the chosen NOAEL to calculate a safe dose or RfD. The RfD is calculated by dividing the chosen NOAEL by all applicable safety or uncertainty factors. Typically, a combination of safety or uncertainty factors providing a hundredfold (100X) margin of safety is used: 10X to account for uncertainties inherent in the extrapolation from laboratory animal data to humans and 10X for 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. Further, 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. 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.

To quantitatively describe risk using the RfD/PAD approach, estimated exposure is expressed as a percentage of the RfD/PAD. Dietary exposures lower than 100 percent of the RfD are generally not of concern.

For non-dietary, and often for combined dietary and non-dietary, risk assessments of threshold effects, the toxicological level of concern is not expressed as a safe dose or RfD/PAD but rather as the margin of exposure (MOE) that is necessary to be sure that exposure to a pesticide is safe. A safe 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 interspecies differences, 10X factor for intraspecies differences, and 10X factor for FQPA, the safe or target MOE would be a MOE of at least 1,000. To calculate the MOE for a pesticide, human exposure to the pesticide is divided into the lowest NOAEL from the available studies. In contrast to the RfD/PAD approach, the higher the MOE, the safer the pesticide. Accordingly, if the level of concern for a pesticide is 1,000, MOEs exceeding 1,000 would generally not be of concern. Like RfD/PADs, specific MOEs are calculated for exposures of different durations. For non-dietary exposures, EPA typically examines short-term, intermediate-term, and long-term exposures. Additionally, non-dietary exposure often involves exposures by various routes including dermal, inhalation, and oral.

The RfD/PAD and MOE approaches are fundamentally equivalent. For a given risk and given exposure of a pesticide, if the pesticide were found to be safe under an RfD/PAD analysis it would also pass under the MOE approach, and vice-versa.

ii. *Non-threshold effects*. For risk assessments for non-threshold effects, EPA does not use the RfD/PAD or MOE approach if quantitation 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 model that assumes that any amount of exposure will lead to some degree of risk. The slope of the dose-response curve can then be used to estimate the probability of occurrence of additional adverse effects as a result of exposure to the pesticide. For non-threshold cancer risks, EPA generally is concerned if the probability of increased cancer cases exceeds the range of 1 in 1 million.

b. *Estimating human exposure*. Equally important to the risk assessment process as determining the toxicological level of concern 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*. (A) *In General*. 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 U.S. Department of Agriculture. (Ref. 2 at 12). Information on residue values comes from a range of sources including crop field trials, data on pesticide reduction 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, conducts its exposure assessment using the extreme 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. Second, as discussed above, the tolerance value is set above the highest value observed in crop field trials using maximum use rates. 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. (Id. 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 Food and Drug Administration, the U.S. Department of Agriculture, 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. Although 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 maximum residue values for acute risk assessment tends to greatly overstate exposure in narrow increments of time where it matters how much of each treated food a given consumer eats and what the residue levels are in the particular foods consumed. 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.

(B) Computer modeling of dietary exposure. EPA uses a computer program known as the Dietary Exposure Evaluation Model – Food Commodity Intake Database (''DEEM-FCID'') to estimate exposure by combining data on human consumption amounts with residue values in food commodities. DEEM-FCID also compares exposure estimates to appropriate RfD/PAD values to estimate risk. DEEM-FCID can estimate exposure for the general U.S. population as well as 32 subgroups based on age, sex, ethnicity, and region. DEEM-FCID is closely modeled on its predecessor program DEEM. DEEM-FCID includes the DEEM software modeling program but has revised inputs bearing on consumption patterns that were developed by EPA to insure that all underlying aspects of the model are publicly available. (Ref. 6).

EPA uses a computer program to make exposure and risk estimates because EPA has great volumes of data on human consumption amounts and residue levels. Matching consumption and residue data can be done more efficiently by computer. Additionally, certain risk assessment techniques involve thousands of repeated analyses of the consumption database and this cannot practically be done by hand. However, the actual structure and logic of DEEM-FCID is relatively simple.

DEEM-FCID contains consumption and demographic information on the individuals who participated in the USDA's Continuing Surveys of Food Intake by Individuals (''CSFII'') in 1994-1996 and 1998. The 1998 survey was a special survey required by the FQPA to supplement the number of children survey participants. DEEM-FCID also contains translation factors that convert foods as consumed (e.g., pizza) back into their component raw agricultural commodities. This is necessary because residue data are generally gathered on raw agricultural commodities rather than on finished ready-to-eat food. Data on residue values for a particular pesticide and the RfD/PADs for that pesticide have to be inputted into the DEEM-FCID program to estimate exposure and risk.

DEEM-FCID can make three types of risk estimates: a single point estimate; a simple distribution; or a probabilistic distribution. A point estimate provides a single exposure and risk value for each population subgroup. Generally, these exposure and risk values are derived by combining single values for consumption and residue amount on consumed commodities. For example, point estimates are commonly computed for chronic exposure and risk by combining data on average consumption with data on average residue levels. (Ref. 7-).

In contrast to a point estimate, DEEM-FCID can also do two types of distributional analyses. A simple distribution combines a single residue value for each food with the full range of data on individual consumption amounts to create a distribution of exposure and risk levels. More specifically, DEEM-FCID creates this distribution by calculating an exposure value for each reported day of consumption per person (''person/day'') in CSFII assuming that all foods potentially bearing the pesticide residue contain such residue at the chosen value. The exposure amounts for the thousands of person/days in the CSFII are then collected in a frequency distribution.

Added complexity is introduced if DEEM-FCID computes a distribution taking into account both the full range of data on consumption levels and the full range of data on potential residue levels in food. Combining these two independent variables (consumption and residue levels) into a distribution of potential exposures and risk requires use of probabilistic techniques.

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

1. for each person/day in the CSFII, identification of any food(s) that could possibly bear the residue of the pesticide in question;

2. calculation of an exposure level for each person/day based on the foods identified in Step #1 by randomly selecting residue values for the foods from the residue database;

3. repetition of Step #2 one thousand times for each person/day; and

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

In this manner, a probabilistic assessment presents a range of exposure/risk estimates.

Point estimates are used for chronic risk assessments. EPA does not use DEEM-FCID to calculate distributional assessments for chronic risk because EPA's current view is that its consumption database is not sufficiently robust to support a distributional analysis for chronic exposure. Both simple and probabilistically-derived distributions are used for acute risk assessment. EPA generally estimates exposure and risk from a simple distribution based on the 95th percentile of such a distribution. EPA's reason for relying on the 95th percentile with simple distribution assessments is that for these assessments EPA typically uses very conservative assumptions regarding residue levels (100 percent of the crop is treated and all treated food bears residues at the tolerance level) and thus the 95th percentile is protective of the general population as well as all major, identifiable population subgroups. Because probabilistic assessments generally use more realistic residue levels, EPA's starting point for estimating exposure and risk for such assessments is the 99.9th percentile.

This value can change depending on the degree of conservatism in the residue estimates. (Ref. 8).

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.

EPA has developed models for estimating exposure in both surface water and ground water. EPA uses a two-tiered approach to modeling pesticide exposure in surface water. In the initial tier, EPA uses the FQPA Index Reservoir Screening Tool (FIRST) model. FIRST replaces the GENeric Estimated Environmental Concentrations (GENEEC) model that was used as the first tier screen by EPA from 1995-1999. If the first tier model suggests that pesticide levels in water may be unacceptably high, a more refined model is used as a second tier assessment. The second tier model is actually a combination of the models, Pesticide Root Zone Model (PRZM) and the Exposure Analysis Model System (EXAMS). For estimating pesticide residues in groundwater, EPA uses the Screening Concentration In Ground Water (SCI-GROW) model. Currently, EPA has no second tier groundwater model.

EPA's water exposure models have been extensively peer-reviewed and/or validated, and have proved highly conservative in practice. In fact, an evaluation conducted in conjunction with NRDC objections to tolerances for other pesticides found that EPA's surface water models never under-estimated the highest values measured in monitoring studies, and that EPA's groundwater model had only rarely under-estimated such results, and those underestimations were relatively small. (69 FR at 30061-30064).

Whether EPA estimates pesticide exposure in drinking water through monitoring data or modeling, EPA uses the higher of the two values from surface and ground water in quantifying overall exposure to the pesticide. In most cases, pesticide concentrations in surface water are significantly higher than in groundwater.

iii. *Residential exposures*. Generally, in assessing residential exposure to pesticides EPA relies on its Residential Standard Operating Procedures (''SOPs''). 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.

C. EPA Policy on Cholinesterase Inhibition as a Regulatory Endpoint

On August 18, 2000, EPA issued a science policy document entitled ''The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.'' (Ref. 9). Although assessing the risk from organophosphorous and carbamate pesticides was a primary reason for updating EPA guidance on cholinesterase inhibition, the policy addressed the topic generally and not just in the context of these two families of pesticides.

Cholinesterase inhibition is a disruption of the normal enzymatic 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 enzyme, 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 the policy explains, ''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.'' (Id. 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.

The cholinesterase inhibition policy statement explains EPA's approach to evaluating the hazard posed by cholinesterase-inhibiting pesticides. 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 a safe 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. Due to strict ethical limitations, however, 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).

The policy advises that, in selection of a Point of Departure for deriving a RfD/PAD, all data on clinical signs and cholinesterase inhibition should be considered in a weight-of-the-evidence analysis. This weight-of-the-evidence analysis should focus, according to the policy, on (1) ''[a] comparison of the pattern of doses required to produce physiological and behavioral effects and cholinesterase inhibition'' in the central and peripheral nervous systems and in blood; (2) ''comparisons of the temporal aspects (e.g., time of onset and peak effects and duration of effects) of each relevant endpoint;'' and (3) ''the potential for differential sensitivity/susceptibility of adult versus young animals (i.e., effects following perinatal or postnatal exposures).'' (Id. at 35). This analysis can lead EPA to ''select as the critical effects any one or more of the behavioral and physiological changes or enzyme measures listed above.'' (Id.). In comparing studies across the entire database to select an endpoint for the Point of Departure, the policy stresses that ''parallel analyses of the dose-response (i.e., changes in magnitude of enzyme inhibition or of a different effect with increasing dose) and the temporal pattern of all relevant effects will be compared across all of the different compartments affected (e.g., plasma, RBC, peripheral nervous system, brain), and for the functional changes to the extent the database permits.'' (Id. at 38). Further, the policy states that ''[t]he consistency (or, the lack thereof) of LOAELs, NOAELs, or BMDs for each category of effects (e.g., clinical signs, cholinesterase inhibition in the various compartments, etc.) for the test species/strains/sex available and for each duration and route of exposure should be noted.'' (Id.).

D. 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 differences between animals and humans when relying on studies in animals (inter-species safety factor) and differences among humans (intra-species safety factor) as well as the additional 10X children's safety factor added by the FQPA.

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).

E. Endocrine Disruptor Screening Program

To aid in the design of the endocrine screening 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. 10). 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 androgenic and thyroid effects as well. (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. (Endocrine Disruptor Screening and Testing Advisory Committee Final Report, 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 these assays, however, is not yet 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.

Recently, 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.)

IV. DDVP Tolerances

A. Regulatory Background

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. 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 108.235 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.

DDVP is closely related to the pesticides naled and trichlorfon. Naled and trichlorfon both metabolize or degrade to DDVP in food, water, or the environment. All three pesticides 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 and thus, in addition to assessing the risks posed by exposure to these pesticides individually, EPA has assessed the potential cumulative effects from concurrent exposure to organophosphate pesticides.

B. FFDCA Tolerance Reassessment and FIFRA Pesticide Reregistration

As required by the Food Quality Protection Act of 1996, EPA reassessed the safety of the DDVP tolerances under the new safety standard established in the FQPA. In the Interim Reregistration Eligibility Document (''IRED'') for DDVP, EPA determined that aggregate exposure to DDVP as a result of use of DDVP, naled, and trichlorfon, complied with the FQPA safety standard. (Ref. 11). Separately, EPA determined that cumulative effects from exposure to all organophosphate residues were safe. (Ref. 12). 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 the only technical product registrant, Amvac Corporation (''Amvac''), an irrevocable request to cancel certain uses and include additional pest strip label restrictions on the DDVP technical 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. 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)).

C. Toxicity Overview

Animal and human studies with DDVP demonstrate that the toxic effect of concern for DDVP is inhibition of cholinesterase activity. These studies showed decreases in cholinesterase activity in plasma, red blood cell, and the brain. These effects were consistently found whether the exposure duration was acute or chronic and across all tested routes of exposure. Studies involving *in utero*, as well as pre- and post-natal, exposure of young animals showed no evidence of increased sensitivity in the young to these effects. Cholinesterase inhibition was also the effect used to assess potential cumulative effects from exposure to organophosphate pesticides. Based on numerous cancer studies with DDVP, EPA has classified the evidence

on DDVP's potential carcinogenicity as ''suggestive;'' however, due to the lack of relevance to humans of the tumors identified, EPA has determined that DDVP poses a negligible cancer risk to humans.

D. Exposure Overview

Exposure to DDVP can occur through the consumption of food treated with DDVP, naled, or trichlorfon, consumption of drinking water bearing DDVP residues, or from exposure in the residential setting from use of DDVP or trichlorfon. EPA has extensive food monitoring data on DDVP. These data show that with one exception, strawberries, DDVP is rarely found at detectable amounts in food. About 5 percent of sampled strawberries have shown detectable DDVP residues. These monitoring results are consistent with metabolism data on DDVP which shows that it is rapidly degraded into non-toxic substances. EPA has limited water monitoring data showing no detectable residues of DDVP. Due to the fact that these data do not identify whether they were collected from areas of DDVP, naled, or trichlorfon usage and the lack of data from shallow groundwater wells, EPA has relied upon conservative modeling estimates of drinking water. EPA has estimated residential exposure to DDVP based primarily on one of several monitoring studies conducted using DDVP pest strips in houses.

V. The Petition to Revoke Tolerances

On June 2, 2006, the Natural Resources Defense Council (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 SAP 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. 1). Shortly after the petition was filed, on June 30, 2006, EPA released the Interim Reregistration Eligibility Decision (''IRED'') for DDVP which addressed DDVP's eligibility for reregistration under FIFRA and assessed 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. 13).

NRDC asserted numerous grounds as to why the DDVP tolerances do not meet the FQPA safety standard and should be revoked. EPA has divided NRDC's grounds for revocation into four categories – toxicology; dietary exposure; residential exposure; and risk characterization – and addressed separately each claim under these categories. Each specific claim of NRDC is summarized in Unit VII immediately prior to EPA's response to the claim.

VI. Public Comment

In response to the aspects of the petition addressing the DDVP tolerances, 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, the party holding the registration for DDVP under FIFRA. (Ref. 14). Amvac's comments on the specific claims by NRDC are summarized in Unit VII immediately following the summary of NRDC's claim but prior to EPA's response to the claim.

VII. Ruling on Petition

This order addresses NRDC's petition to revoke DDVP tolerances. As noted, in responding to NRDC's petition, EPA has broken the issues into four categories — toxicology; dietary exposure; residential exposure; and risk characterization. Below, EPA addresses each of the claims raised in these categories and explains why they do not support revocation of the tolerances.

EPA has not addressed claims that concern DDVP uses that have been canceled since the time of the petition. Specific uses cancelled were the largest (100 gram) pest strip; lawn, turf, and ornamentals; pet collars; and in-home crack and crevice. Additionally, the remaining ''large'' pest strips (80 and 65 grams) were limited to unoccupied portions of the home. The only pest strips permitted in occupied areas were smaller strips (16, 10.5, 5.25 grams) for use in closets, wardrobes, and cupboards.

A. Toxicological Issues

1. *Cancer*—a. *NRDC's claims*. NRDC claims that ''the rejection by EPA of the 'probable carcinogen' cancer classification of previous Agency reviews is inadequately supported .. ..'' (Ref. 1 at 17). According to NRDC, EPA has not explained why its prior analysis was ''flawed,'' and the reasons EPA has given for the change in cancer classification are ''speculative, at best.'' (Id.). NRDC urges EPA to drop its new classification of DDVP as having ''suggestive'' evidence of carcinogenicity and restore the ''original classification.'' (Id. at 18).

Specifically, NRDC argues with EPA's decision to discount, in its weight-of-the-evidence evaluation for DDVP, mononuclear cell leukemia (MCL) seen in a rat study and forestomach tumors identified in a mouse study. NRDC claims that EPA's assertion that a finding of MCL in the Fischer rat is of limited usefulness due to variability of occurrence of this cancer in the Fischer rat ''may be an artifact of the design of such studies and is not an adequate basis for ignoring a positive result.'' (Id. at 17). NRDC suggests that a larger scale study could have resolved this issue. As to forestomach tumors, NRDC disputed EPA's conclusion that these tumors have limited relevance to humans given that humans do not have forestomachs. NRDC notes that all animals have some difference in their organs and tissues and thus the lack of a forestomach in humans does not ''automatically mean that the effect is irrelevant to humans.'' (Id.). According to NRDC, EPA ''must provide convincing explanations based on reliable data that their rejection of forestomach tumors is a reasonable certainty and will adequately protect the public health.'' (Id.).

NRDC also suggests that a study in Denver, Colorado ''specifically linked'' DDVP pest strips to leukemia in children under 15 (Leiss, J.K., Savitz, D.A. ''Home pesticide use and childhood cancer: a case-control study,'' *American Journal of Public Health* 1995; 85:249-52) and a study of adult men with leukemia in Iowa and Minnesota (Brown, L.M., Blair, A., Gibson, R., *et al.* ''Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota,'' *Cancer Research* 1990;50(20):6585-91) found that these men were twice as likely to have a history of exposure to DDVP.

b. *Amvac's comments*. Disagreeing with NRDC's claims, Amvac argues that NRDC has ignored an extensive DDVP cancer database and the confounding effect that corn oil played in the two positive studies relied upon by NRDC. (Ref. 14 at 27-28). Amvac asserts that 11 cancer studies have been performed with DDVP, involving both oral and inhalation exposure routes, and that the only two positive studies were gavage studies in which the DDVP was administered by gavage in corn oil.

