ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPPT–2004–0109; FRL–8146–3]

Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food, Drug, and Cosmetic Act; Extension of Comment Period

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice; extension of comment period.

SUMMARY: EPA issued a notice in the **Federal Register** of June 18, 2007, concerning the draft list of the first group of chemicals that will be screened in the Agency's Endocrine Disruptor Screening Program (EDSP). The draft list was produced using the approach described in the September 2005 notice, and includes chemicals that the Agency, in its discretion, has decided should be tested first, based upon exposure potential. This document is extending the comment period for 60 days, from September 17, 2007, to November 16, 2007.

DATES: Comments, identified by docket identification (ID) number EPA–HQ–OPPT–2004–0109 must be received on or before November 16, 2007.

ADDRESSES: Follow the detailed instructions as provided under **ADDRESSES** in the **Federal Register** document of June 18, 2007.

FOR FURTHER INFORMATION CONTACT: Linda Phillips, Office of Science Coordination and Policy (7203M), Office of Prevention, Pesticides, and Toxic Substances, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (202) 564–1264; e-mail address: *Phillips.linda@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

The Agency included in the June 18, 2007 notice a list of those who may be potentially affected by this action. If you have questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. What Should I Consider as I Prepare My Comments for EPA?

When preparing comments follow the procedures and suggestions given in Unit I.B. of the **SUPPLEMENTARY INFORMATION** of the June 18, 2007 **Federal Register** notice.

C. How and to Whom Do I Submit Comments?

To submit comments, or access the public docket, please follow the detailed instructions as provided in Unit I.B.3. of the **SUPPLEMENTARY INFORMATION** of the June 18, 2007 **Federal Register** notice. If you have questions, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

II. What Action Is EPA Taking?

This document extends the public comment period established in the **Federal Register** of June 18, 2007 (72 FR 33486) (FRL–8129–3). In that document, EPA announced the draft list of the first group of chemicals that will be screened in the Agency's EDSP. The draft list was developed using the approach described in the **Federal Register** notice of September 27, 2005 (70 FR 56449) (FRL–7716–9). As required by the Federal Food, Drug, and Cosmetic Act (FFDCA), all pesticides must eventually be screened under the EDSP, and this first group is simply a starting point. Because EPA developed this draft list of chemicals based upon exposure potential, it should not be construed as a list of known or likely endocrine disruptors, and it would be inappropriate to do so. Following consideration of comments on this draft list of chemicals, EPA will issue a second **Federal Register** notice containing the final list of chemicals. EPA is hereby extending the comment period, which was set to end on September 17, 2007, to November 16, 2007.

III. What Is the Agency's Authority for Taking this Action?

Section 408(p) of FFDCA requires EPA to ''develop a screening program, using appropriate validated test systems and other scientifically relevant information, 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 [EPA] may designate.'' (21 U.S.C. 346a(p)). The statute generally requires EPA to ''provide for the testing of all pesticide chemicals.'' (21 U.S.C. 346a(p)(3)). However, EPA is authorized to exempt a chemical, by order upon a determination that ''the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen.'' (21 U.S.C. 346a(p)(4)). ''Pesticide chemical'' is defined as ''any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act, including all active and inert ingredients of such pesticide.'' (21 U.S.C. 321(q)(1)).

List of Subjects

Environmental protection, Chemicals, Endocrine Disruptors, Pesticides

Dated: September 4, 2007.

James B. Gulliford,

Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances.

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ENVIRONMENTAL PROTECTION AGENCY

[OPP-2004–0292; FRL–8144–4]

Pyraclostrobin; Order Denying Objections to Issuance of Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: The Natural Resource Defense Council (''NRDC'') filed objections with EPA to a final rule under section 408 of the Federal Food, Drug, and Cosmetic Act (''FFDCA''), (21 U.S.C. 346a), establishing tolerances for the pesticide pyraclostrobin on various food commodities. NRDC argues that EPA has unlawfully removed the additional safety factor for the protection of infants and children required by Food Quality Protection Act of 1996. This order denies the objections for the reasons stated herein.