Amvac claims that it is well-recognized that corn oil as a confounding factor in cancer studies and that, in fact, the National Toxicology Program (''NTP'') has found corn oil to be carcinogenic. Finally, Amvac cites to a recent review by the European Food Safety Agency, which Amvac asserts concluded, after reviewing all of the evidence, ''that the carcinogenic risk from exposure to DDVP is very low.'' (Ref. 15).

c. *EPA's response*. Initially, EPA responds to NRDC's claims regarding EPA's cancer classification by noting that NRDC's request to amend the cancer classification is not a sufficient ground for seeking revocation of the DDVP tolerances. A cancer classification does not determine whether a pesticide is safe or not; rather, a cancer classification is one step in a multi-stage risk assessment process that ascertains and examines not only the toxicological effects a pesticide causes, but also the potency of the pesticide and the extent of human exposure to the pesticide. A pesticide found to be a ''probable'' human carcinogen may nonetheless meet the FFDCA section 408 safety standard if it has a low potency and/or low exposure. NRDC's petition contains no arguments or evidence that if DDVP is reclassified as a probable human carcinogen, a cancer risk assessment would show that DDVP is not safe. Accordingly, EPA denies NRDC's petition to revoke DDVP tolerances to the extent that the petition cites EPA's alleged cancer misclassification of DDVP as grounds for such a revocation.

Nonetheless, to clarify the issue, EPA will explain the basis for its revision of the cancer classification of DDVP. EPA's Cancer Assessment Review Committee (CARC) in the Health Effects Division of the Office of Pesticide Programs has held six cancer reviews for DDVP over the past two decades. These multiple reviews have been necessary due to the development of new information on DDVP as well as on carcinogenicity generally. What these reviews show is that EPA has taken a conservative approach to the cancer classification of DDVP, only weakening the classification (i.e., adopting a classification of lower human carcinogenic potential) upon the repeated advice of independent expert scientific panels.

EPA's reviews bridge two versions of its cancer assessment guidelines. These guidelines have slightly different descriptive categories for classifying chemicals as to their carcinogenic potential. In its 1986 Cancer Assessment Guidelines, EPA created the following categories regarding cancer potential: ''human carcinogen'' (Group A), ''probable human carcinogen'' (Group B), ''possible human carcinogen'' (Group C), ''not classifiable as to human carcinogenicity'' (Group D), and ''evidence of non-carcinogenicity for humans'' (Group E). (51 FR 33992 (September 24, 1986)). Under the 1986 Guidelines, Group B was further subdivided into Groups B1 and B2 with the former for chemicals categorized on the basis of data from humans and the latter based on data in animals. In an update to these guidelines in 2005, EPA adopted the following classifications: ''carcinogenic to humans,'' ''likely to be carcinogenic to humans,'' ''suggestive evidence of carcinogenic potential,'' ''inadequate information to assess carcinogenic potential,'' and ''not likely to be carcinogenic to humans.'' (70 FR 17765, April 7, 2005). The revised guidelines dropped the alphabetic labeling of the classifications.

In its first review of DDVP in June 1987, the CARC's predecessor, the Carcinogenicity Cancer Peer Review Committee [hereinafter referred to as the CARC for simplicity], classified DDVP as a probable human carcinogen (Group B2), under EPA's 1986 cancer classification system. (Ref. 16). The CARC's classification of DDVP as a probable human carcinogen was based on its conclusion that the evidence showed DDVP satisfied two separate criteria for a ''probable human carcinogen:'' (1) carcinogenicity seen in multiple species; and (2) carcinogenicity seen in an unusual degree in a single experiment. To show cancer in multiple species, the CARC cited (1) a finding of statistically significant dose-related trend and statistically significant increase in forestomach tumors (combined papillomas and carcinomas) in female mice in a cancer study in the mouse conducted by the National Toxicology Program (NTP); and (2) a finding of a statistically significant dose-related trend and statistically significant increase in mononuclear cell leukemia (MCL) and pancreatic acinar adenomas in male rats in a cancer study in the rat conducted by the NTP. These two findings were supported by a significant positive trend for forestomach tumors in male mice in the NTP mouse study and a finding of statistically significant increased (but overall numbers within the range of historical controls) lung adenomas and combined mammary fibroadenomas and carcinomas in male and female rats, respectively, in the NTP rat study. To satisfy the criterion of cancer in an unusual degree in a single study, the CARC noted that forestomach tumors are a rare tumor in the female mouse. Finally, the CARC relied on positive *in vitro* mutagenicity data in support of the ''probable human carcinogen'' classification.

In September, 1987, the CARC's classification was evaluated by the FIFRA Scientific Advisory Panel (''SAP''), an independent expert panel created by statute for the purpose of providing EPA advice on scientific matters concerning pesticides. The SAP disagreed with EPA's classification and recommended that DDVP be classified as only a possible human carcinogen (Group C) based on its conclusions that: (1) DDVP only induced benign tumors; (2) the tumors did not show a dose-related trend; and (3) DDVP was not mutagenic in *in vivo* assays. (Ref. 17).

The CARC met for a second time on DDVP in September, 1987, to take the SAP's view into consideration. The CARC refused to alter its Group B2 carcinogen classification. It cited essentially the same reasons from the first review and emphasized the following evidence of malignancy to explain its difference with the SAP: (1) MCL is considered a malignant tumor; (2) both the pancreatic adenomas in rats and forestomach papillomas in mice had the potential to progress to malignancies; and (3) the presence of ''some'' rare forestomach carcinomas in female mice. (Id.)

A third meeting of the CARC was held in July, 1988 to review a report from the NTP Panel of Experts on the classification of DDVP. (Ref. 18). NTP scientists had reexamined the pancreata of the rats in the NTP rat study and concluded that the statistically significant increase in pancreatic lesions was diminished. For this reason, the NTP recommended that the evidence for carcinogenicity in male rats be downgraded from ''clear'' evidence to ''some'' evidence. Nonetheless, the CARC again refused to change DDVP's cancer classification relying on the MCL finding in rats, findings of multiple benign tumors in rat and mouse NTP studies, and DDVP's mutagenic properties. The CARC noted this classification was interim until new cancer and mutagenicity data could be reviewed.

A fourth meeting of the CARC in September, 1989, again reviewed the reanalysis of the pancreatic lesions in the rat, and also examined new cancer studies. (Ref. 19). The CARC noted that, although the NTP reexamination had found pancreatic tumors in treated rats to be statistically increased, albeit to a diminished degree than first thought, a new statistical review by EPA using two common statistical procedures found no statistical significance at all. Further, the CARC examined a DDVP inhalation cancer study in rats and two cancer

studies in which DDVP was administered in drinking water. The inhalation study was negative for cancer effects. The drinking water studies had several deficiencies making quantitative analysis inappropriate but had qualitative evidence that showed some of the tumors seen in previous studies. Taking this information into account, as well as new information questioning the relevance of MCL in rats and forestomach tumors in mice to humans, the CARC downgraded DDVP to a possible human carcinogen (Group C). Nonetheless, the CARC maintained that a quantitative cancer assessment was warranted using the geometric mean of the tumor rates of MCL in rats and forestomach tumors in mice.

The fifth meeting of the CARC, in March 1996, considered new information from Amvac including an evaluation of the severity of the MCL seen in the NTP rat study, studies on the mechanism of forestomach tumors, and *in vivo* mutagenicity testing. (Ref. 20). The evaluation of the severity of the rat MCL in the NTP study showed that there was no statistically significant difference in the severity of the MCL between control and treated animals. (Ref. 21 at 10). Further, the new *in vivo* testing was negative. The CARC, however, rejected Amvac's argument that the studies it submitted demonstrated the mechanism of tumor formation for the mouse forestomach tumors. Weighing all of this information, the CARC retained the possible human carcinogen classification (Group C) and recommendation for quantitative low dose linear cancer assessment. Based on its conclusion that the MCL in rats but not the forestomach papillomas are malignant tumors, however, the CARC concluded that the linear low dose extrapolation should be based on the MCL in rats alone.

The sixth cancer review, finalized in February, 2000, principally focused on the significance of the MCL in the rat NTP study taking into account three new analyses of this cancer. (Ref. 22). The first was a report submitted by Amvac titled ''An Evaluation of the Potential Carcinogenicity of Dichlorvos: Final Report of the Expert Panel.'' (Ref. 23). That report was prepared by various experts in the field, primarily academics, who had been assembled by a consulting firm hired by Amvac. The report describes the steps taken to avoid conflicts of interest and to insure that the substance of the report was not influenced by its sponsor. The report concludes that the ''incidence of MCL in the NTP DDVP rat study (1989) . . . does not support a conclusion of carcinogenicity.'' (Id. at 21). The report summarized the main reasons for this conclusion as follows:

1. The results are species-, strain-, and sex-specific.
2. The endpoint is dramatically affected by administration of corn oil by gavage.
3. There was no significant effect on the relative severity of the disease, time-to-tumor latencies or percentage of rats surviving to study termination.
4. The data do not demonstrate a classic dose-response.
5. The results are not replicated in a very large number of carcinogenicity studies on DDVP and related substances (e.g., Trichlorfon, Metrifonate, Naled).
6. Many other studies are more appropriate to estimate human risks since the routes of administration employed more closely approximated potentially hazardous routes in man (e.g., inhalation, dietary or in drinking water) rather than the gavage method employed in the NTP study.
7. The incidences are similar to normal background rates that are increasing over time.

(Id.). The report further stated that effects seen in the NTP rat study showed ''the extremely wide variability that is typically observed with this tumor.'' (Id.). The finding of a lack of carcinogenicity, the report asserted, is consistent with ''similar positions taken by other organizations (e.g., Joint FAO/WHO Panel of Experts on Pesticide Residues, NTP, and OSTP).'' (Id.). Additionally, the report concluded that ''metabolic considerations and the genotoxic potential of DDVP'' do not support a finding of carcinogenicity. Finally, the report concluded that DDVP does cause forestomach tumors in mice but that this ''endpoint has no relevance to man and therefore, should not be employed for extrapolation to human risk.'' (Id.).

The second new analysis was from the SAP review of the CARC's fourth review of the carcinogenicity of DDVP. (Ref. 24). The SAP concluded that ''[t]here is compelling evidence to disregard MCL in the Fischer rat.'' The SAP gave several reasons for this conclusion based both on general information on MCL in Fischer rats and specific information on the NTP rat cancer study with DDVP. In terms of general evidence, the SAP explained that (1) ''MCL is one of the most common background tumor types'' in the Fischer rat; (2) that there is a high variability in MCL in Fischer rats; and (3) MCL is a strain specific cancer. (Id. at 17). On this last point, the SAP noted that MCL ''has been referred to as Fischer rat leukemia . . . [and] [o]ther rat strains and mice do not develop MCL, and there is no human correlate to this disease.'' (Id.). Turning to the NTP rat study with DDVP, the SAP noted that (1) although MCL was seen at both the low and high doses in the study there was no clear dose-response relationship seen in the study; and (2) chemically-related increases in MCL are marked by advanced severity of the MCL but that the NTP rat study ''showed no significant increase in severity of the MCL with increasing dose, indicating that these lesions are background.'' (Id.).

The SAP also ratified the CARC's earlier position that the forestomach tumors in the NTP mouse study should not be relied upon to estimate risk to humans. The SAP explained that these tumors are ''likely due to the chronic irritancy, inflammation, and cytotoxicity during chronic bolus dosing, resulting in extraordinary high local concentration of the chemical.'' (Id.). Such conditions would not exist outside of the laboratory. Further, such tumors have only limited relevance to humans because ''the forestomach in rodents acts as a storage site where irritant chemicals in food have prolonged contact with the sensitive squamous epithelium lining, a situation that does not pertain to humans.'' (Id.).

The SAP reached an overall conclusion that ''the weight of the evidence suggests carcinogenicity in animals treated with DDVP with a non-linear dose-response. However, the compound is considered a weak carcinogen acting via a secondary or indirect mechanism.'' (Id. at 18.).

The third new analyses was a short memorandum summarizing a conversation with Dr. Gary Boorman of the NTP. (Ref. 25). Dr. Boorman opined that the MCL ''tumor type in males[] [Fisher rats] had a high and variable background.'' (Id.). Further, Dr. Boorman is cited as stating that although ''this tumor type can not be dismissed as [ir]relevant to humans, [] it does seem to be found mainly in the Fisher rat and does not appear to be the same type of leukemia as found in [human] adults or children.'' (Id.).

Relying heavily on the advice of these expert scientific opinions (particularly, the views of the SAP), the CARC in its sixth report softened its view regarding the importance of the MCL seen in the NTP rat study and reaffirmed its view that the forestomach tumors in the NTP mouse study were a localized tumor of limited relevance to humans. Although the CARC maintained that the MCL in the rat study could ''not be totally disregarded,'' it accepted the advice of the expert panel of the SAP and as well

as the report commissioned by Amvac that the evidence on MCL did not warrant use of this cancer to quantitatively estimate cancer risk to humans using a low-dose linear extrapolation. The CARC specifically cited the high background rates and variability of MCL in the Fischer rat, the lack of a dose-response effect in the NTP rat study, and negative results in other cancer studies as justifying its decision to change the cancer classification of DDVP from a ''possible human carcinogen'' to ''suggestive evidence of carcinogenic potential'' and to recommend that the data did not support a quantitative cancer risk assessment.

To recap, EPA's initial DDVP cancer classification of ''probable human carcinogen'' was based on a MCL and pancreatic adenomas in the rat, forestomach papillomas in the mouse, and positive *in vitro* mutagenicity data. EPA only downgraded this classification following: (1) a re-analysis of the rat study showed no statistically significant increase in pancreatic adenomas; (2) presentation of strong evidence concerning the non-relevance of MCL in rats and forestomach tumors in mice to humans; (3) submission of a negative DDVP cancer study in rats by the inhalation route; (4) submission of *in vivo* data showing a lack of mutagenicity for DDVP; and (5) repeated recommendations from independent scientific groups to downgrade the DDVP cancer classification.

A recent review by the European Food Safety Agency (''EFSA'') supports EPA's DDVP cancer assessment. (Ref. 15). The EFSA found the only treatment-related tumors from the DDVP studies to be the mouse forestomach tumors: ''[The Scientific Panel on Plant health, Plant protection products and their Residues] concludes that with the exception of tumours of the forestomach in the mouse, there was no convincing evidence for a compound-related, relevant tumour response. Tumours observed in other tissues (pancreas, mammary, mononuclear leukaemia) showed no dose-response, were inconsistent between studies and sexes, were reduced in control animals relative to historical control data, or were unique to the experimental conditions of the assay.'' (Id. at 33). Further, the EFSA found the forestomach tumors to be ''a site of contact effect, and a consequence of the very high, sustained concentrations of dichlorvos to the forestomach that would be achieved by gavage dosing in corn oil.'' (Id.). These tumors, the EFSA concluded, were subject to a threshold dose unlikely to be exceeded in humans due to cholinesterase inhibition effects at a much lower threshold. (Id. at 34).

NRDC is wrong to suggest that variability in MCL occurrence alone drove EPA's decision to change its views regarding the importance of the MCL findings. To the contrary, variability along with several other factors were considered in EPA's weight of the evidence approach. If anything, EPA took a more conservative approach to this cancer than its scientific advisory panel. Further, EPA did not discount the forestomach tumors simply because humans do not have forestomachs. Rather, both EPA and the SAP explained why the unique aspects of the rodent forestomach in connection with the artificial condition of corn oil bolus dosing are likely to produce results of limited relevance to humans.

Further, NRDC's reliance on epidemiological studies by Liess and Brown is misplaced. EPA reviewed the Liess study and identified biases and confounders in the studies that are a more likely explanation for the findings of increased cancer than exposure to pest strips. (Ref. 11 at 142). As to the Brown study, EPA has rejected it as inadequate because the subjects were exposed to other pesticides in addition to DDVP and there was no adjustment made for these other exposures. Other confounders such as multiple statistical comparisons were identified as well. (Ref. 26).

2. *NOAEL/LOAEL*—a. *NRDC's claims*. NRDC notes that a NOAEL for cholinesterase inhibition was not established in a mouse oncogenicity study relied upon by EPA. NRDC claims that failure to identify a NOAEL not only renders the mouse oncogenicity study invalid but ''undermines the entire risk assessment and precludes the Agency from finding that the DDVP tolerances are safe . . . .'' (Ref. 1 at 47). NRDC argues that if there is no NOAEL identified in a study, the LOAEL from that study is ''virtually meaningless information.'' (Id.). Finally, NRDC argues that EPA cannot legally make the reasonable certainty of no harm finding for DDVP or any other pesticide if EPA is relying on a LOAEL rather than a NOAEL.

b. *EPA's response*. EPA has repeatedly rejected NRDC's legal arguments concerning reliance on LOAELs in making safety findings under FFDCA section 408. (70 FR 46706, 46729; 69 FR 30042, 30066-30067; Ref. 27 at 165-166). EPA incorporates those prior responses herein. Further, EPA disagrees with NRDC's contention that a LOAEL in a study that does not identify a NOAEL provides ''virtually meaningless information.'' Depending on the severity and consistency of the effect at the LOAEL as well as the severity and consistency at higher doses, the LOAEL can provide substantial information bearing on the no adverse effect level. It is for this reason that EPA and FDA, as well as other public health agencies, have long relied on LOAELs, in appropriate circumstances, in making safety findings. (69 FR at 30066; Ref. 28).

EPA relied upon a LOAEL in assessing the risk posed by DDVP for the following exposure scenarios: short-term incidental oral; short-, intermediate-, and long-term dermal; short- and intermediate-term inhalation. The LOAEL was from a single blind, placebo controlled, randomized study to investigate the effects of multiple oral dosing on erythrocyte cholinesterase inhibition in healthy male volunteers and involved a dose of 0.1 milligrams/kilogram of body weight/day (''mg/kg/day''). This value was adjusted with a safety factor of 3X to approximate the value of a NOAEL. The LOAEL provided sufficient information to estimate the NOAEL (using a 3X safety factor) because the study measured the severity of the cholinesterase inhibition response observed. Cholinesterase inhibition is a continuous endpoint where no fixed generic percentage of change from baseline separates potential adverse effects from non-adverse effects. Generally, cholinesterase inhibition of 20 percent from baseline is regarded as showing a potential for adverse effects on the nervous system with lower levels evaluated on a case-by-case basis. (Ref. 9 at 37-38). In the DDVP human study, the cholinesterase inhibition fell at the very low end of the scale (cholinesterase inhibition in individuals varied from baseline within a range from 8 to 23 percent at the end of the study) indicating that the NOAEL was not significantly lower.

NRDC is mistaken to claim that the mouse oncogenicity study was invalid for failure to identify a NOAEL. Oncogenicity (carcinogenicity) studies are not designed to produce NOAELs but rather to examine the cancer responses at high doses. EPA relies on chronic studies in the rodent and non-rodent (generally the rat and dog, respectively) to evaluate and define the level of threshold chronic, non-cancer effects. (40 CFR 158.340(a)). Acceptable chronic rat and dog studies are available for DDVP. (Ref. 11). NRDC also errs in contending that EPA, by examining cholinesterase effects in the mouse oncogenicity study, indicates that it does not have valid and reliable chronic toxicity data. As noted, EPA does not specifically require a chronic toxicity

study in the mouse and it has an acceptable study meeting the requirement for a chronic study in rodents. Nonetheless, where an oncogenicity study in the mouse does shed light on effects seen in chronic studies, EPA certainly will consider that information in its overall weight-of-the-evidence evaluation for the pesticide.

3. *Human studies*—a. *NRDC's claims.* NRDC asserts that none of the DDVP human studies satisfy the standards in EPA's human testing rule because they ''violate the Nuremburg Code and fail to satisfy the standards in EPA's human testing rule.'' (Ref. 1 at 26.). Therefore, NRDC petitions EPA to reject all intentional dosing human studies for DDVP as unethical and unscientific.

NRDC raises various specific concerns as to a particular human study commonly referred to as the Gledhill study (MRID # 44248801). Citing a draft report by EPA's Human Studies Review Board (HSRB), NRDC claims that this study is ''statistically meaningless'' because it had too few test subjects. Further, NRDC argues that the variability in the cholinesterase inhibition in the study demonstrates that ''even greater than the customary numbers of test subjects would be required to permit detection of effects caused by the test substance above background variation.'' (Ref. 13 at 15). Other scientific defects in the Gledhill study alleged by NRDC include failing to promptly measure red blood cell (''RBC'') effects; failing to measure blood plasma effects; not restricting subjects in controlled conditions for living and eating; and failing to properly obtain informed consent. NRDC claims the study was ethically deficient because reference in the consent form to DDVP as a drug made it impossible to obtain informed consent and study conductors failed to monitor the health of subjects after the conclusion of the study. Finally, NRDC argues that if EPA relies on the study, EPA cannot conclude that the DDVP tolerances are safe because the LOAEL for humans in the study (reported by NRDC to be 0.01 mg/kg/day) is well below the lowest LOAEL in animal studies (0.1 mg/kg/day).

NRDC also objects to EPA's reliance on a number of other human studies which NRDC describes as ''ethically repugnant'' due to involvement of children as test subjects.

b. *Amvac's comments.* In its comments, Amvac argues that ''there is a large body of human data from a variety of sources that provide information directly relevant to the DDVP risk assessment process.'' (Ref. 14 at 32). According to Amvac these human studies show that the most sensitive endpoint for DDVP is inhibition of red blood cell cholinesterase; DDVP operates by a common mechanism in animals and humans; DDVP inhibits RBC cholinesterase at similar levels in animals and humans; and DDVP has similar effects no matter what the route of exposure. (Id. at 33). As to the Gledhill study, Amvac disputes NRDC's criticisms of its scientific value and ethics. (Id. at 37). Amvac claims that ''[t]he number of subjects employed, six per dose, is . . . a standard number of test subjects sufficient to provide statistical power in human studies.'' (Id. at 38). Measuring plasma cholinesterase was not essential, according to Amvac, because RBC cholinesterase ''is relevant to assessing the risk of inhibition of the toxicologically important brain cholinesterase enzyme.'' (Id. at 37).

c. *EPA's response.* In responding to the petition, EPA would first note that the petition simply asks EPA not to rely on any of the DDVP human studies but does not contend that reliance on animal studies instead of the human studies will show the DDVP tolerances to be unsafe. Subsequent to NRDC's petition, EPA did rely on the Gledhill study in assessing the risk posed by DDVP. (Ref. 11 at 133). To clarify the basis for EPA's decision to rely on the Gledhill study, EPA has described its decision-making process below.

EPA decisions regarding the ethics and scientific value 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 Research Rule rests on the basic principle that EPA will not, in its actions, rely on data derived from unethical research. The rule divides human studies into two groups: ''new'' studies—those initiated after April 7, 2006—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).

Whether the data are ''new'' or ''old,'' the Human Research Rule forbids EPA to rely on data from any study involving intentional exposure of pregnant women, fetuses, or children. (40 CFR 26.1704).

To aid EPA in making ethical determinations under the Human Research Rule, the rule established an independent Human Studies Review Board (HSRB) to review both proposals for new research and reports of covered human research on which EPA proposes to rely. (40 CFR 26.1603). The HSRB is 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 intends to rely on the results from ''old'' human research, 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).

In the risk assessment for DDVP, EPA has relied upon one human study for several exposure scenarios. The study, conducted by A.J. Gledhill, involved a single blind, randomized placebo-controlled oral study in which 6 healthy male volunteers were administered a daily dose of DDVP for 21 days at approximately 0.1/mg/kg/day and 3 volunteers were administered a placebo

(Ref. 11 at 133). Prior to relying on the Gledhill study in the IRED, EPA presented this study as well as 10 other DDVP human studies to the HSRB for review. In its presentation to the HSRB, EPA stated that it had concluded that the Gledhill study ''is sufficiently robust for developing a Point of Departure for estimating dermal, incidental oral, and inhalation risk from exposure to DDVP'' for the purpose of assessing DDVP by itself but not for conducting a cumulative assessment of DDVP and other organophosphate pesticides. (Ref. 29 at 19). EPA recommended that the other 10 studies should not be used. (Id. at 20).

As part of the public participation procedures that have been adopted by the HSRB, NRDC appeared before the HSRB when DDVP was being considered to make the points it has raised in this petition. (Ref. 30).

The HSRB agreed with EPA on the appropriateness of using the Gledhill study after a detailed evaluation of the scientific merit of the study as well as an evaluation of other ethical considerations. (Ref. 31). In examining scientific merit, the HSRB identified both strengths and weaknesses of the Gledhill study. Identified as strengths were: 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. Weaknesses seen included: use of a single dose; preventing establishment of a dose-response relationship; small sample size and use of males subjects only; measurement of RBC cholinesterase inhibition at 24 hours after dosing which may have missed peak inhibition; no analysis of plasma cholinesterase; sampling and analysis of enzyme inhibition ended 3 days before the end of dosing; lack of clarity as to whether steady state inhibition was achieved; and lack of follow-up with subjects following completion of dosing. After carefully considering these factors, the HSRB concluded that despite the ''numerous technical difficulties'' with the study that it ''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.'' (Id. at 41). The HSRB's reasoning was that ''[a]lthough a study using a single dose level is not ideal for establishing a LOAEL, there was general consensus that RBC cholinesterase is a well-characterized endpoint for compounds that inhibit acetylcholinesterase activity and therefore, 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.'' (Id.).

Turning to other ethical considerations, the HSRB examined whether there was clear and convincing evidence that prevailing ethical standards had been violated. Specifically, the HSRB considered whether informed consent had been compromised by certain references in test subject disclosure forms to DDVP as a ''drug,'' or by deficiencies in the monitoring of subjects both during and after conclusion of the study. Ultimately, the HSRB concluded that although the study ''failed to fully meet the specific ethical standards prevalent at the time the research was conducted, . . . [t]here was no clear and convincing evidence that the research was fundamentally unethical—intended to seriously harm participants or that informed consent was not obtained.'' (Id. at 46). The 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.'' (Id.). Deficiencies 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. (Id.).

The HSRB also agreed with EPA that the technical difficulties identified with the Gledhill study limited its usefulness in the organophosphate cumulative assessment. (Id. at 41). Finally, the HSRB agreed with EPA that there were scientific value or other ethical considerations that precluded reliance by EPA on the other ten DDVP human studies. (Id. at 41–42).

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. In fact, NRDC has not raised in its petition any arguments not considered and rejected by the HSRB.

EPA would add the following further information regarding NRDC's criticisms of the Gledhill study's use of males only, the number of test subjects in the study, the 24-hour period between dosing and measurement of cholinesterase inhibition, the failure to measure plasma cholinesterase, and purported increased sensitivity in humans demonstrated by the study.

As to the use of males only, EPA would note that no sex differences were observed in the comparative cholinesterase studies in animals. (Ref. 32). With regard to statistical significance of the study results due to the number of test subjects, EPA strongly disagrees with the claims of NRDC. The results of the repeated dose study of 9 subjects (6 DDVP and 3 placebo) in the Gledhill study were analyzed statistically for significance in addition to being analyzed for biological significance. Although 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. Indeed, all of the 6 dosed subjects exhibited statistically significant (with respect to their pre-dose levels) RBC cholinesterase depression on one or more days. One of the three placebo controls exhibited statistically significant depression on one day. However, the group means of RBC cholinesterase activity in treated subjects are statistically below the group means of the placebo controls on days 7, 11, 14, 16 and 18 by repeated measures analysis of variance. (Ref. 33). The statistics of the study clearly show the ability to demonstrate a statistically significant response. For the sake of comparison it is worth noting that use of 6 male test subjects exceeds the long-standing EPA recommendation for 4/sex/dose subjects in non-rodent (usually dog) animal studies. (Ref. 34). Nor does EPA agree with NRDC that the variability in cholinesterase inhibition for test subjects shows that more subjects are required to detect effects above background variations. First, the variability seen in the study (cholinesterase inhibition in individuals varied from baseline within a range from 8 to 23 percent at the end of the study) is not large, particularly since the percentage inhibition in all instances was at the marginal end of the range. Second, EPA concluded, and the HSRB agreed, that the study did identify an effect above background. Moreover, an intra-species safety factor of 10X was applied to the study results to address variability in human sensitivity.

As to failure of the study to assess inhibition of plasma cholinesterase, EPA does not believe that this deficiency has much significance. Although the study should have had measurements of both RBC and plasma cholinesterase, the use of RBC cholinesterase findings provides a more

useful regulatory estimate for assessing the effects of DDVP on brain and peripheral cholinesterase depression in humans. In its policy on use of data on cholinesterase inhibition in assessing the risk of organophosphates and carbamates, EPA made clear that ''[r]ed blood cell measures of acetylcholinesterase inhibition, if reliable, generally are preferred over plasma data.'' (Ref. 9 at 29). 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.). Although testing for plasma inhibition may have provided additional information, given that the study identified statistically significant effects on RBC at a marginal level, data on a less preferred endpoint such as plasma cholinesterase adds little meaningful information.

With regard to the study procedure of waiting 24 hours after dosing to measure cholinesterase inhibition, the study was designed to evaluate the cumulative effect of repeat dosing with DDVP. While a shorter interval between dosing and measurement would have provided more information about acute effects of DDVP, this study has not been relied upon to assess acute risks.

Finally, NRDC is mistaken to claim that the Gledhill study showed humans to be more sensitive than test animals. The LOAEL from the Gledhill study is 0.1 mg/kg/day, not 0.01 mg/kg/day, as claimed by NRDC. (Ref. 11 at 133). The correct LOAEL is similar to the LOAEL from animal studies.

4. *Mutagenicity*—a. *NRDC's claim.* NRDC claims that EPA cannot find the DDVP tolerances are safe because EPA has not ''reliably establish[ed] the bounds of risk posed by the mutagenic potential of DDVP.'' (Ref. 1 at 47). NRDC notes that EPA has found DDVP to be mutagenic in *in vitro* assays and asserts EPA has not taken this mutagenic risk into account in assessing the safety of DDVP.

b. *Amvac's Comment.* Amvac claims that NRDC has focused on *in vitro* assays to the exclusion of the more important *in vivo* studies. These later studies, Amvac asserts ''provide[] support for the lack of *in vivo* carcinogenic activity seen in the DDVP animal bioassays.'' (Ref. 14 at 31). According to Amvac, ''[p]harmacokinetic data have demonstrated that DDVP is quickly metabolized and this likely accounts for the difference in the *in vitro* and *in vivo* response in the mutagenicity testing.'' (Id.).

c. *EPA's response.* NRDC's claim that EPA has not taken mutagenic risk into account is mistaken. EPA has fully examined the data on DDVP's potential for mutagenic effects and concluded that these data do not raise a safety concern.

Mutagenicity data on DDVP shows the following: (1) DDVP does produce positive *in vitro* results in the absence of activation by rat derived liver enzymes; (2) these positive results generally disappear in the presence of activation by liver enzymes; (3) there is some evidence that DDVP is a weak mutagen in *in vivo* testing; and (4) an *in vivo* chromosome aberrations study requested to address the *in vivo* mutagenicity study was negative. (Refs. 11, 20 at 13, 35 and 36).

Mutagenicity data are considered by EPA both as evidence bearing on a pesticide's carcinogenic potential and on whether the pesticide can result in heritable mutagenic effects. As described in Unit VII.A.1.c., EPA fully considered the mutagenicity data in its cancer evaluation. As to DDVP's potential to cause heritable mutagenic effects, EPA specifically requested that an *in vivo* chromosome aberrations study be performed in which germ cells as well as somatic cells were examined to address this question. This study was negative resolving any concern with heritable mutagenic effects. (Ref. 20 at 13). One agency reviewer suggested a further mutagenicity study at higher doses addressing heritable effects but EPA has not required such testing because existing testing already tests at the maximum tolerated dose. (Ref. 37).

5. *Endocrine effects*—a. *NRDC's claim.* NRDC asserts that EPA has failed to assess the endocrine disruption effects of DDVP. NRDC notes that the statute requires EPA to consider, in making safety determinations as to tolerances, whether a pesticide has an effect that mimics estrogen or has other endocrine effects, (see 21 U.S.C. 346a(b)(2)(D)(viii)), and to establish an endocrine screening program, (see 21 U.S.C. 346a(p)), but that EPA has not collected any data under this program. NRDC claims that ''[i]n light of [EPA's] failure to carry out its mandatory statutory duty to investigate the potential of DDVP to cause endocrine disruption, EPA cannot conclude that . . . the [DDVP] tolerances are safe.'' (Ref. 1 at 49).

b. *Amvac's Comment.* Amvac, in its comments, notes that EPA has already indicated that it will rely on several studies currently required for pesticides to assess endocrine effects and that EPA has these studies for DDVP. (Ref. 14 at 74-75).

c. *EPA's response.* In a prior order adjudicating a petition to revoke tolerances, EPA has rejected the argument that data gathered under the Endocrine Disruptor Screening Program (''EDSP'') is a prerequisite to a safety determination under FFDCA section 408. (71 FR 43906, 43919-43921 (August 2, 2006)). There, EPA noted that the proposed study to be used for chemicals that initial screening suggests may have the potential to interact with the endocrine system (the two generation reproduction study in rats) is a study that is currently required for approval of agricultural or other food use pesticides. (Id. at 43920). Additionally, EPA pointed out that several other toxicological studies required for pesticides provide information relevant to potential endocrine disruption.

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 estrous cycling in females and sperm number, motility, and morphology in males. The study did identify an adverse effect on estrous 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 estrous 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.

Finally, based on a comprehensive evaluation of the testicular toxicity of dichlorvos in rats, a recent publication reported that there were no testicular effects, except for slightly decreased

sperm motility, at doses causing significant inhibition of cholinesterase. (Ref. 38). The NOAEL for dichlorvos with respect to reproductive organ weights, sperm counts, sperm morphology, plasma testosterone, and testes histopathology was 4 mg/kg, the highest dose tested.

Given that EPA has (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, EPA believes it has adequate data to make a safety finding as to DDVP's potential endocrine-related effects.

6. *Neurotoxicity*—a. *NRDC's claim*. NRDC notes that in the 2000 preliminary risk assessment, EPA imposed a 3X uncertainty factor because there was no measurement for cholinesterase inhibition in an acute neurotoxicity rat study. NRDC contends that in light of the failure to measure cholinesterase inhibition, EPA should have required the study to be redone and that in the absence such data, EPA cannot make its FFDCA safety finding. (Ref. 1 at 47–48). NRDC also faults the Agency for failing to explain why, in these circumstances, a 3X uncertainty factor is safe.

b. *EPA's response*. Subsequent to the 2000 preliminary risk assessment, EPA has received additional acute neurotoxicity data in the rat which measured cholinesterase inhibition and thus the deficiency in the prior acute neurotoxicity study has been cured. (Ref. 11 at 130). Accordingly, the Agency has removed the 3X uncertainty factor that had been retained due to the deficiency in the prior study.

7. *Translation of oral study to dermal endpoint*—a. *NRDC's claim*. NRDC asserts that EPA cannot make a safety finding for DDVP because EPA relied on a rabbit oral study to derive a safe level of acute dermal exposure. (Ref. 1 at 48). According to NRDC, this approach is ''based on unwarranted and unsubstantiated assumption that the toxicology and pharmacokinetics of oral exposure are the same as for dermal exposure.'' (Id.) Moreover, NRDC argues that even if it were appropriate to use oral data in place of dermal data, the ''inherent'' uncertainty requires the imposition of a properly supported uncertainty factor. (Id.). Similarly, NRDC argues that using an oral dog study for an intermediate-term dermal toxicity scenario is legally inappropriate and scientifically unsupportable.

b. *Amvac's comments*. Amvac states that ''[i]t is common practice in risk assessments . . . to extrapolate across exposure routes if the characteristics of the chemical being considered, and the available data, support such extrapolation.'' (Ref. 14 at 40). Amvac argues that extrapolation from the oral route to the dermal route is appropriate for DDVP because the data show that both DDVP's metabolism and types of toxicity it causes are consistent across all routes of exposure. (Id.). Additionally, Amvac asserts that the greater absorption of DDVP in oral studies than in dermal studies makes it more likely that oral studies will show DDVP-related effects than dermal studies.

c. *EPA's response*. Initially, EPA would note that in the IRED EPA relied upon an oral rat and oral human study for assessing dermal risks. Presumably, however, NRDC would have similar objections to reliance on translation of these oral data to the dermal route.

Use of oral studies to assess dermal risks is, and has been, a common practice at EPA for some time. (Ref. 39). Data specific to DDVP confirm that this is a reasonable approach for this pesticide. First, numerous toxicity studies have been performed with DDVP, involving both acute and chronic dosing and dosing by all routes of exposure. These studies consistently show that DDVP is an inhibitor of cholinesterase, if doses are high enough, regardless of the duration or route of exposure. Similar results are consistently found across the class of organophosphate pesticides. (See, e.g., Refs. 40 and 41). Second, oral metabolism studies indicate both that DDVP is well-absorbed from the gastro-intestinal tract and that there are no significant differences in excretion of DDVP doses given orally and intravenously. (Refs. 42 and 43). Accordingly, an orally-administered dose is a reliable prediction of systemic dose. Thus, it is reasonable to use a RfD derived from an oral DDVP study to evaluate the safety of systemic exposures occurring as a result of dermal absorption of DDVP. Moreover, there are two reasons to believe that EPA's use of a dermal absorption factor of 11 percent for DDVP in translating the oral RfD into dermal RfD tends to overstate dermal absorption, exposure, and risk. (Ref. 44). First, dermal absorption studies with volatile chemicals such as DDVP are likely to overstate the degree of absorption because such studies attempt to minimize losses of the chemical through evaporation. Outside of the laboratory, there are usually no such barriers to evaporation. Second, human skin is generally less permeable than the rat skin (largely due to species differences in epidermal anatomy, such as skin thickness, sebaceous secretions, and the density of hair follicles, (Ref. 45), and thus dermal absorption studies with the rat, such as the DDVP dermal absorption study, tend to overstate absorption in humans.