FOR FURTHER INFORMATION CONTACT: Tony Kish, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 308-9443; e-mail address: *kish.tony@epa.gov.*

SUPPLEMENTARY INFORMATION:

Response to NRDC Objections

Table of Contents

I. General Information

A. Does This Action Apply to Me?

In this document EPA denies objections to a tolerance actions filed by the Natural Resources Defense Council (''NRDC''). This action may also be of interest to agricultural producers, food manufacturers, or other pesticide manufacturers. Potentially affected categories and entities may include, but are not limited to:

- Crop Production (NAICS code 111).
- Animal Production (NAICS code 112).
- Food Manufacturing (NAICS code 311).
- Pesticide Manufacturing (NAICS code 32532).

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities who may be interested in today's action.

B. How Can I Get Additional Information, Including Copies of this Document and Other Related Documents?

An electronic copy of this **Federal Register** document and all other documents included in the rulemaking docket for this action may be accessed through the EPA's electronic docket. EPA has established a docket for this action under docket identification (ID) number EPA-HQ-OPP-2004-0292. 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 web site to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic docket at *http://www.regulations.gov,or*, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Building), 2777 S. Crystal Drive, Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket telephone number is (703) 305–5805.You may also access this **Federal Register** document electronically through the EPA Internet under the **Federal Register**'' listings at *http://www.epa.gov/fedrgstr.*

II. Introduction

A. What Action Is the Agency Taking?

On June 5, 2006, the Natural Resource Defense Council (''NRDC'') filed objections with EPA to a final rule under section 408 of the Federal Food, Drug, and Cosmetic Act (''FFDCA''), (21 U.S.C. 346a), establishing tolerances for the pesticide pyraclostrobin on various food commodities. (Ref. 1). NRDC makes two main claims in its objections: (1) that EPA has unlawfully removed the additional safety factor for the protection of infants and children; and (2) that EPA's decision to promulgate the tolerances was arbitrary and capricious because EPA made its decision in the absence of data that EPA had determined were necessary to evaluate pyraclostrobin's safety. NRDC did not exercise the option provided in section 408(g)(2) to request a hearing on its objections. This Order responds to those objections.

EPA published notice of the objections in the **Federal Register**, (71 FR 41015 (July 19, 2006)), and held a 60–day public comment period.

The body of this document contains the following sections. First, there is a background section which explains the applicable statutory and regulatory provisions, EPA risk assessment practices, and the relevant EPA science policy documents. Second, EPA describes the objected-to tolerance action. Third, there is a section setting forth in greater detail the substance of the objections. Fourth, a summary of the public comment is presented. Finally, EPA's announces its response to the objections.

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

The procedure for filing objections to tolerance actions and EPA's authority for acting on such objections is contained in section 408(g) of the FFDCA and regulations at 40 CFR Part 178. (21 U.S.C. 346a(g)).

III. Statutory and Regulatory Background

A. Statutory Background

EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food under section 408 of the FFDCA. (21 U.S.C. 346a). Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is ''adulterated'' under section 402 of the FFDCA and may not be legally moved in interstate commerce. (21 U.S.C. 331, 342). Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration (''FDA'') and the U. S. Department of Agriculture (''USDA'').

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 directs EPA, in making a safety determination, to ''consider, among other relevant factors– . . . .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.'' (21 U.S.C. 346a(b)(2)(D)(vi)). Other provisions address in greater detail exposure considerations involving ''anticipated and actual residue levels'' and ''percent of crop actually treated.'' (See 21 U.S.C. 346a(b)(2)(E) and (F)). Section 408(b)(2)(C) requires EPA to give special consideration to risks posed to infants and children. This provision directs that ''an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.'' (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 notice as the ''children's safety factor.''] These provisions establishing the detailed safety standard for pesticides were added to section 408 by the Food Quality Protection Act of 1996 (''FQPA''), an act that substantially rewrote this section of the statute.

Tolerances are established by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, the rulemaking is initiated by the party seeking the 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 along with a summary of the petition, prepared by the petitioner. (21 U.S.C. 346a(d)(3)). After reviewing the petition, and any comments received on it, EPA may issue a final rule establishing the tolerance, issue a proposed rule, or deny the petition. (21 U.S.C. 346a(d)(4)). Once EPA takes final action on the petition by either establishing 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)). Objections must state with ''particularity'' their basis. (40 C.F.R. 178.25(a)(2)). EPA's final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

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)).