For all of these reasons, EPA concludes that using oral DDVP studies in assessing risk from dermal DDVP exposures is a well-supported scientific assessment technique that would not underestimate risks from dermal DDVP exposure. Consequently, the application of an additional safety factor to account for uncertainty of the route to route extrapolation is not necessary.

8. *Degradates*—a. *NRDC's claim*. NRDC asserts that the Agency has an incomplete database regarding degradates of DDVP. (Ref. 1 at 9). Specifically, NRDC contends that degradates identified by the Agency were never searched for ''or even detectable in the various monitoring and metabolism studies relied upon by the Agency.'' (Id.). Further, NRDC states that ''[t]here is no indication whether these degradates were ever separately subjected to toxicological testing.'' (Id.). Based upon this assumption, NRDC contends that it is impossible for EPA to find that the DDVP tolerances are ''safe.''

b. *Amvac's comments*. Amvac claims that NRDC has failed to consider whether the DDVP degradates are toxicologically significant. (Ref. 14 at 68). According to Amvac, ''[i]t is clear just from the structures of some of these degradates that they are either not toxicologically significant, and/or, based on structure activity relationships and knowledge concerning mechanisms of toxicity, that these degradates have much lower toxicity than the parent compound.'' (Id.).

c. *EPA's response*. NRDC's concern that EPA has not searched for DDVP's major metabolites in magnitude of the residue studies is misplaced because EPA has determined that these metabolites are rapidly degraded to harmless chemicals in the normal course of plant and mammalian metabolism. The residue of concern is DDVP and that is the chemical identified by DDVP's analytical method.

EPA has a robust understanding of DDVP's metabolites and degradates derived from multiple metabolism studies in several different animal and

plant species. (Refs. 46, 47, 48, 49, 50 and 51). In animals, DDVP's primary metabolites are dichloroacetaldehyde or (minor pathway) des-methyl DDVP. Des-methyl DDVP also breaks down into dichloroacetaldehyde. Dichloroacetaldehyde is rapidly dechlorinated and oxidized and either expelled from the body through respiration as carbon dioxide or through excretion in the urine and feces as urea or hippuric acid or converted into basic carbon compounds which are incorporated in amino acids (e.g., glycine, serine) and proteins. In metabolism studies using radioactive-labeled DDVP, little or no DDVP or its primary metabolites were found in animal tissues and milk.

In plants, DDVP is hydrolyzed to dimethyl phosphate and dichloroacetaldehyde. Dimethyl phosphate is sequentially degraded to monomethyl phosphate and inorganic phosphates. Dichloroacetaldehyde is converted to 2,2-dichloroethanol which is conjugated and/or incorporated into naturally-occurring plant components after additional metabolism.

9. *Inerts*—a. *NRDC's claims*. NRDC asserts that the ''apparent absence of data on the risks posed by the inert ingredients and impurities in all DDVP end-use products compels . . . the revocation of all DDVP tolerances.'' (Ref. 1 at 68).

b. *EPA's response*. If an inert ingredient that is combined with DDVP in an end-use product poses a risk of concern, then there would be grounds for modifying or revoking the tolerance or tolerance exemption pertaining to the inert ingredient. It would not be grounds for revoking the DDVP tolerance, which is evaluated based on the safety of DDVP. All impurities in technical active ingredient DDVP, which would be included at lower levels in DDVP end use products, were tested as part of the technical active ingredient when the toxicology tests on the technical active ingredient DDVP were conducted.

10. *Other allegedly missing toxicity data*—a. *NRDC's claims*. NRDC contends that the Agency cannot make its statutory determination of safety for DDVP dependent upon the submission of data. Specifically, NRDC asserts that in the absence of a dermal sensitization study and a developmental neurotoxicity test (DNT) study, EPA cannot make a safety finding for DDVP under the FFDCA.

b. *EPA's response*. EPA has received and reviewed a DNT study for DDVP. (Ref. 11 at 127). Additionally, NRDC is incorrect in asserting that EPA does not have any dermal sensitization data for DDVP. On the contrary, the Agency has four dermal sensitization studies for DDVP. (Refs. 52, 53, 54 and 55). The DDVP dermal sensitization studies were conducted with formulations, containing varying levels of technical DDVP. All four of the studies were negative for sensitization in guinea pigs. Although none of the studies tested DDVP in isolation, sufficient information was obtained from the four studies to define the dermal sensitization toxicity of DDVP.

B. Dietary Exposure Issues

1. *Revised dietary exposure and risk assessment*. NRDC's petition challenges numerous aspects of EPA's 2000 proposed dietary exposure and risk assessment of DDVP. This exposure and risk assessment was incorporated into the 2006 DDVP IRED without major changes. In responding to NRDC's petition, EPA has updated the DDVP dietary exposure and risk assessment. The main changes in the revised assessment include: (1) use of EPA's current dietary assessment program, DEEM-FCID, instead of DEEM; (2) incorporation of residue estimates for drinking water directly into the DEEM-FCID program; (3) updated monitoring data (principally from the USDA-Pesticide Data Program (''PDP'')) and percent crop treated data; and (4) incorporation of estimated exposure from use of naled as a wide area treatment for mosquitoes. A summary of the revised dietary risk assessment is presented in this unit and NRDC's specific comments are responded to individually below. (Ref. 56).

The estimated risk levels, presented in Table 1, are largely unchanged from the 2006 IRED when both food and water are considered. Although this risk assessment is highly refined as to some commodities it still contains numerous conservatisms. More details concerning the revised risk assessment are provided in responding to NRDC's specific objections.

TABLE 1.—DIETARY (FOOD AND WATER) EXPOSURE AND RISK FOR DDVP

Population Subgroup	Acute Dietary (99.9 Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.001313	16	0.000060	*COM041*12
All Infants (< 1 year old)	0.003735	47	0.000116	23
Children 1-2 years old	0.001523	19	0.000111	22
Children 3-5 years old	0.001312	16	0.000103	21
Children 6-12 years old	0.000911	11	0.000069	14
Youth 13-19 years old	0.000967	12	0.000048	10
Adults 20-49 years old	0.001475	18	0.000057	11
Adults 50+ years old	0.000929	12	0.000051	10
Females 13-49 years old	0.001000	13	0.000050	10

2. *Drinking water models*—a. *NRDC's claims*. NRDC argues that the DDVP tolerances are unsafe because EPA has inadequate data on DDVP levels in drinking water. (Ref. 1 at 40). NRDC notes that EPA has limited groundwater monitoring data and no surface water monitoring data for DDVP, naled, and trichlorfon. In the absence of DDVP

water monitoring data, NRDC claims EPA cannot find the DDVP tolerances to be safe. Further, NRDC claims that the surface water exposure model used by EPA in the preliminary risk assessment (PRA), GENEEC, has not been properly validated, and that ''EPA has failed to demonstrate that the surrogate data [in the model] are properly matched to DDVP and that the model's assumptions and parameters are justified.'' (Id. at 54). NRDC makes similar claims regarding the matching of surrogate groundwater data to DDVP through the operation of the SCI-GROW ground water model. (Id. at 55). According to NRDC, ''if the SCI-GROW model employed surrogate data [on DDVP], it cannot be assumed to be reliable unless full disclosure of its construction and inputs is made and this information demonstrates its reliability.'' (Id.).

In its comments on the DDVP IRED, NRDC raised similar issues. (Ref. 13 at 9). Citing a number of alleged uncertainties pertaining to the SCI-GROW model, NRDC argues that because ''[n]one of these uncertainties is quantitatively bounded ... the Agency has not or cannot determine with reasonable certainty that the risks from groundwater contamination by DDVP will not harm people.'' (Id.). Additionally, NRDC claims the assessment for groundwater is incomplete, because EPA has not aggregated DDVP in groundwater resulting from uses of DDVP, naled, and trichlorfon. (Id.).

Finally, in its petition, NRDC asserts that EPA's conclusion that DDVP will not be persistent in surface waters is mere speculation. (Ref. 1 at 44).

b. *Amvac's comments*. Amvac disputes NRDC's criticism of EPA's drinking water models stating ''NRDC appears to not understand the underlying assumption and highly conservative nature of these models.'' (Ref. 14 at 63). Further, Amvac argues that, because of the highly conservative nature of the models, the targeted monitoring data NRDC calls for would show that DDVP exposure in drinking water is lower than projected. (Id. at 70-71). Amvac further notes that targeted monitoring data has limited applicability and would be unlikely ''to be representative of potential exposure on a wider geographical scale.'' (Id. at 71).

c. *EPA's response*. NRDC's general claims regarding EPA's drinking water models are addressed for the most part in a prior EPA order denying NRDC objections to use of these models in making a safety finding for a pesticide tolerance. (69 FR 30042, 30058-30065 (May 24, 2006). In that order, EPA explained in detail as to each of the models: (1) the basic principles on which the model is based; (2) the data underlying the models; (3) the numerous conservatisms built in to each of the models; (4) the extensive independent peer review used in the development of the models; and (5) the external and internal testing of the accuracy of the models. After this extensive analysis, EPA concluded the models ''are based on reliable data and have produced estimates that EPA can reliably conclude will not underestimate exposure to pesticides in drinking water.'' (Id. at 30065). Not only does this order provide a detailed description of the models and data underlying the models but it referenced the many SAP reviews and Agency policy documents that further explained the models. Additionally, it should be noted that detailed information concerning the models is available on EPA's website. EPA has recently updated this information to insure that the website provides not only the ability to run the models but also a description of the how the models work and the underlying codes included in the structure of the model. (Ref. 57)

NRDC's more specific allegations are also without merit. First, EPA took the characteristics of DDVP, naled, and trichlorfon into account in modeling DDVP levels in drinking water. Specific information concerning these pesticides' mobility and persistence was combined with information pertaining to application amounts in use of PRZM-EXAMS to model surface water DDVP levels and SCI-GROW to model groundwater DDVP levels. In addition, information on soil properties, cropping characteristics, and weather appropriate to use of these pesticides was incorporated in the PRZM-EXAMS model run. (Ref. 58). Second, EPA has adequately addressed uncertainties in the PRZM-EXAMS model through peer review and validation. NRDC claims that EPA has not quantified the uncertainties in the SCI-GROW model and thus cannot rely on it; however, NRDC's listing of uncertainties (e.g., small drinking water reservoir, runoff prone soils) applies to considerations relative to the surface water model PRZM-EXAMS not SCI-GROW. These apparent criticisms of the PRZM-EXAMS model are without merit. As noted above, while EPA has not specifically quantified each individual uncertainty associated with the model, the overall model has been extensively peer-reviewed and validated, and has proved very conservative in practice. Third, EPA's estimation of surface water DDVP levels is not flawed for failure to combine exposures from DDVP, naled, and trichlorfon. The highest estimated surface water DDVP levels are from the naled use on brassica and the trichlorfon use on turf ((33 parts per billion (''ppb'') and 60 ppb, respectively, for acute exposure and 1.83 ppb and 1.56 ppb, respectively, for chronic exposure). These estimates are based on the conservative assumption that 87 percent of the area of the watershed is cropped to either brassica or turf and all of the brassica or turf is treated with naled or trichlorfon, respectively. The figure of 87 percent is based on the fact that ''87 percent cropped was the largest cropped area in any 8-digit hydrologic unit in the continental United States.'' (69 FR 30042, 30060 (May 26, 2004)). Thus, there is no reason to combine these estimates. A watershed may be 87 percent turf or 87 percent brassica but not both. Moreover, the available data indicate that both trichlorfon and naled are used relatively infrequently on turf and brassica, respectively; thus, the water level estimate is overstated to begin with. (Refs. 56 and 59). In theory, the DDVP use producing the highest estimated surface water levels (wide area treatment for mosquitoes) could overlap somewhat with these uses but not only is estimated water concentration from the DDVP use insignificant compared to the levels used to assess acute and chronic drinking water exposure (10X and 20X lower, respectively) but relevant survey data show no report of DDVP for this use. (Ref. 60).

EPA has chosen to rely on modeling estimates of DDVP in drinking water because the drinking water modeling data it has were not necessarily collected in areas of DDVP, naled, or trichlorfon usage and there is inadequate data on drinking water from shallow, groundwater wells. Nonetheless, the sampling data give some indication of the conservativeness of the modeling estimates. USDA's Pesticide Data Program (''PDP'') collected finished drinking water samples from California and New York in 2001 (214 samples) and from California, Colorado, Kansas, New York, and Texas in 2002 and 2003 (371 and 699 samples, respectively). In 2004, PDP sampled raw and finished water from 171 community water systems from Michigan, North Carolina, Ohio, Oregon, Pennsylvania, and Washington (234 samples). Although the samples were analyzed for DDVP, no detectable residues of DDVP were found in any sample. The limits of detection for these

monitoring data were between 0.4 and 22.5 parts per trillion (ppt). By comparison, the estimates from EPA's drinking water models that EPA is using in the DDVP risk assessment are 60 ppb for acute risk and 1.83 ppb for chronic risk. (Ref. 11). In parts per trillion, these values would be 60,000 ppt and 1,830 ppt.

As to NRDC's claims that EPA is simply speculating in stating that DDVP is unlikely to persist in surface water, NRDC is mistaken. The conclusion that DDVP will not be persistent in surface water is based on the physical and chemical properties of DDVP and the results of the suite of environmental fate and transport studies on the compound. As EPA noted in the DDVP IRED, ''dichlorvos should not be persistent in any surface waters due to its susceptibility to rapid hydrolysis and volatilization.'' (Ref. 11 at 152).

2. *Dietary exposure models*—a. *NRDC's claims*. NRDC contends that the Dietary Exposure Model (DEEM) cannot be used to demonstrate the safety of the DDVP tolerances because ''[t]he model is secret in that the codes, internal structure and assumptions have not been made available to the public for scrutiny and comment.'' (Ref 1 at 44). Additionally, NRDC argues that the model cannot be relied upon because it has never been validated. (Id.).

b. *Amvac's comments*. Amvac notes that EPA has used DEEM for many years and claims that the DEEM ''software and its use have received many peer reviews ....'' (Ref. 14 at 57). Further, Amvac asserts that ''[t]his model and the other models that EPA uses to assess dietary risk (i.e., LifelineTM and CARES) have all been made available to the public and their computer codes are available for public review and comment.'' (Id. at 57-58).

c. *EPA's response*. DEEM and its successor, DEEM-FCID, are not secret models. As explained in Unit III.B.3.b.i.(B)., these dietary assessment models use relatively simple formulas to combine consumption information with residue levels in food to estimate exposure and risk. In 2000, the company that developed DEEM made a detailed explanation of the model public so that the model could be reviewed by the FIFRA SAP. (Ref. 7). That explanatory paper documented the data included in DEEM and the algorithms DEEM uses to manipulate that data to estimate exposure and risk. In addition to the algorithms, the paper contained a full delineation of underlying computer segment codes that comprise the DEEM program. In response to the SAP's concern that the DEEM paper did not make public the ''recipes'' used to translate the CSFII consumption data back to the precursor agricultural commodities (e.g. translating pizza into tomatoes, wheat, cheese, etc.), EPA contracted to have a new set of translations produced that would not be subject to proprietary restrictions. Those new translations have been completed and incorporated into DEEM-FCID, DEEM's successor, and are fully available to the public. (Ref.61).

Thus, NRDC is wrong in its assertion that DEEM is a ''secret'' model. The fundamental logic of this model is available to the public (including both the algorithms and computer codes) and data on food recipes is available on DEEM's successor DEEM-FCID, the model used to run EPA's latest dietary risk assessment for DDVP. NRDC's concerns regarding validation are misplaced as well in that DEEM and DEEM-FCID have been reviewed by the SAP and produce similar results to other publicly-available dietary exposure models. (See, e.g., 70 FR 77363 (December 30, 2005); 70 FR 40202 (July 13, 2005)). Accordingly, NRDC's request that the DDVP tolerances be revoked because of reliance on DEEM is denied.

3. *Percent crop treated data*—a. *NRDC's claims*. NRDC asserts that EPA has used percent crop treated data in calculating aggregate exposure for DDVP without making the findings required by section 408(b)(2)(F). (Ref. 1 at 39). That section imposes certain conditions upon EPA's use of percent crop treated data when assessing chronic dietary risk. Among the specified conditions are the requirements that EPA find (1) ''the data are reliable and provide a valid basis to show what percentage of the food derived from such crop is likely to contain such pesticide chemical residue;'' (2) ''the exposure estimate does not understate exposure for any significant subpopulation group;'' and (3) ''if data are available on pesticide use and consumption of food in a particular area, the population in such area is not dietarily exposed to residues above those estimated by [EPA].'' (21 U.S.C. 346a(b)(2)(F)). Finally, if EPA does rely on percent crop treated data EPA must provide for the periodic reevaluation of the estimate of anticipated dietary exposure. (Id.). NRDC claims that EPA, having failed to make the foregoing findings cannot rely on percent crop treated in making a safety finding for the DDVP tolerances.

b. *Amvac's comments*. Amvac asserts that adequate data are available on percent crop treated referring to an EPA memorandum (Hummel, 2000). (Ref. 14 at 47-48). According to Amvac, ''[t]hat memorandum describes the source of the data and states that the upper end of the range was assumed for acute dietary exposure analysis and that the typical or average was used for the chronic dietary exposure analysis, as is typical EPA practice.'' (Id.).

c. *EPA's response*. EPA conducted a comprehensive evaluation of the usage of DDVP, naled, and trichlorfon for the DDVP IRED. That evaluation was described in the memorandum cited by Amvac and the memorandum was included in the docket and on EPA's website page for DDVP. In response to NRDC's petition EPA has updated its analysis of percent crop treated information. Specifically, in its revised analysis EPA used percent crop treated data in estimating exposure from use of: (1) DDVP on livestock; (2) trichlorfon on turf; (3) DDVP and naled as a mosquito (wide area) treatment; and (4) naled on agricultural crops.

Based on the findings below, EPA concludes that its consideration of usage or percent crop treated data to estimate percent crop treated conforms to the requirements in section 408(b)(2)(F).

i. *Reliable data*. The primary source of data for estimating the percent of a commodity treated with a pesticide is the United States Department of Agriculture's National Agricultural Statistics Service (''NASS''). NASS collects data on a wide variety of agricultural topics including pesticide usage. NASS uses the Agricultural Resources Management Survey (''ARMS'') as well as other surveys to collect data on pesticide usage and other agricultural topics. These surveys are designed to produce statistically representative estimates of pesticide usage on targeted crops in the surveyed States using a probabilistically-based sampling procedure. (See *http://www.usda.gov/nass/nassinfo/surveyprograms/index.htm* and https://arms.ers.usda.gov/GlobalDocumentation.htm).

ARMS is a multi-phase, multi-frame, stratified, probability-weighted sampling design. There are three phases to the annual survey: a screening phase to update data and help target sampling for phases two and three; a second phase that collects information on agricultural practices and chemical usage; and a third phase that collects costs and financial information. ARMS consists of two ''frames'' collecting farms and ranches. The main frame is the ''list frame'' that is intended to contain the names and addresses of all farms and ranches in the continental United States along with the acreage of the farms/ranches and the crops grown or livestock raised. The list frame is compiled based on the Census of Agriculture as well as numerous other

surveys and governmental and non-governmental sources. The list frame is back-stopped by the ''area frame'' which is constructed from satellite images of the continental United States broken down into segments based upon degree and type of cultivation. Both frames are divided into different strata such as crop type. Due to the complexity of the sample design, ARMS uses a weighting system to adjust data gathered in reports from sampling of the frames.

Data is gathered by a statistically-designed sampling of the list and area frames. The sampling is done on a state basis with the focus for any particular crop on the major production states. Generally, samples are conducted in states representing 90 percent or better of the production acreage. Reports are usually prepared based on face-to-face interviews with the identified growers. Surveys for field crops are conducted annually with the crops varying each year. (See *http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1560)* Surveys for fruits and surveys for vegetables are conducted in alternating years with fruits surveyed in odd years and vegetables in even years. (See *http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1567* and *http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1572)*. There is some variation in the crops sampled in each survey. NASS data on pesticide use on livestock are published periodically by USDA (1999 (summary of 1997 livestock and general farm survey), 2000 (summary of 1999 swine and swine facilities survey), 2001 (summary of 2000 sheep and sheep facilities survey), 2002 (summary of 2001 dairy cattle and dairy cattle facilities survey), and 2006 (summary of 2005 swine and swine facilities survey), see *http://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1569)*.

To estimate percent crop treated for pre-harvest pesticide uses, EPA has created a database containing NASS data from the years 1999-2005. Also included in this database is data from a private service, Doane Marketing Research, Inc., now known as dmrkynetec. This database was used for making the majority of the percent crop treated estimates for the DDVP assessment, namely, the estimates pertaining to the use of naled as an agricultural pesticide. The 2007 estimates show that naled is generally used on a very small percentage of crop acreage. This is consistent with the estimates made for the 2000 dietary risk assessment. Most estimates from the two assessments were similar with a few crops showing declining use over time and one crop (strawberries) showing increased use. (Refs. 62 at 27-30; 56 at 29).

Dmrkynetec is a market research company. Originally, it focused on providing market and tracking data to agribusiness but has expanded its services to a wide range of industry sectors. In the agriculture area, dmrkynetec gathers information by survey research on, among other things, crop acres grown, pesticide active ingredients used, total acres treated with pesticides, pesticide application rates and timing, number of pesticide applications, and pesticide prices. For over 30 years, EPA has purchased dmrkynetec's proprietary database, which provides pesticide usage information for over 50 crops. As part of EPA's contract with dmrkynetec, EPA requires both a quality management plan and a quality assurance project plan to insure that dmrkynetec's survey practices and data compilation are well-designed and reliably executed. Data from dmrkynetec is relied upon not only by EPA but by other Federal agencies and private industry. (Ref.63).

For one commodity, poultry, for which sufficient NASS and dmrkynetec data were not available, EPA followed a different approach in estimating percent crop treated. EPA interviewed agricultural extension agents and professors in agricultural colleges in major poultry-producing states and reviewed crop profiles compiled by USDA and other literature from the extension services to obtain rough estimates of usage. Because this information was not based on statistically-designed surveys, EPA used it in a very conservative manner to estimate worst case percent crop treated estimates. Information gathered on broilers indicated that, DDVP was rarely, if ever used in broiler production in most of the major producing states. The one exception is Georgia, the largest broiler producing state, where approximately 1/3 of the broiler flock is treated with a product containing DDVP. As to layers (egg producers), DDVP is also not used in significant amounts in most of the major producing states. However, an expert in California (fourth in egg production among states) indicated that a product containing DDVP was used on approximately 75 percent of the state's layers. As a very conservative estimate, EPA assumed that 75 percent of the broilers and layers nationwide are treated with DDVP. (Ref. 64).

Estimates of the percent of crops that receive incidental treatment with naled or DDVP as a result of these pesticides' usage as a wide area treatment for the control of mosquitoes was based on a combination of data from NASS and Kline and Company, Inc., a private market research firm. Data from NASS' Census of Agriculture was used to determine the total farm acreage in the United States. Data from Kline provided information on the poundage of naled and dichlorvos used for mosquito treatment. This information was combined in a very conservative fashion with the data on total crop acreage in the United States. EPA calculated what percentage of the total crop acreage could have been treated with the naled and DDVP used for mosquito control and assumed that every crop in the United States was treated to that extent (3 percent). Although some treatment of agricultural crops will occur from the mosquito usage, a significant part, if not most, of the treatment area will be in wetlands, forest, urban and suburban land, and other non-crop areas. Even where agriculture land is treated, such treatment may occur when no crop is present or, even if a crop is present, at such a time that all residues would be expected to degrade prior to harvest. Estimates of percent crop treated for turf uses was also based on data from Kline. This information was not used to quantitatively estimate exposure but simply to qualitatively characterize the conservativeness of the drinking water concentration estimates from turf usage produced by EPA's drinking water model.

NASS's Census of Agriculture is as the name would suggest a complete count of United States farms and ranches. Additionally, the Census collects information on land use and ownership, agricultural practices, and farm income and costs. The Census is conducted every 5 years by law and involves individual contact with all farmers and ranchers in the United States. (See *http://www.agcensus.usda.gov*).

Kline, like dmrkynetec, conducts market research through surveys on a wide range of products. EPA has been purchasing data on non-agricultural pesticide usage from Kline for over 20 years. As with the dmrkynetec contract, EPA has required both a quality management plan and a quality assurance project plan to insure that Kline's survey practices and data compilation are well-designed and reliably executed. Data from Kline is relied upon not only by EPA but by other federal agencies and private industry. (Ref. 63).

EPA concludes these data sources provided reliable data for the percent crop treated estimates that were used by EPA.

ii. *Significant subpopulation group*. EPA considered DDVP exposure to the general population as well as 32 subpopulation groups based on regional location, ethnicity, and age. Reliance on the estimates of percent crop treated discussed above will not underestimate exposure for any of these population subgroups.

iii. *Data on pesticide use and consumption*. EPA takes information on regional consumption patterns into account in estimating exposure to significant subpopulation groups. EPA's information on percent crop treated is primarily national in scope and does not indicate that regional groups have greater exposures to DDVP than estimated by EPA.

iv. *Periodic evaluation*. The statute provides that EPA shall periodically reevaluate the estimate of anticipated dietary exposure. This is a prospective requirement. Although it may do so sooner, EPA expects that the exposure estimates will be reevaluated periodically through the registration review process. (21 U.S.C. 346a(b)(2)(F); Ref. 65).

To evaluate the sensitivity of dietary risk assessment to EPA's percent crop treated findings, EPA conducted an alternate dietary assessment assuming 100 percent crop treated for all commodities. (Ref. 56). As Table 2 shows, even using this very conservative assumption, dietary exposure is well below the RfD/PAD for DDVP.

TABLE 2.—DIETARY (FOOD AND WATER) EXPOSURE AND RISK FOR DDVP INCORPORATING 100 PERCENT CT FOR ALL COMMODITIES

Population Subgroup	Acute Dietary(99.9 Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.002274	28	0.000112	22
All Infants (<1 year old)	0.004152	52	0.000154	31
Children 1-2 years old	0.004663	58	0.000252	50
Children 3-5 years old	0.003533	44	0.000214	.....
Children 6-12 years old	0.002677	33	0.000138	28
Youth 13-19 years old	0.001660	21	0.000092	18
Adults 20-49 years old	0.001850	23	0.000102	20
Adults 50+ years old	0.001437	18	0.000088	18
Females 13-49 years old	0.001603	20	0.000097	19

4. *Anticipated residues*— a. *NRDC's claims*. NRDC asserts that because EPA relied upon anticipated residue data, EPA must issue a data call-in to demonstrate that actual residues are not higher than the anticipated residues relied upon by the Agency. (21 U.S.C. 346a(b)(2)(E)(ii)).

b. *EPA's response*. This is a prospective requirement. To the extent that NRDC is claiming that EPA must revoke all DDVP tolerances because the FFDCA provides that EPA must require the registrant to submit data in the next 5 years pursuant to section 408(f), that claim is rejected.

5. *Trichlorfon and naled*—a. *NRDC's claims*. Based solely upon EPA's statement in the prelimanry risk assessment that ''[n]on-detectable Dichlorvos residues in livestock commodities are expected as a result of Trichlorfon use[,]'' NRDC speculates that the method for detecting DDVP in beef may not be sensitive enough to detect toxicologically significant residues. (Ref. 1 at 40). Based on this speculation, NRDC claims that the DDVP tolerances do not comply with the requirement in section 408(b)(3) that ''a tolerance ... shall not be established at ... a level lower than the limit of detection of the method for detecting and measuring the pesticide chemical residue ... .'' (21 U.S.C. 346a(b)(3)(B)). Further, NRDC claims that EPA has not explained its conclusion that residues from trichlorfon use are estimated not to increase residues from the use of DDVP. (Ref. 1 at 51). In addition, NRDC contends that the Agency's analysis of DDVP residues from the use of naled (which also degrades into DDVP) for mosquito control is inadequate.

b. *EPA's response*— i. *Trichlorfon*. Trichlorfon degrades in plants and livestock and one of the products (metabolites) that forms is dichlorvos. Trichlorfon livestock feeding studies did not detect residues of dichlorvos using a level of detection (''LOD'') of 0.05 ppm. The trichlorfon RED concluded that dichlorvos was not a significant residue in the cattle based on the feeding study and a metabolism study. The metabolism study found DDVP in subcutaneous fat at 4 percent of the total radioactive residue (TRR), and less than 1 percent of the TRR in loin muscle (0.006 ppm). (Ref. 66). Subcutaneous fat is not used for human consumption, and often has residues higher than that in fat more distal from the site of application. Thus, it is highly unlikely that livestock will contain residues of dichlorvos from the use of trichlorfon. In any event, the residue monitoring data on DDVP includes DDVP as a degradate of trichlorfon and thus any DDVP in beef from use of trichlorfon would be captured by the monitoring data.

The Agency has substantial data showing that residues of dichlorvos as a result of trichlorfon use will be non-detectable in beef. USDA-FSIS has sampled for trichlorfon and dichlorvos in the past. Although there is no U.S. registration for trichlorfon on cattle, there are tolerances so that foreign cattle can be treated and imported to the United States. From 1993 through 1997, FSIS monitored over 12,000 samples of beef. (Ref. 67). No residues of dichlorvos

or trichlorfon were detected at a LOD of 0.2 ppm. However, detectable residues of other organophosphates were found.

In addition, monitoring data from PDP were available for milk at the time the last anticipated residues were determined for the 2000 IRED, and were used in the dietary exposure assessment for the IRED. One detectable residue was reported at 0.003 ppm out of 1,881 samples, with an LOD of 0.001 - 0.002 ppm (avg. 0.0014 ppm). (Ref. 62 at 12). Since that time, PDP collected over 300 samples of beef fat, liver, and muscle from 2001 to 2002 and found no detectable dichlorvos at a LOD of 1.0 ppb; over 300 samples of pork in 2005 and found no detectable dichlorvos residues at an LOD of 0.9 ppb in fat; and LOD of 0.45 ppb in pork muscle; and over 600 samples of poultry commodities in 2000-2001 with no detectable residues of dichlorvos at an LOD of 6.3 ppb. PDP also analyzed over 100 samples of heavy cream, and found no detectable residues of dichlorvos at a LOD of 1-2 ppb. Finally, no detects of DDVP were found 1,485 samples of milk analyzed in 2004-2005, at an LOD of 0.06 ppb. (Refs. 56 at 13; and 68).

NRDC is mistaken to claim that the detection method for DDVP in meat is not adequately sensitive. Generally, the Agency accounts for non-detectable residues by using ½ the LOD or LOQ in its calculations. (Ref. 69). If this calculation shows a potential risk problem, then the limits of detection must be lowered. In the case of dichlorvos, no risks of concern were identified for livestock commodities when they were assessed at ½ the LOD. In fact, total dietary risk from DDVP in food is just a small fraction of the RfD. Thus, the LODs are low enough to be below the level of risk concern and to ensure detection of toxicologically significant metabolites.

ii. *Naled*. DDVP exposure from use of naled to control mosquitoes through wide area treatment is likely to be very low to non-existent for two reasons: (1) The treatment rate is very low—0.25 lb ai naled/Acre, compared to the usual application rate for field crops of 1.8 lb ai naled/Acre; (2) residues from treatment degrade rapidly; and (3) the usage rate indicates few crops will be impacted by the mosquito use. Residue data from field trials showed most samples to be 0.03 ppm or less. One DDVP residue from the wide area treatment with naled was as high as 0.27 ppm, with the duplicate of this sample having a residue of 0.08 ppm (average residue 0.18 ppm DDVP). (Ref. 70). Additional data show that residues of DDVP are formed 1-3 days after field treatment with naled, and decline to non-detectable within 7 days of treatment with naled. (Ref. 71). Further, PDP data showed no detectable levels of DDVP in crops not registered to be treated with naled out of roughly 10,000 samples. (Ref. 56 at 19-20).

Despite these data suggesting there will be little to no exposure in the diet from use of naled to control mosquitoes, EPA took a very conservative approach to estimating exposure from the naled mosquito use in its revised risk assessment. (Ref. 56). First, EPA examined usage data to determine a rough estimate of the acreage treated with naled for mosquito control. (Ref. 72). EPA assumed that all acres treated were cropped farmland and not wetlands, woodlands, urban or suburban areas, or other non-cropped areas. This acreage was then expressed as a percentage of the overall farm acreage in the United States. That percentage (3 percent) was the value used in estimating the percent crop treated for all crops grown in the United States. If DDVP or naled is not registered for use on a crop, EPA assumed that three percent of that crop was treated. If DDVP or naled are registered on a crop and EPA has data on the percent of that crop treated as an agricultural use with DDVP or naled, EPA summed the percentages from the agricultural use and the mosquito use in estimating percent crop treated. Finally, if DDVP or naled are registered on a crop and EPA does not have data on the percent of that crop treated as an agricultural use with DDVP or naled, EPA assumed 100 percent of the crop was treated with DDVP or naled. In the latter circumstance, EPA considered but rejected somehow incorporating the mosquito use as an overlapping use because, for among other reasons, exposure from crops was based not on data from field trials but from monitoring data.

6. *Translation of reside levels*—a. *NRDC's claims*. NRDC contends that EPA cannot make the safety finding for DDVP because EPA has translated data from grain dust to soybean aspirated grain fractions and data from cattle to swine based on speculation and not validated data. Indeed, NRDC argues that every translation of data from one plant or species to another is a major data gap that cannot be addressed through worst case or default assumptions because plant or animal metabolism can produce metabolites that are more toxic than the parent compound.

b. *EPA's response*. EPA's translation of other residue data to soybean aspirated grain fractions is reasonable. EPA translated magnitude of the residue data from wheat and corn aspirated grain fractions to soybean aspirated grain fraction. Another name for ''aspirated grain fractions'' is ''grain dust.'' This is the dust that is removed from the grain by the rubbing of the grains together during storage. Residues in grain dust are generally surface residues and thus grain crops that have otherwise similar residues tend to have similar residue levels in grain dust. This is especially the case for DDVP given that it is applied in equal amounts to all grains post-harvest. Post-harvest application generally results in surface residues, and there would be no reason to expect different levels of residues across grains. For similar reasons, metabolism of the pesticide in the crop, which can play a role in residue levels, is unlikely to be a factor with DDVP grain dust residues because metabolism occurs primarily when a plant incorporates a pesticide through uptake and not when the pesticide is applied to the crop surface post-harvest. Thus, EPA's analysis is not based upon mere speculation, but rather a reasoned analysis of the similarity between commodities and how DDVP is used.

EPA's treatment of potential residue levels in swine is also reasonable. EPA requires radio-labeled metabolism studies in a few plant and animal commodities to identify all potential metabolites. (Ref. 73). Then magnitude of the residue studies are generally required for each treated plant and animal commodity for the purpose of selecting tolerance values and, in the absence of monitoring data, assessing risk.

EPA has all required animal metabolism studies for DDVP. EPA has required an additional study on the magnitude of DDVP residues in swine. These data are needed to verify that a proper tolerance value has been identified for pork commodities. In the absence of those data, EPA has relied on data on cattle and poultry products because it is likely that the residues will be similar to those in cattle and poultry commodities. These additional magnitude of the residue data are not needed for risk assessment because EPA has monitoring data on swine commodities. These data show no detectable residues.

7. *Food monitoring data*—a. *NRDC's claims*. NRDC asserts that the FDA and USDA monitoring programs are inadequate because the number of samples examined in these programs is too small to be representative of the total quantity of food potentially having DDVP residues. (Ref. 1 at 49, 61-62). In addition, NRDC claims that the monitoring data are old and, therefore,

do not represent current use patterns. NRDC also asserts that the consumption data are insufficient because they have a limited number of individuals in the age group of infants less than one year old. NRDC further notes that samples collected from the FDA Total Diet Study were collected in supermarkets in only four cities per year and residues in other locations may be different and very little monitoring data are available for fumigated commodities, requiring extensive translation from one fumigated commodity to another. Moreover, NRDC raises the concern that some of the FDA data were generated with an analytical methodology that is not capable of detecting ''early eluters'' such as DDVP and EPA has not taken this fact into account. Finally, NRDC contends that residues potentially present at roadside produce stands or farmer's markets are not represented and, additionally, that EPA failed to consider such consumers major identifiable subgroup of consumers. NRDC therefore concludes that EPA does not have reliable food monitoring data and argues that EPA should use the default assumption of 100 percent crop treated for all foods which may be treated with DDVP as well as the default assumption of tolerance level DDVP residues in all treated commodities.