B. Setting Tolerances Under the FFDCA

1. *In general.* The process EPA follows in setting 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 ''safe'' and requirements concerning risk assessment. Only on completion of the second step can EPA make a decision on whether a tolerance may be established. Below, EPA explains in detail, the reasons for this approach.

2. *Choosing a tolerance value.* In the first step of the tolerance setting 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. (Ref. 3 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 The Pesticide Coordination Policy; Response to Petitions, (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. To prevent such an outcome, crop field trials require application of the pesticide in the manner most likely to produce maximum residues. 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

overtolerance 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 a pesticide's potential hazards (e.g., liver effects, carcinogenicity), 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 EPA identifies a hazard for a durational scenario, 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 appropriately protective dose from the relevant studies (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, taking into account the route and duration of exposure, as a starting point in estimating the level of concern for humans for a given exposure scenario (e.g., acute oral exposure). This selected NOAEL is usually referred to as the Point of Departure. In estimating and describing the level of concern, however, the Point of Departure is at times manipulated differently depending on whether the risk assessment addresses dietary or non-dietary exposures. (Refs. 2 at 3–8; 5 at 8, 52–52; and 6).

For dietary risks, EPA uses the Point of Departure to calculate a safe dose or RfD. The RfD is calculated by dividing the Point of Departure by 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. Further, to account for deficiencies in the database or the results seen in the database, EPA has traditionally applied additional safety factors on a case-by-case basis. The FQPA amendments to FFDCA section 408 require an additional safety factor of 10X to protect infants and children (to address data completeness and pre- and post-natal toxicity concerns), 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 children's safety factor that does not correspond to one of the traditional additional safety factors used in general Agency risk assessment. (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/PAD 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. To calculate the MOE for a pesticide for a given exposure scenario, the expected human exposure to the pesticide is divided into the dose identified as the Point of Departure. 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, a 10X factor for intraspecies differences, and a 10X FQPA children's safety factor, the safe or target MOE would be a value of at least 1,000. In contrast to the RfD/PAD approach, the higher the MOE, the safer the pesticide. Accordingly, if the target MOE 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 a 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. 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 exceed the range of 1 in 1 million. Because NRDC's petition concerns the children's safety factor and

the children's safety factor is only applicable to threshold risks, no further discussion of non-threshold risk assessment is included here.

b. *Estimating human exposure*. Equally important to the risk assessment process as identifying hazards and 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)). There are two critical variables in estimating exposure in food: (1) The types and amount of food that is consumed; and (2) the residue levels in those foods. 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 levels comes from a range of sources including crop field trials, data on pesticide reduction due to processing 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 an initial, screening-level exposure assessment using the worst case assumptions that 100 percent of the crop in question is treated with the pesticide and 100 percent of the food from that crop contains pesticide residues at the tolerance level. (Id. at 11). When such an assessment shows no risks of concern, EPA's resources are conserved because a more complex risk assessment is avoided 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. (71 FR 43906, 43909–43910 (August 2, 2006)).

In estimating pesticide exposure levels in drinking water, EPA most frequently uses mathematical water exposure models rather than pesticide-specific monitoring data. (69 FR 30042, 30058 (May 26, 2004). EPA's models are based on extensive monitoring data and detailed information on soil properties, crop characteristics, and weather patterns. These models calculate estimated environmental concentrations of pesticides using laboratory data that describe how quickly the pesticide breaks down to other chemicals and how it moves in the environment (i.e., does it bind to the soil or is it highly water soluble). Although computer modeling provides an indirect estimate of pesticide concentrations, 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. Whether EPA assesses pesticide exposure in drinking water through monitoring data or modeling, EPA uses the higher of the two values from surface and ground water in assessing overall exposure to the pesticide. In most cases, pesticide residues in surface water are significantly higher than in ground water.