In a related comment on the IRED, NRDC takes issue with EPA's decision not to sum potential residues resulting from multiple treatments of a food with DDVP at different stages of the food production process. (Ref. 13 at 8). NRDC claims EPA's conclusion that sufficient time would pass between such treatments that only the last treatment needs to be considered in estimating exposure is arbitrary and capricious.

b. *EPA's response*. In general, EPA disagrees that the monitoring data are unreliable. To the contrary, EPA believes that the monitoring data provide for an appropriately conservative risk assessment.

i. *Adequacy of data – Age and number of samples and sample location*. Contrary to NRDC's characterization, FDA and USDA each analyze thousands of samples per year. FDA analyzed several hundred samples per year for DDVP, but now analyzes less than 100. USDA analyzes most of their samples for DDVP, generally 350 to 700 samples per commodity per year, although sometimes only about 175 samples per commodity per year. FDA targets their monitoring toward commodities which have historically had residue problems. USDA-PDP uses a more random sampling plan, which is statistically designed to be representative of the U. S. food supply.

In response to NRDC's concerns regarding the age of the monitoring samples, EPA has updated its dietary risk assessment based almost exclusively on USDA PDP data from the years 2000 to 2005. In the updated assessment, FDA monitoring data was used for only one commodity, berries (not including strawberries). The updated assessment confirms what the earlier assessment found: DDVP residues are rarely found in food commodities. Not including strawberries, PDP data showed only 20 samples with detectable residues of DDVP out of more than 43,000 samples from 34 commodities which could potentially bear DDVP residues. Even focusing on foods covered by registered agricultural uses for DDVP or naled, there were only 20 samples with DDVP residues out of approximately 33,000 samples (not including strawberries). In the PDP data, strawberries were the only commodity with more than a marginal number of detections – with 104 samples showing DDVP out of 1,986 samples. (Ref. 56 at 19-20).

ii. *Infant consumption*. NRDC objects to EPA's reliance on an alleged lack of infant consumption data. In response, EPA notes that there is no more comprehensive a consumption survey in the United States than the CSFII surveys. Moreover, the revised dietary assessment relies upon more recent and updated CSFII data. Specifically, the FQPA required additional sampling of infant and children for information on their consumption has been completed. The results of the additional sampling were incorporated into DEEM and DEEM-FCID. These surveys are available to the public. (Ref. 6).

iii. *Fumigant monitoring data*. EPA believes it has adequate data on the fumigant use of DDVP. EPA has data from residue studies conducted in warehouses with packaged and bagged commodities for the following foods: flour, cocoa beans, coffee, dry beans, walnuts, and soybeans. (Ref. 74). These studies were conducted by fumigating pallets containing these commodities at a maximum rate and then sampling both the outside layer and interior of the foods on the pallet. These data were translated to other packaged and bagged commodities based on starch and moisture content. Although translating these data to other commodities creates some uncertainty as to the residue estimate, this uncertainty is more than offset by other factors. First, the studies used maximum treatment rates and sampled the commodities 6 hours after treatment. Not only does this approach overstate residues that would occur from lower treatment rates but it does not take into account the rapid disappearance of DDVP that occurs due to its volatile nature. Second, EPA assumed 100 percent of bagged and packaged commodities were treated.

iv. *Early eluter*. Because DDVP is an early eluter (i.e., DDVP will avoid detection unless samples are analyzed under low temperature chromatographic conditions), fewer samples are analyzed by FDA for DDVP than are typically analyzed by the Luke multiresidue method. In its prior dietary DDVP assessment EPA relied heavily on FDA monitoring but only used monitoring that used early eluter conditions which are known to detect DDVP. This issue has limited relevance given EPA's revised dietary risk assessment which relies almost entirely on PDP monitoring data which uses analytical methods which are known to detect DDVP.

v. *Farmers' markets and roadside produce stands*. In an order responding to NRDC objections to tolerances for different pesticides, EPA has addressed NRDC's claims regarding pesticide exposure to persons who purchase food at roadside stands or farmers' markets. (70 FR 46733). As EPA explained there, whether EPA relies on data from crop field trials or monitoring data in estimating pesticide exposure, given the sampling methods in field trials and food monitoring, residue levels identified from these sources are unlikely to understate residue levels at farm stands.

EPA also rejects NRDC's challenge to EPA's decision not to sum residues from treatments of a commodity at different stages of the production process. Multiple treatments are a possibility for commodities such as grains which may be treated as a bulk commodity and later as a bagged and packaged commodity. EPA has estimated DDVP exposure based on the treatment of bagged and packaged commodities. EPA's decision was based on a number of inter-related considerations. First, there are data showing that DDVP is a volatile compound that rapidly degrades. Second, general monitoring data consistently show very low to non-existent residues in food with the exception of one commodity (strawberries) that are marketed very promptly. Third, EPA has assumed that 100 percent of all bagged and packaged foods are treated with DDVP and EPA's estimate of residue values in these commodities is based on a conservative value from sampling of bagged and packaged commodities 6 hours after treatment. Finally, the latest data from FDA's Total Diet Study, a study measuring pesticide residues and other

contaminants in food as consumed, has shown zero detections of DDVP in the time period from the survey conducted in 1991 up until the latest survey in 2003. (Ref. 75). The Total Diet Study examines 280 foods, including many bagged and packaged foods, that are collected from different regions in the United States. DDVP is one of many pesticides analyzed for in the study.

8. *Cooking factors*—a. *NRDC's claims*. NRDC takes issue with the Agency's practice of using cooking factors to reduce estimates of residues for particular commodities as well as the Agency's practice of translating these factors to other commodities based upon similarity of cooking time and temperature. In particular, NRDC asserts that in the absence of empirical data demonstrating that each commodity will be affected identically by cooking, EPA cannot use cooking factors in its assessment of DDVP residues. In addition, NRDC contends that ''EPA apparently failed to take into account vastly different cooking practices for different commodities, including consumption of some commodities raw.'' (Ref. 1 at 50). As such, NRDC asserts that EPA should not assume cooking will result in any reduction in observed residue levels.

b. *EPA's response*. EPA's use of cooking factors is reasonable. Amvac submitted a cooking study which examined residue decline due to cooking in the following commodities: cocoa beans, dry pinto beans, tomato juice, coffee beans, hamburger meat, eggs, and raw whole milk. (Ref. 76 at 34-37). The study showed that DDVP residue reduction was time and temperature dependent with dramatic reductions occurring when items were cooked at high temperatures for more than a few minutes. For example, eggs cooked for 3 minutes at greater than 100 degrees C resulted in a residue decline of 38 percent, hamburger cooked at a similar temperature for six minutes showed a 70 percent decline in DDVP residues, and cocoa beans cooked for 10 minutes at 135 degrees C resulted in a residue decline of 99.7 percent. Residue decline factors (i.e., cooking factors) were translated from tested items only to similar commodities which are cooked in a similar manner. For example, data on dry pinto beans was translated to other dried beans and peas and to boiled peanuts; data on hamburger was translated to other meats; and data on tomato juice was translated to celery juice. EPA believes these cooking times and temperatures are reasonable, conservative estimates. Although certain of these commodities may occasionally be cooked for shorter times or at lower temperatures, EPA expects those instances to be infrequent. Moreover, given the conservative assumptions on cooking times any variations are very unlikely to be ''vastly different.'' As to consumption of some of these foods uncooked, NRDC's concern about use of cooking factors is unwarranted because EPA's consumption database differentiates between amounts of foods consumed cooked and uncooked and only applies cooking factors as to the former. Further, EPA concludes that its choice of translation commodities is also reasonable given the similarity between the cooking methods for the tested commodity and the translated commodity and the strong relationship shown in the data between cooking time and temperature and residue decline.

In any event, EPA disagrees that it cannot rely on cooking data unless it has data on all varieties of cooking practices within the United States and its cooking data take that full range of cooking practices into account. Implicit in this argument, is the view that EPA must adopt a cooking factor that reflects the shortest possible cooking time, no matter how infrequently such practice is used. Section 408, however, does not take such an extreme approach to assessing exposure. Rather, section 408, directs EPA to focus on major, identifiable subgroups of consumers not worst case scenarios or maximally-exposed individuals. EPA believes that use of reasonable, conservative exposure assumptions are consistent with this statutory mandate.

Additionally, it is important for EPA to adapt the assumptions underlying any exposure assessment to the complexity of the assessment. For simple assessments – a single pesticide to which a human is exposed by a single route (e.g., oral) from a single source (e.g., apples) – a more conservative approach to assumptions such as cooking factors may be necessary to assure high end exposures are captured because high end exposure may be defined by consumption of a single food. This is not the case with complex assessments like for DDVP that involve multiple pesticides, multiple routes of exposure, and multiple sources of exposure within routes. In evaluating exposure to DDVP in food alone, EPA's exposure assessment takes into account residues in hundreds of food commodities. If EPA were to assume worst case residue values for each of these commodities (worst case pesticide usage, worst case potential residues on the raw crop, worst case processing values, worst case cooking factors, etc.) and then combine that information with the assumption of worst case consumption for each commodity, the exposure assessment would not reflect reality. Just as no one person, and certainly no major subgroup of consumers, is a worst-case consumer of every commodity, no one person, or major subgroup of consumers, is likely to be consumers of every commodity at its worst-case residue amount. To make such assumptions when multiple commodities are involved compounds multiple conservatisms and would produce an assessment that overstates exposure probably by several orders of magnitude. For this reason, EPA's exposure assessment guidance advises using a mixture of high end and central tendency assumptions to produce a high end exposure assessment. (Ref. 77). Accordingly, EPA's use of conservative, but not worst case, cooking factors in the DDVP exposure assessment is reasonable.

9. *Missing data*—a. *NRDC's claims*. NRDC claims that various data are missing: storage stability data for meat, milk, poultry, and egg residue studies; crop field trials on tomatoes; and tomato processing studies. (Ref. 1 at 43).

b. *EPA's response*. The tomato use has been canceled so no data are needed on tomatoes. Although the IRED stated that data are needed on storage stability, that statement was in error. (Ref. 11 at 189). In fact, storage stability requirements have been met. The IRED noted that storage stability data were needed in connection with some of the residue data used in the 1987 Registration Standard for DDVP. Subsequent to 1987, the registrant submitted new residue data on the commodities in question and that residue data met the requirements for storage stability data. (See, e.g., Ref. 74 at 10).

10. *Uncertainties in estimating residues in foods*—a. *NRDC's claims*. NRDC argues that EPA has identified uncertainties in its dietary assessment but fails to take these uncertainties into account. Uncertainties cited by NRDC include lack of data on residue values in foods sold at farm stands, use of cooking data, the limited sampling sites in the FDA Total Diet Study, the reliance on residue trial instead of monitoring data for warehouse uses of DDVP, the extensive translation between commodities in estimating residues from DDVP warehouse uses, and the reliance on field trial data for some commodities. (Refs. 1 at 52; and 13 at 8-9).

b. *EPA's response*. EPA does take into account any uncertainties in its food exposure analysis in determining whether it has estimated risk in a manner that is protective of the general

population and all major identifiable consumer subgroups. For DDVP there were a number of factors that might have led to an underestimation of exposure levels but these factors are dwarfed by considerations indicating that EPA has overestimated exposure. Each of the factors highlighted by NRDC as well as others are discussed below:

i. *Food from farm stands*. As discussed above, EPA does not believe that farm stands are likely to sell food containing a significantly different residue profile than found in PDP monitoring data. This factor introduces little to no uncertainty concerning the possibility of underestimation of residues into EPA's analysis.

ii. *Use of cooking factors*. As discussed above, EPA used cooking factors in a conservative fashion in estimating exposure. For several reasons, EPA believes its use of cooking factors did not fully take into account the degree of reduction of DDVP residues that occurs with cooking. First, cooking factors were only applied to a relatively small number of commodities that may contain DDVP residues. Cooking of other commodities containing DDVP residues (e.g., grains and vegetables) will undoubtedly decrease residues in those commodities substantially. Second, the manner in which EPA translated the residue reduction data will tend to exaggerate residue levels in many commodities. For example, data on the residue reduction that occurs from cooking hamburger for six minutes was translated to all cooked meats. Given that most meats are cooked substantially longer than six minutes, this use of the cooking data will understate exposure. This factor will overestimate exposure to DDVP.

iii. *FDA Total Diet Study*. In the updated risk assessment the FDA Total Diet Study data was not relied upon to quantitatively estimate residues in food. This factor has no bearing on the DDVP exposure assessment.

iv. *Residues from warehouse use*. EPA did do extensive translation of data between commodities for the warehouse use. There was a reasonable basis for these translations; nonetheless, some uncertainty attends any such translation. However, EPA's estimation of exposure from the warehouse use will clearly overstate DDVP exposure for two reasons. First, EPA is not relying on monitoring data from warehouses but data from residue trials in the warehouse. Invariably, residue trials result in findings of higher residue values than monitoring data because residue trials involve prompt sampling after treatment whereas monitoring can occur days or weeks later. Thus, residue trials do not take into account the normal degradation that occurs over time. With DDVP, this decline in residues is likely to be exaggerated given the data showing both DDVP's volatility and rapid degradation. Monitoring data that is available on other commodities confirms the rapid decline of residues. Second, EPA assumed that all food in warehouses is treated with DDVP. This is a very conservative estimate. Accordingly, this factor will tend to significantly overstate exposure to DDVP.

v. *Reliance on field trial data*. For many commodities that may be legally treated with naled, EPA relied upon field trial data or assumed tolerance level residues rather than monitoring data. For the reasons noted immediately above, this assumption will significantly overstate residues on those commodities.

vi. *Percent crop treated*. For many commodities that may be legally treated with DDVP or naled (other than in warehouses), EPA assumed that 100 percent of the commodity is treated. Again, this is a very conservative estimate and will significantly overstate DDVP exposure from those commodities.

vii. *Default processing factors*. For several processed commodities, EPA relied on default processing factors in estimating DDVP residues in the processed food. EPA's default processing factors project worst case levels of pesticides in processed food. (70 FR at 46733-46734). Thus, use of default processing factors instead of specific processing data for DDVP will overestimate residues in food.

Considering all of this information, EPA's conclusion is 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.

In any event, EPA's 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. (Ref. 56). To the extent food is a driver, that food is food with residue estimates from its treatment as a bagged and packaged food. As explained above, estimates of residues in bagged and packaged foods are likely to be a significant overestimate due to the assumption of 100 percent treatment and use of magnitude of the residue study rather than actual monitoring data.

C. Residential Exposure

1. *Aggregating Exposures*. The safety standard in FFDCA section 408 for tolerances requires that there be a reasonable certainty of no harm from ''aggregate exposure to the pesticide chemical residue, including all dietary exposures and all other exposure for which there is reliable information.'' (21 U.S.C. 346a(b)(2)(A)(ii)). Further, EPA in evaluating the safety of tolerances is directed to ''consider ... available information concerning the aggregate exposures of consumers ... to the pesticide chemical residue ... including dietary exposure under [all] tolerance[s] ... in effect for the pesticide chemical residue and exposure from other non-occupational sources.'' (21 U.S.C. 346a(b)(2)(D)(vi)).

Unit VII.B. discusses EPA's assessment of aggregate dietary exposure to DDVP from residues in food and water. That assessment showed that these aggregate exposure levels were well below the acute and chronic RfD/PADs. Although refined, these exposure estimates still are likely to overstate exposure and risk. This is particularly apparent when it is considered that the commodities that drove the risk numbers were those commodities (drinking water and bagged and packaged goods) for which the most conservative assumptions were made. (Ref. 56).

Pesticide residues to which humans are exposed from residential uses of pesticides must be considered as part of section 408's aggregate exposure calculus. The concern, of course, is that pesticide tolerances should not be established or left in effect if dietary exposures, when combined with other sources of exposure, exceed safe levels. As the analysis in Unit VII.D.2. shows, however, dietary exposures are insignificant compared to residential exposures and thus the safety determination turns on an evaluation of the exposure and risk from the residential uses of DDVP.

2. *Revised residential exposure – pest strips*. In light of the numerous issues raised by NRDC concerning EPA's assessment of the risk posed by DDVP pest strips, EPA has substantially revised its assessment of exposure and risk from this use. EPA first discusses that revised assessment before turning to NRDC's specific claims. The changes in the assessment come in three areas: (1) analysis of exposure data and exposure assumptions used; (2) the types of durational scenarios assessed; and (3) the endpoint used for chronic exposure. (Ref. 78).

Currently, there are four sizes of DDVP pest strips that are registered. The largest strip (65-80 grams) may only be used in unoccupied areas in and around the house (garage, attic, crawl space,

shed) where humans are present for no greater than four hours per day. There are three smaller strips (16, 10.5, and 5.25 grams) that may be used in the home in closets, wardrobes, or cupboards. The IRED recommended, and Amvac has accepted, label restrictions for these smaller strips which bars use in closets of rooms where infants or children or sick or elderly people will be confined for an extended period or generally in closets of rooms for which any person will be present for extended periods. (Refs. 11 at 161; and 79). EPA's risk assessments examined each of these pest strips.

a. *Exposure data and assumptions*. In assessing exposure from pest strips, EPA has relied on a study (Collins and DeVries) measuring air concentrations in 15 houses treated with multiple large DDVP pest strips hung directly in the living areas of the houses. (Id.). In its prior assessment, EPA averaged air concentrations measured in the study across houses. To insure its assessment is conservative, EPA, in its most recent assessment, estimated risk based on the air concentrations in the individual houses. (Id.). Additionally, for chronic risk assessment, rather than project exposure from the 91 days of the Collins and DeVries study over a period of 120 days (the period for which a pest strip is generally designed to be effective), EPA used the air concentration measured over the 91 days in the study. This approach increases exposure estimates as the data show that DDVP air concentrations are higher in the first weeks. Finally, rather than calculate MOEs for different time periods in the home for strips used in occupied portions of the home, EPA calculated MOEs assuming that people are exposed in their homes 24 hours per day and spend 24 hours per day in a room with a pest strip. For strips used in unoccupied portions of the home, EPA assessed the risk based on 4 hours of exposure per day.

b. *Durational scenarios*. Previously, EPA focused only on chronic exposure to DDVP from pest strips and compared that chronic exposure to the chronic RfD/PAD. In its revised risk assessment, EPA assessed risks for acute, short/intermediate-term, and chronic exposures. (Id.). The acute assessment examined risk based on the air concentrations in the 15 houses in the Collins and DeVries studies for the first 24 hours after the pest strip is installed. The short/intermediate-term assessment examined risk based on the air concentrations for the first two weeks after installation of a pest strip. Appropriate acute and short/intermediate-term endpoints were used.

c. *Chronic endpoint*. EPA's prior risk assessment used the benchmark dose level of 10 percent ($BMDL_{10}$) for RBC cholinesterase from a chronic inhalation study in rats to assess chronic risk from exposure to pest strips. EPA reexamined this choice in light of its policy on the use of cholinesterase inhibition in risk assessments. Consistent with that policy, EPA determined that it would be more appropriate to use the $BMDL_{20}$ for RBC cholinesterase from that study in assessing chronic risk (but not for acute risk). That decision was based on the consistent and large difference in doses between indications of RBC cholinesterase inhibition at both the $BMDL_{10}$ and the $BMDL_{20}$ and inhibition of brain cholinesterase and clinical signs in numerous studies when exposure was for 90 days or greater. (Id.).

d. *Revised risk assessments*. EPA's revised assessment shows that (1) for the large strips permitted only in unoccupied portions of a home, the target MOE is exceeded (i.e., there is not a risk of concern) for all homes for four hours of exposure for acute, short/intermediate-term, and chronic scenarios (Table 3, Table 5, and Table 7); (2) for the largest closet strip the target MOE is exceeded for all homes for 24 hours of exposure for the acute scenario (Table 4); (3) for the largest closet strip the target MOE is exceeded for most homes for 24 hours of exposure for the short/intermediate-term and chronic scenarios (Table 6 and Table 8); (4) for the smaller closet strip and the cupboard strip the target MOE is all but met or exceeded for all homes for acute, short/intermediate-term, and chronic scenarios (Table 9 and Table 10); and (5) dietary exposure is insignificant compared to pest strip exposure for all scenarios. (Id.). The MOEs for all of these scenarios for the large pest strip and the large closet strip are presented in the tables below.