Generally, in assessing residential exposure to pesticides, EPA relies on its Residential Standard Operating Procedures (''SOPs'')(Ref. 7). The SOPs establish models for estimating application and post-application exposures in a residential setting where pesticide-specific monitoring data is 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. Children's Safety Factor Policy

As part of implementation of the major changes to FFDCA section 408 included in the FQPA, EPA has issued a number of policy guidance documents addressing critical science issues. On January 31, 2002, EPA released its science policy guidance on the children's safety factor. (Ref. 5) [This policy is hereinafter referred to as the ''Children's Safety Factor Policy'']. The Children's Safety Factor Policy emphasizes throughout that EPA interprets the children's safety factor provision as establishing a presumption in favor of application of an additional 10X safety factor for the protection of infants and children. (Id. at 4, 11, 47, A-6). Further, the policy notes that the children's safety factor provision permits a different safety factor to be substituted for this default 10X factor only if reliable data are available to show that the different factor will protect the safety of infants and children. (Id.). Given the wealth of data available on pesticides, however, the policy indicates a preference for making an individualized determination of a protective safety factor if possible. (Id. at 11). The policy states that use of the default factor could under- or over-protect infants and children due to the wide variety of issues addressed by the children's safety factor. (Id.). Further, the policy notes that ''[i]ndividual assessments may result in the use of additional factors greater or less than, or equal to 10X, or no additional factor at all.'' (Id.).

In making pesticide-specific assessments regarding the magnitude of the children's safety factor, the policy stresses the importance of focusing on the statutory language that ties the children's safety factor to concerns regarding potential pre- and post-natal toxicity and the completeness of the toxicity and exposure databases. (Id. at 11–12). As to the completeness of the toxicity database, the policy recommends use of a weight-of-the-evidence approach which considers not only the presence or absence of data generally required under EPA regulations and guidelines but also the availability of ''any other data needed to evaluate potential risks to children.'' (Id. at 20). The policy indicates that the principal inquiry concerning missing data should center on whether the missing data would significantly affect calculation of a safe exposure level. (Id. at 22; accord 67 FR 60950, 60955 (September 27, 2002) (finding no additional safety factor necessary for triticonazole despite lack of developmental neurotoxicity (''DNT'') study because the ''DNT [study] is unlikely to affect the manner in which triticonazole is regulated.'')). When the missing data are data above and beyond general regulatory requirements, the policy states that the weight of evidence would generally only support the need for an additional safety factor where the data ''is being required for 'cause,' that is, if a significant concern is raised

based upon a review of existing information, not simply because a data requirement has been levied to expand OPP's general knowledge.'' (Ref. 5 at 23).

As to potential pre- and post-natal toxicity, the Children's Safety Factor Policy lists a variety of factors that should be considered in evaluating the degree of concern regarding any identified pre- or post-natal toxicity. (Id. at 27–31). As with the completeness of the toxicity database, the policy emphasizes that the analysis should focus on whether any identified pre- or post-natal toxicity raises uncertainty as to whether the RfD/PAD is protective of infants and children. (Id. at 31). Once again, the presence of pre- or post-natal toxicity, by itself, is not regarded as determinative as to the children's safety factor. Rather, the policy stresses the importance of evaluating all of the data under a weight of evidence approach focusing on the safety of infants and children. (Id.).

In evaluating the completeness of the exposure database, the policy explains that a weight-of-the-evidence approach should be used to determine the confidence level EPA has as to whether the exposure assessment ''is either highly accurate or based upon sufficiently conservative input that it does not underestimate those exposures that are critical for assessing the risks to infants and children.'' (Id. at 32). EPA describes why its methods for calculating exposure through various routes and aggregating exposure over those routes generally produce conservative exposure estimates – i.e. health-protective estimates due to overestimation of exposure. (Id. at 40–43). Nonetheless, EPA emphasizes the importance of verifying that the tendency for its methods to overestimate exposure in fact were adequately protective in each individual assessment. (Id. at 44).

IV. The Challenged Tolerance Decision

On April 5, 2006, EPA promulgated a final rule establishing tolerances for the fungicide pyraclostrobin on shelled succulent beans; foliage in the legume crop group; mangoes; and papayas. (71 FR 17014 (April 5, 2006)). Pyraclostrobin is a synthetic analog of a natural antifungal substance which inhibits spore germination, mycelial growth, and sporulation of the fungus on the leaf surface. (Ref. 8 at 4). The tolerances were requested in petitions from the pyraclostrobin registrant, BASF Corporation, and the Interregional Research Project Number 4 (''IR-4''). The IR-4 is a program sponsored by the U.S. Department of Agriculture and land grant universities and directed toward obtaining regulatory approval for pesticide uses on minor and speciality food crops that are not likely to be supported by private sector companies. EPA evaluated the petitions in a joint effort with the Pest Management Regulatory Agency of Canada.