The acute risk assessments for large pest strips (Table 3) and closet, wardrobe, and cupboard pest strips (Table 4) use a hazard value of 0.800 mg/kg which is the $BMDL_{10}$ for RBC cholinesterase from a rat study. Exposure is based on Day 1 air concentrations in the Collins and DeVries study. Four hours of exposure is assumed for the large strip and 24 hours of exposure is assumed for the closet, wardrobe, and cupboard strips. The MOE of concern is 30, as opposed to 100, because when exposure is expressed in units of air concentration such as part per million (''ppm'') or milligrams/meter^3 (''mg/m^3'') (as it is in the Collins and Devries data), then the pharmacokinetic component of the interspecies factor is decreased from 10X to 3X to account for the different breathing rates between species. (Id.).

TABLE 3.—ACUTE RISK FROM EXPOSURE TO LARGE (65 G) STRIPS FOR 4 HOURS

Collins and DeVries Home ID	Day 1 Concentration (mg/m^3)	MOE
6N	0.11	45
7W	0.11	45
2C	0.08	61
14W	0.08	61
10C	0.07	70
13W	0.07	70
5N	0.05	98
11C	0.05	98
12N	0.05	98
3C	0.04	123
15N	0.04	123
1W	0.02	245
4N	0.02	245
8W	0.02	245
9C	0.01	490

TABLE 4.— ACUTE RISK FROM EXPOSURE TO LARGE CLOSET (16 G) PEST STRIPS FOR 24 HOURS

Collins and DeVries Home ID	Day 1 Concentration (mg/m^3)	MOE
6N	0.028	30
7W	0.028	30
2C	0.020	41
14W	0.020	41
10C	0.018	47
13W	0.018	47
5N	0.013	66
11C	0.013	66
12N	0.013	66
3C	0.010	82
15N	0.010	82
1W	0.005	165

TABLE 4.— ACUTE RISK FROM EXPOSURE TO LARGE CLOSET (16 G) PEST STRIPS FOR 24 HOURS—Continued

Collins and DeVries Home ID	Day 1 Concentration (mg/m^3)	MOE
4N	0.005	165
8W	0.005	165
9C	0.003	329

The smaller closet strip and cupboard strip will have higher MOEs. Background dietary DDVP exposure when expressed in mg/m^3 is 0.00026 and this value is insignificant compared to the air concentration levels in higher concentration houses.

The short/intermediate-term risk assessments for large pest strips (Table 5) and for closet, wardrobe, and cupboard pest strips (Table 6) use a hazard value of 0.1 mg/kg/day which is the LOAEL for the human repeat dose oral study. Exposure is based on the average air concentration of the first 2 weeks of exposure in the Collins and DeVries study. Four hours of exposure is assumed for the large strip and 24 hours of exposure is assumed for the closet, wardrobe, and cupboard strips. The MOE of concern is 30 based on an intraspecies safety factor of 10X and an additional safety factor of 3X for reliance on a LOAEL.

TABLE 5.—SHORT/INTERMEDIATE-TERM RISK FROM EXPOSURE TO LARGE (65 G) STRIPS FOR 4 HOURS/DAY

Collins and DeVries Home ID	2-Week Average Concentration (mg/m^3)	MOE
7W	0.074	29
2C	0.073	29
10C	0.072	29

TABLE 5.—SHORT/INTERMEDIATE-TERM RISK FROM EXPOSURE TO LARGE (65 G) STRIPS FOR 4 HOURS/DAY—Continued

Collins and DeVries Home ID	2-Week Average Concentration (mg/m^3)	MOE
6N	0.066	32
13W	0.065	32
14W	0.059	36
12N	0.048	43
11C	0.038	55
3C	0.032	65
5N	0.030	69
15N	0.028	74
8W	0.019	109
1W	0.019	112
4N	0.017	126
9C	0.012	177

TABLE 6.—SHORT/INTERMEDIATE-TERM RISK FROM EXPOSURE TO LARGE CLOSET (16 G) PEST STRIPS FOR 24 HOURS/DAY

Collins and DeVries Home ID	2-Week Average Concentration (mg/m^3)	MOE
7W	0.018	19
2C	0.018	19
10C	0.018	20
6N	0.016	21
13W	0.016	22
14W	0.015	24

TABLE 6.—SHORT/INTERMEDIATE-TERM RISK FROM EXPOSURE TO LARGE CLOSET (16 G) PEST STRIPS FOR 24 HOURS/DAY—Continued

Collins and DeVries Home ID	2-Week Average Concentration (mg/m^3)	MOE
12N	0.012	29
11C	0.010	37
3C	0.008	43
5N	0.008	46
15N	0.007	50
8W	0.005	73
1W	0.005	75
4N	0.004	84
9C	0.003	118

The smaller closet strip and cupboard strip will have MOEs of 29 or higher. Background dietary DDVP exposure when expressed in mg/m^3 is 0.00026 and this value is insignificant compared to the air concentration levels in higher concentration houses.

For the chronic risk assessments for large pest strips (Table 7) and closet, wardrobe, and cupboard pest strips (Table 8, Table 9, and Table 10), EPA calculated MOEs for a range of hazard values: the $BMDL_{10}$ and $BMDL_{20}$ for RBC cholinesterase from a 2–year chronic rat study, $BMDL_{10}$ for brain cholinesterase from a 90–day rat study, and the NOAEL for clinical signs from a 7–day rat study. Exposure is based on the average air concentration for the 91 days of the Collins and DeVries study. Four hours of exposure is assumed for the large strip and 24 hours of exposure is assumed for the closet, wardrobe, and cupboard strips. The MOE of concern is 30 for the same reason as with the acute exposure assessment.

TABLE 7.—CHRONIC RISK FROM EXPOSURE TO LARGE (65 G) STRIPS FOR 4 HOURS/DAY

Study		Rat 2-Year Inhalation			Rate 90 Day oral	Rate 7 Day oral
POD Type		$BMDL_{10}$		$BMDL_{20}$	$BMDL_{10}$	LOAEL
POD (mg/m^3)		0.078	0.41	0.196	0.4	7.3
Home ID	CD avg ÷ 6	RBC	Brain	RBC	RBC	Clincal signs
10C	0.00607	13	67	32	66	1200
2C	0.00575	14	70	34	70	1300

TABLE 7.—CHRONIC RISK FROM EXPOSURE TO LARGE (65 G) STRIPS FOR 4 HOURS/DAY—Continued

Study		Rat 2-Year Inhalation			Rate 90 Day oral	Rate 7 Day oral
POD Type		$BMDL_{10}$		$BMDL_{20}$	$BMDL_{10}$	LOAEL
POD (mg/m^3)		0.078	0.41	0.196	0.4	7.3
Home ID	CD avg ÷ 6	RBC	Brain	RBC	RBC	Clincal signs
13W	0.00483	16	84	41	83	1500
7W	0.00337	23	120	58	119	2200
12N	0.00330	24	123	59	121	2200
14W	0.00330	24	123	59	121	2200
6N	0.00212	37	191	93	189	3400
3C	0.00212	37	191	93	189	3400
11C	0.00207	38	196	95	194	3500
15N	0.00192	41	211	102	208	3800
8W	0.00161	48	251	122	248	4500
1W	0.00137	57	295	143	291	5300
9C	0.00127	61	318	154	314	5700
5N	0.00109	71	370	179	366	6700
4N	0.00099	79	409	198	404	7400

TABLE 8.—CHRONIC RISK FROM EXPOSURE TO LARGE (16 G) CLOSET STRIPS FOR 24 HOURS/DAY

Study		Rat 2-Year Inhalation			Rate 90 Day oral	Rate 7 Day oral
POD Type		$BMDL_{10}$		$BMDL_{20}$	$BMDL_{10}$*	LOAEL
POD (mg/m^3)		0.078	0.41	0.196	0.4	7.3
Home ID	CD avg ÷ 4	RBC	Brain	RBC	RBC	Clinical signs
10C	0.00910	9	45	22	44	780
2C	0.00862	9	47	23	46	830
13W	0.00725	11	56	27	55	980
7W	0.00506	15	80	39	79	1400
12N	0.00495	16	82	40	81	1400
14W	0.00495	16	82	40	81	1400
6N	0.00318	25	127	62	126	2100
3C	0.00318	25	127	62	126	2200
11C	0.00310	25	131	63	129	2300
15N	0.00288	27	141	68	139	2500
8W	0.00242	32	168	81	166	3000
1W	0.00206	38	196	95	194	3400
9C	0.00191	41	212	103	209	3800
5N	0.00164	48	247	119	244	4100
4N	0.00148	53	273	132	270	4700

TABLE 9.—CHRONIC RISK FROM EXPOSURE TO SMALL CLOSET (10.5 G) STRIPS FOR 24 HOURS/DAY

Study		Rat 2-Year Inhalation		
POD Type		$BMDL_{10}$		$BMDL_{20}$
POD (mg/m^3)		0.078	0.41	0.196
Home ID	CD avg ÷ 6	RBC	Brain	RBC
10C	0.00607	13	67	32
2C	0.00575	14	70	34
13W	0.00483	16	84	41
7W	0.00337	23	120	58
12N	0.00330	24	123	59
14W	0.00330	24	123	59
6N	0.00212	37	191	93
3C	0.00212	37	191	93
11C	0.00207	38	196	95
15N	0.00192	41	211	102
8W	0.00161	48	251	122
1W	0.00137	57	295	143
9C	0.00127	61	318	154
5N	0.00109	71	370	179
4N	0.00099	79	409	198

TABLE 10.—CHRONIC RISK FROM EXPOSURE TO CUPBOARD (5.25 G) STRIPS FOR 24 HOURS/DAY

Study		Rat 2-Year Inhalation		
POD Type		$BMDL_{10}$		$BMDL_{20}$
POD (mg/m^3)		0.078	0.41	0.196
Home ID	CD avg ÷ 12	RBC	brain	RBC
10C	0.00303	26	134	65
2C	0.00287	27	141	68
13W	0.00242	32	168	81
7W	0.00169	46	240	116
12N	0.00165	47	245	119
14W	0.00165	47	245	119
6N	0.00106	74	382	185
3C	0.00106	74	382	185
11C	0.00103	75	392	190
15N	0.00096	81	422	204
8W	0.00081	97	503	243
1W	0.00069	113	589	285
9C	0.00064	123	636	308

TABLE 10.—CHRONIC RISK FROM EXPOSURE TO CUPBOARD (5.25 G) STRIPS FOR 24 HOURS/DAY—Continued

Study		Rat 2-Year Inhalation		
POD Type		$BMDL_{10}$		$BMDL_{20}$
POD (mg/m^3)		0.078	0.41	0.196
Home ID	CD avg ÷ 12	RBC	brain	RBC
5N	0.00055	143	740	358
4N	0.00049	158	819	396

Background dietary DDVP exposure when expressed in mg/m^3 is 0.00026 and this value is insignificant compared to the air concentration levels in higher concentration houses.

Despite the fact that some homes from the Collins and DeVries study do not have acceptable MOEs for the short/intermediate-term and chronic scenarios for the large closet strip, EPA concludes that the pest strips do not pose a risk of concern for the following reasons. First, use of $BMDL_{20}$ for RBC cholinesterase is a conservative endpoint based on the DDVP database. As Table 7 indicates, target MOEs are well exceeded for all homes for chronic risk if the $BMDL_{10}$ for brain cholinesterase or the NOAEL for clinical signs are used as the Point of Departure. Second, for short/intermediate-term risk, EPA has used the results of the human oral study in a conservative fashion. The maximum inhibition of RBC cholinesterase from the 0.1 mg/kg/day dose used in that study was 16 percent (group mean) after 18 days of exposure. As discussed above, however, 20 percent inhibition is a more appropriate line of demarcation for DDVP given, among other things, the wide margin between RBC cholinesterase inhibition and clinical effects. If that approach is followed the one dose from that study, then 0.1 mg/kg/day would be a NOAEL not a LOAEL and the additional 3X safety factor would be unnecessary. Without that 3X safety factor, the MOE of concern would drop to 10. The conservativeness of the 3X safety factor is also supported by the HSRB's conclusion that a dose lower than 0.1 mg/kg/day would not be expected to show a significant inhibition response.

Finally, EPA made numerous conservative assumptions regarding interpretation of the Collins and DeVries data in using it to estimate exposure, including that: (1) the large strips used in the Collins and DeVries study emitted the same amount of DDVP as the largest strip currently registered even though the current large strip (65 – 80 grams) is smaller than the strip used in the Collins and DeVries study (100 grams); (2) placement of a strip in a closet is the same as hanging it in the adjacent living area; (3) for closet, wardrobe, and cupboard strips, exposure is 24 hours per day (despite label restrictions barring use in rooms where people would be exposed for extended periods); (4) during the 24 hours per day a person is in a home that person is continually in a room with a pest strip; and (5) strips are replaced every 90 days.

3. *Issues raised by NRDC concerning pest strips*—a. *NRDC's claims*. NRDC argues that EPA's exposure assessment for pest strips ''is based on unsupported assumptions and inadequate data'' and therefore EPA cannot conclude that aggregate exposure to DDVP is safe. NRDC's specific allegations are described below.

i. *Reliance on an inadequate exposure study*. NRDC notes that EPA relied on a single study (Collins and DeVries) monitoring 15 homes in one geographic area to estimate residential exposure to DDVP from pest strips. NRDC claims this study is inadequate because (1) the number of homes monitored is too small to be representative of the housing stock in the United States; (2) the study was conducted in only one geographic area and at one time of year and thus would not be representative of weather conditions (including humidity and temperature) in other regions of the United States; (3) sampling in the homes was done in only one location and thus the study ''provides no information about the movement of residues from room-to-room and [] exposure in other rooms in the homes;'' (4) homes were only treated with three or four pest strips but homeowners with severe pest problems may ''place pest strips in every room or most rooms in the house;'' and (5) the study contained insufficient information to estimate exposure levels for pest strips of different sizes. (Ref. 1 at 19, 58-59).

ii. *Unsupported assumption that users will not replace pest strips more frequently than every 120 days*. NRDC claims that EPA's assumption that homeowners will not replace pest strips until the strip has been in use for at least 120 days is unreasonable because the label does not prohibit more frequent replacement and EPA has no empirical data to support this assumption. (Id. at 59). NRDC argues that ''[i]n the absence of reliable empirical data demonstrating that consumers do not ... replace the strips more often than is assumed by EPA, at a minimum, the labels of these products should be amended to place restrictions on use consistent with the assumptions made in the risk assessment.'' (Ref. 13 at 10).

iii. *Only considered average exposure over 120 days*. NRDC argues that EPA erred by averaging exposure levels over a 120–day period. According to NRDC, EPA should have considered ''the higher, more dangerous exposures that occur when a strip is first hung ....'' (Ref. 1 at 59). Instead, NRDC asserts, EPA ''should have presented the range of risks displayed over time.'' (Id.).

iv. *Failure to consider exposure from use in unoccupied spaces*. NRDC claims that EPA has not taken into account that DDVP residues could migrate from use of the full-size pest strips in attics, crawl spaces, and garages to the main living areas of a home. (Ref. 13 at 10). NRDC notes that EPA has found that use of chlorpyrifos in crawl spaces leads to residues in living areas. (Id.). NRDC further contends that attics can be part of the air exchange for the living areas in a house.

v. *Estimates of exposure durations in homes are too low*. While NRDC concedes that an estimate of 16 hours/day in a home would be a high end estimate for most people, NRDC argues that this estimate ignores ''several significant population groups'' such as ''[p]eople who work or stay at home, retired and elderly people, and pre-school children.'' (Id.). Further, NRDC asserts that EPA's low end estimate of 2 hours/day in the home is ''absurd on its face.'' (Id.).

vi. *No consideration of incidental oral and dermal exposure*. NRDC claims that

EPA had insufficient data to conclude that incidental oral and dermal exposure resulting from DDVP residues that settle on home surfaces would be minimal. (Id. at 19.). According to NRDC, the only information EPA relied upon was data on residues that settle on foodstuffs and such data would not be representative of other home surfaces.

vii. *Failure to collect data on consumer use practices with pest strips*. Echoing comments from the SAP that ''better knowledge of real world use practices would serve to improve residential exposure analyses,'' NRDC argues that the failure of EPA to collect such data ''undermines the risk analysis for pest strips.'' (Ref. 1 at 62).

viii. *Failure to consider aggregation of pest strip exposure with other residential exposures*. NRDC claims that EPA does not support its statement that pest strip exposures would not co-occur with high dietary exposures. NRDC also argues that EPA should consider co-occurrence of exposure between pest strips and other DDVP residential products. (Ref. 13 at 12-13).

b. *Amvac's comments*. Amvac contends that the Collins and DeVries study is adequate for assessing exposure from pest strips citing several other studies which it states contain similar results. (Ref. 14 at 45). Further, Amvac argues that ''the estimated time-weighted average concentration used by EPA (0.015mg/m^3) is higher than found in many other studies.'' (Id.). Amvac also defends EPA's use of a time-weighted average in estimating risk noting that ''EPA is assessing chronic exposure and thus it is appropriate to average over the entire period to compare to a chronic endpoint.'' (Id.). Finally, Amvac argues that, if EPA assessed acute risk from pest strips, it would be appropriate for EPA to use the highest concentration from the Collins and DeVries study (0.11 mg/m^3) but that this exposure level does not show an acute risk concern. (Id.).

c. *EPA's response—adequacy of the Collins and DeVries Study*. EPA believes this study is sufficiently representative to estimate exposure and EPA disagrees with each of NRDC's contentions. First, EPA does not believe the study is inadequate due to being performed in a single location on 15 houses during a single season of the year. As noted by Amvac, there are a number of studies other than Collins and Devries that test DDVP pest strips in houses. Specifically, data on DDVP air concentrations from the use of pest strips are available for over 100 homes in the United States, United Kingdom, and France. (Ref. 80). There was no major difference in the DDVP air concentration in the 100 houses and the DDVP air concentration in the study of the 15 houses that were used for exposure estimates.

Second, EPA does not view the study as flawed because it only sampled DDVP concentrations in one location in each home. Importantly, 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. Thus, EPA has assessed MOEs in an appropriately conservative fashion given the sampling location in the Collins and DeVries study.

Third, NRDC's suggestion that some homeowners may put a pest strip in every room fails to take into account that (1) the label now bars use of full-size pest strips except in infrequently-occupied spaces (attics, crawl spaces, sheds, and garages); (2) in-home pest strips must contain significantly less DDVP than full-size strips and are limited to use in closets, wardrobes, and cupboards; and (3) EPA's risk assessment assumes a person spends all of their time in a room with a closet or cupboard that contains a pest strip. Relevantly, the largest closet strip is only labeled as effective in a 200 cubic foot area. Areas beyond that efficacious zone of treatment are likely to contain significantly lower air concentrations.

Fourth, the Collins and DeVries study does provide sufficient information to estimate exposure from different size strips. The Collins and Devries study used a pest strip that was larger than the largest size available today and EPA made the conservative assumption that the currently-registered large strip would have similar exposure to the older, larger version and extrapolated exposure levels for smaller strips proportionately based on that conservative assumption.

Finally, to insure that EPA has the most accurate information possible on exposure for pest strips, EPA plans to require as part of the data call-in to be issued in connection with reregistration that an additional study be conducted that measures DDVP air concentrations in houses from use of pest strips.

i. *Replacement of strips*. EPA's risk assessment has a built-in margin of error in the event strips are replaced more frequently than every 120 days because it is based on an average of the first 91 days of exposure which was the period of time air concentrations were measured in the Collins and DeVries study.

ii. *Use of time-weighted average exposure*. EPA believes that use of a time-weighted average of the DDVP concentration levels is appropriate for chronic risk and does not understand NRDC to be contesting this approach to assessing chronic risk. As to acute exposures that occur during the first day after a strip is hung, EPA has now expanded its risk assessment to address both this scenario and a short/intermediate-term exposure scenario (exposure for the two weeks after a strip is installed).

iii. *Exposure from use in unoccupied spaces*. EPA believes it unlikely that DDVP residues will migrate from attics, crawl spaces, garages, and sheds to living areas within a house because it would be unusual for these spaces to be connected to the air exchange for a house. On the other hand, basements may be included in a home's air exchange system and, for that reason, the large pest strips may not be used in a basement. This is likely part of the explanation for the result in the cited chlorpyrifos study. In that study, the chlorpyrifos was injected into the foundation and migrated to the basement of the house. From there, it is likely that chlorpyrifos moved to other rooms in the house through air exchange. Further, the chlorpyrifos study cited by NRDC has little relevance to pest strips given the vastly different amounts of active ingredient involved. (Ref. 81). In the chlorpyrifos study, approximately 100 gallons of a solution containing 1 percent of pesticide product (Dursban TC) was injected into basement walls. According to the label, Dursban TC contains 4 pounds per gallon of chlorpyrifos. Thus, that study used approximately 4 pounds of chlorpyrifos. A large pest strip contains, at most, 80 grams of pesticide product, of which 18.6 percent is DDVP. Accordingly, the pest strip exposure in unoccupied areas would contain roughly 15 grams of DDVP compared to approximately 1,800 grams of chlorpyrifos in the study cited.

iv. *Exposure durations in homes*. First, EPA believes it is unlikely that a person would spend four hours per day, day in and day out for an extended period in an attic, crawl space, garage, or shed. In any event, the label forbids use of the large pest strips in such locations should they be occupied that regularly. Second, as to the closet, wardrobe, and cupboard strips, EPA has assumed 24 hours per day exposure in calculating margins of exposure. Amvac has agreed to modify labels on these products so that they bar use of these strips in closets in rooms where infants or children, or sick or elderly people are confined for extended periods. Additionally, the label prohibits use of

the strip in any area of the house where people are present for extended periods.

v. *Incidental oral and dermal exposure*. NRDC is incorrect in its assertion that EPA's risk assessment does not take into account incidental oral and dermal exposure. Although dermal and incidental oral exposure from contact with DDVP adsorbed on solid surfaces was not assessed directly, the inhalation study used for assessing inhalation risk includes dermal and oral exposure components because the study involved continuous whole-body exposure resulting in adsorption of DDVP vapors to the animal's fur and food. In other words, the inhalation study is actually a total exposure study accounting for exposure by all routes when DDVP is delivered as a vapor. Further, the pest strip use is unlikely to leave significant DDVP residues on residential surfaces leading to dermal or incidental oral exposures. DDVP is highly volatile and degrades rapidly. Thus, even if a person repeatedly uses pest strips in the home, significant long-term dermal exposure is unlikely. The Collins and DeVries study showed very low concentrations of DDVP in the air and almost all food sampled in the home had no detectable residues. EPA reasonably concluded that any dermal exposures from deposit of air residues on surfaces would be negligible compared to residues inhaled directly.

vi. *Data on real world use practices*. Data on ''real world'' use practices of pest strips might make it possible for EPA to determine the extent to which EPA is likely overestimating exposure. EPA believes its conservative projection of exposure, given the clarity and reasonableness of the label directions, as amended, preclude the need to require additional data on use practices.

vii. *Aggregating pest strip exposure with other residential exposures*. In assessing aggregate risks, EPA believes it is unrealistic to add high-end exposures from intermittent and unconnected pesticide exposures which are likely to affect relatively small population groups. Thus, in aggregating dietary exposures to pest strip exposures, EPA has compared chronic (rather than acute) dietary exposure levels of DDVP as a background exposure to the various pest strip durational scenarios (acute, short/intermediate-term, chronic). It should also be noted that the dietary exposure estimates for DDVP are driven by high-end model estimates of residues in drinking water which is an additional conservatism.

For similar reasons, EPA does not believe it is realistic to add high-end acute or short-term exposures for the residential use of trichlorfon on turf and DDVP as a spot insect treatment by aerosol spray. Although dietary exposure to DDVP, and possibly exposure from a DDVP pest strip, may be appropriately aggregated as a background exposure to the turf or spot treatment uses, assuming that the windows for high-end acute exposures from the turf use and the spot treatment overlap is overly conservative. In any event, however, even if exposures from turf and spot treatment uses are aggregated with each other and with background exposures from food and water and pest strips, the aggregate exposure still does not show a risk of concern. Aggregating the MOEs of 100 for both the turf and spot treatment uses, (Ref. 11 at 160, 165), with MOEs for background exposure for dietary (900) and pest strips (93) gives an aggregate short-term MOE of 31 for the child who simultaneously experiences outdoor exposures from the trichlorfon turf use with indoor exposures from DDVP spot treatments and pest strips. The target MOE here is 30. This aggregation relies upon average dietary exposure for the most highly exposed subgroup which may have turf post-application exposures (children aged 1-2) compared to the short-term oral Point of Departure and average pest strip exposure over 91 days compared to the short-term inhalation Point of Departure. (Refs. 11 at 138, 162; 56 at 18).

D. Risk Characterization

1. *99.9th percentile*—a. *NRDC's claims*. NRDC asserts that EPA has failed to provide a rationale for using the 99.9th percentile in the DDVP risk assessment for acute population effects. (Ref. 1 at 51). NRDC further contends that some 300,000—0.1 percent of the U.S. population—will not be considered because they ''fall below the level of sensitivity of the calculation method.'' (Id.). NRDC therefore argues that EPA cannot make its FFDCA safety finding.

b. *EPA's response*. Contrary to NRDC's assertion, EPA has not ignored 300,000 of the U.S. population in estimating acute DDVP risks through reliance on the 99.9th exposure percentile in the DDVP risk assessment. As EPA has repeatedly explained in the past – in science policy documents and in responses to NRDC's objections to tolerances – ''the use of a particular percentile of exposure is a tool to estimate exposures for the entire population and population subgroups and not a means to eliminate protection for a certain segment of a subgroup.'' (69 FR 30070 and 70 FR 46733).

In examining pesticide exposure, EPA does not have the capability of measuring actual exposure to individuals across the population. Rather, EPA uses data on factors bearing on exposure such as residue levels in food and drinking water, food consumption patterns, and air concentration levels and transferable surface residues to estimate exposure to hypothetical individuals across major identifiable subgroups in the population. These data on exposure factors can range from highly conservative values (e.g., assumption that 100 percent of a crop is treated with a pesticide) to highly realistic values (e.g., market basket monitoring data on pesticide residue levels). In interpreting exposure estimates based on such factors, EPA makes judgments regarding what exposure level (expressed as a percentile) is protective of the relevant population subgroups taking into account the relative conservativeness of the factors which are the basis of the assessment.

Generally, EPA uses the 95th percentile exposure as a starting point for evaluating the safety of pesticide in circumstances where EPA has employed very conservative assumptions on residue values and risk assessment techniques. In EPA's judgment, the 95th percentile exposure, when calculated using such conservative assumptions, will not underestimate exposure for any major identifiable subgroups. However, when EPA uses more realistic residue values and refined risk assessment techniques, it starts its evaluation of safety at the 99.9th percentile of exposure to be sure that it is protecting the entire population and all major, identifiable subgroups. EPA uses the 99.9th percentile as the starting point for refined assessments rather than the 100th percentile because generally its exposure assumptions, even when refined, contain residual conservatisms. Thus, whether EPA is relying on the 95th percentile, the 99.9th percentile, or some other value, the population exposure percentile is a means to an end and not a designation of those people worthy of protection. As EPA noted in a science policy document on this issue: ''just as when OPP uses the 95th percentile with non-probabilistic exposure assessments OPP is not suggesting that OPP is leaving 5 percent of the population unprotected, OPP is not by choosing the 99.9th percentile for probabilistic exposure assessments concluding that only 99.9 percent of the population deserves protection.'' (Ref. 8 at 31). Perhaps the best evidence that use of population percentiles is not identifying those worthy of protection but simply a tool in estimating exposure

is that refined assessments using the 99.9th percentile invariably estimate exposure to be lower for a pesticide than an unrefined assessment for that same pesticide using the 95th percentile. (69 FR 30071). Yet, under NRDC's logic the use of the 95th percentile, by itself, would signal that fewer people are being protected than if the 99.9th percentile was used, and thus an exposure estimate based on the 95th percentile should necessarily be lower than one based on the 99.9th percentile.

2. *Inappropriate use of 100% of the RfD/PAD as a ''Bright Line'' Rule*—a. *NRDC's claims.* NRDC contends that EPA is unlawfully disregarding significant risks by relying on a ''bright line rule'' that risks below 100 percent of the acute population adjusted does (aPAD) are not of concern and risks above 100 percent are of concern. (Ref. 1 at 51-52). Specifically, NRDC argues that (i) EPA treats the 100 percent threshold as a rule that has not been subject to notice and comment rulemakings; (ii) use of a 100 percent threshold is arbitrary and capricious; (iii) use of 100 percent threshold improperly excludes acute risks unless they exceed 100 percent of the aPAD; and (iv) EPA cannot reasonably explain how children aged 1 to 6, the sub-population with the highest percentage exposure, will not be harmed.

b. *EPA's response.* NRDC appears to be suggesting that EPA's approach of comparing estimated DDVP exposure to an EPA-derived safe dose for DDVP is unlawful because (1) EPA cannot adopt an analytical approach of comparing exposure to the safe dose without a regulation that permits such an approach; and (2) EPA has not adequately justified that its chosen safe dose is actually safe. Such claims are baseless.

In assessing risks posed by a pesticide, EPA first examines toxicological studies with the pesticide and calculates a safe dose in humans (RfD/PAD) based on the results of those studies and incorporating appropriate safety factors. This analysis, based on well-established risk assessment principles used both across the federal government and internationally, is designed to establish a dose without appreciable risk to humans. EPA then compares estimated aggregate exposure to humans to the safe dose to make a determination on the safety of the pesticide. EPA believes this type of case-by-case assessment of the risk from exposure to a pesticide is precisely what section 408 demands. Other than the statutory mandates in FFDCA section 408, EPA does not follow ''bright line'' rules in making safety determinations but rather is guided by what the data show on a particular pesticide. Of course, at the end of its pesticide-specific analysis EPA must make a safety determination. EPA does not believe it needs a rule saying so to conclude that, where it has confidence that exposure is below the safe dose, a tolerance is safe. Further, there is no merit to NRDC's bald claim that EPA's safe dose determination for DDVP is arbitrary and capricious because EPA has failed to explain the basis for its safe dose determination. EPA's safe dose determination is supported and explained by extensive documentation including the IRED and numerous EPA-produced data evaluation and other analytical memoranda addressing DDVP as well as long-established and commonly-employed risk assessment principles. (See, e.g., Ref. 11).

3. *FQPA Safety Factor*—a. *NRDC's claims.* NRDC asserts that the Agency has no basis upon which to apply anything lower than a 10X FQPA safety factor in the DDVP risk assessment. According to NRDC, ''[t]he admitted potential for pre- and post-natal toxicity from exposure to DDVP, combined with incomplete data regarding toxicity and exposure to infants and children, compel EPA to retain the default FQPA tenfold safety factor for DDVP.'' (Ref. 1 at 15). As to pre- and post-natal toxicity, NRDC called particular attention to a study in the open literature (Mehl *et al* (1993), which reported brain effects in guinea pig pups. (Id. at 15-16). As to missing data, NRDC placed particular evidence on the absence of a DNT study. NRDC also criticizes EPA's choice of an additional safety factor of 3X arguing that ''[t]he Agency did not explain why it chose 3X as opposed to 4X or any other factor.'' (Id. at 14).

b. *EPA's response.* As discussed above, under the FQPA, EPA presumptively applies an additional tenfold margin of safety (i.e., safety factor) when assessing the risk of pesticide exposure to 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. FQPA, however, authorizes the Agency to use a different margin of safety for pesticide residues if, on the basis of reliable data, such a margin will be safe for infants and children. When EPA issued its preliminary risk assessment for DDVP, it employed an FQPA safety factor of 3X because the Agency lacked an acceptable DNT study as well as an FQPA safety factor of 3X for various residential risk assessments.

Since the preliminary risk assessment was issued for public comment in 2000, the Agency received two Developmental Neurotoxicity Test (DNT) studies. The NOAEL/LOAEL for the two combined DNT studies is 1.0/7.5 mg/kg/day based on increased auditory startle amplitude in male offspring in both studies. The NOAEL is much higher than the points of departure used for regulation of dichlorvos: 0.05 mg/kg/day from a dog study used to assess long-term effects, and 0.1 mg/kg/day from a human study used for short- and intermediate-term scenarios. Now that the DNT studies have been submitted, EPA believes it has reliable data showing it is safe for infants and children to remove the additional safety factor for all risk assessments other than the residential assessments. This conclusion is based on:

(1) The toxicity database is complete.

(2) There are no residual concerns for pre- and/or postnatal toxicity resulting from exposure to dichlorvos. There was no evidence for increased susceptibility of the rat and rabbit offspring to prenatal or postnatal exposure to dichlorvos. In both rat and rabbit developmental studies, no developmental effects were observed. In the reproduction study, the parental/systemic NOAEL/LOAEL was 2.3/8.3 mg/kg/day which was identical to the reproductive/offspring NOAEL/LOAEL. The DNT showed evidence of susceptibility in one parameter, auditory startle amplitude. However, there are no residual concerns for susceptibility from this because the affects in pups were seen at a dose well above the points of departure upon which EPA is regulating and a clear NOAEL for the effect (again, well above the points of departure) was identified. In addition, using a Benchmark Dose Methods (BMD) analysis of studies with pup and adult cholinesterase depression results did not demonstrate any substantial numerical differences in BMDL values for either RBC or brain cholinesterase between young and adult animals.

(3) Although the exposure estimate for DDVP in food is highly refined as to some commodities, EPA is confident that its DDVP exposure estimate from food, if anything overstates DDVP exposure, given the many conservatisms retained in the exposure assessment and DDVP's documented volatility and rapid degradation. Additionally, the very conservative estimate on DDVP exposure through drinking water based on the use of trichlorfon on turf and naled on brassica is likely to significantly overstate DDVP exposure. Finally, EPA believes its residential exposure estimates will also not underestimate exposure given the conservative assumptions used in the

assessment and in EPA's residential exposure models and the data on residential exposure.

With respect to the Mehl study, NRDC has mischaracterized the issue. Although the Mehl study raised an initial concern for potential developmental neurotoxicity, this concern was resolved by the subsequent DNT studies.

EPA has retained a FQPA safety factor of 3X for various residential risk assessments. This additional safety factor is due to these assessments' reliance on a LOAEL rather than a NOAEL. EPA chose a safety factor other than 10X based on its evaluation of the study in question. EPA determined that 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. The HSRB confirmed EPA's interpretation of this study in its review of the scientific merit of the study. Specifically, the HSRB concluded that ''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. 31 at 41).

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. (Ref. 82). 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.

Without in any way implying that there is anything improper with agency decisionmakers making a FQPA safety factor determination, NRDC's comments about who made the decision on the FQPA safety factor for DDVP can be dismissed because NRDC is referring a prior decision on the FQPA safety factor pre-dating the submission of the DNT.

E. Conclusion

NRDC's petition to revoke all DDVP tolerances is denied. NRDC's arguments have not convinced EPA that the DDVP tolerances are unsafe; to the contrary, EPA finds that its risk assessments show that the DDVP tolerances pose a reasonable certainty of no harm. EPA specifically rejects NRDC's claims that (1) EPA has mischaracterized the hazard posed by DDVP; (2) dietary and residential exposure to DDVP pose a risk of concern; and (3) EPA failed to justify removal of the additional 10X safety factor for the protection of infants and children.

VIII. Regulatory Assessment Requirements

As indicated previously, this action announces the Agency's order denying a petition filed, in part, under section 408(d) 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.

IX. 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).

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List of Subjects

Environmental protection, pesticides and pest.

Dated: November 16, 2007

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[FR Doc. E7–23571 Filed 12–4–07; 8:45 a.m.]

BILLING CODE 6560–50–S