Given pyraclostrobin's exposure pattern and toxicological characteristics, EPA determined that pyraclostrobin potentially presented acute, chronic, short-term, and cancer risks and EPA quantitatively assessed these risks in making its safety determination. (71 FR at 17018–17019; 69 FR 63083, 93093–63095 (October 29, 2004); Ref. 8 at 31–32). All of these risks were found to be below the Agency's level of concern. (Id.). EPA concluded that there were reliable data supporting its determination that the additional children's safety factor was not needed to protect the safety of children. In making this determination EPA considered the completeness of the toxicity and exposure database and data bearing on pre- and post-natal toxicity. (71 FR at 17018; 69 FR 63092–63093). EPA found that there was adequate toxicity and exposure data. Although there was some evidence of qualitative and quantitative increased sensitivity in the young from the developmental study in rabbits and reproduction study in rats, respectively, EPA concluded using a weight-of-the-evidence test that residual concerns for increased sensitivity in the young were low. (69 FR at 63093); (Ref. 9 at 8).

V. NRDC Objections

In its objections, NRDC cites various allegedly inadequate studies and pre-natal toxic effects of pyraclostrobin as grounds for claiming it was unlawful for EPA to remove the children's safety factor and EPA's overall decision was arbitrary and capricious.

A. Children's Safety Factor

NRDC argues that EPA should have retained the children's safety factor for two separate reasons: (1) pyraclostrobin demonstrated pre-natal toxicity; and (2) there were inadequacies in the submitted toxicity data on pyraclostrobin and additional toxicity and exposure data are needed. NRDC claims that EPA's decision to remove the children's safety factor violates the FFDCA; however, NRDC does not allege that retention of the children's safety factor would result in the pyraclostrobin tolerances exceeding the FFDCA section 408 safety standard. NRDC expanded on its objections in comments it submitted on its own objections. These comments principally argued that EPA had wrongly interpreted the children's safety factor provision. (Ref. 10).

1. *Legal requirements for imposing the children's safety factor and the standard for choosing a different safety factor.* NRDC describes the children's safety factor provision as requiring that the additional children's safety factor ''shall be applied'' to ''take into account'' (1) ''potential pre- and post-natal toxicity;'' (2) ''completeness'' of toxicity data; and (3) ''completeness'' of the exposure data. With regard to the reference to pre- and post-natal toxicity, NRDC argues that this statutory language ''mandates application of the safety factor to account for any potential for pre- or post-natal toxicity.'' (Ref. 10 at 2). As to completeness of the data, NRDC takes a similarly rigid position: ''Where studies identified by EPA as necessary to ensure safety have never been conducted or reviewed – or have been determined to be inadequate – EPA by definition cannot find that there is a 'reasonable certainty' that 'no harm will result' to children, as required by law[,]'' and therefore, cannot modify the children's safety factor. (Id.).

NRDC acknowledges that EPA may apply a factor different than presumptive tenfold children's safety factor but stresses that a different factor may be applied only if there is reliable data showing the different factor is safe. EPA, NRDC claims, has applied a different standard in the pyraclostrobin tolerance decision – requiring that there be merely adequate data on pyraclostrobin toxicity and exposure and that there be no substantial evidence of increased sensitivity of infants and children to the pesticide. (Id.).

2. *Pre-natal sensitivity.* In discussing evidence on pre-natal sensitivity, NRDC references both the developmental studies in rats and in rabbits. NRDC asserts that the developmental rat study shows qualitative increased sensitivity in the rat fetuses because the effects in the rat fetuses (dilated renal pelvis and cervical ribs with no cartilage) were more severe than the effects in adults (reduced body weight, body weight gain, food intake, and food efficiency). (Ref. 1 at 7). Qualitative increased sensitivity is seen in the rabbit developmental study, according to NRDC, again because the effects in the fetuses were more severe than the effects in the adults (increased resorption and post-implantation loss versus reduced body weight, body weight gain, food intake, and food efficiency). (Id.). NRDC argues that EPA erred by looking beyond the question of whether the animal studies show fetuses to be qualitatively more sensitive than

maternal animals to examine whether it was safe to remove or reduce the factor despite a finding of qualitative increased sensitivity. According to NRDC, because the studies show qualitative increased sensitivity in prenatal animals as compared to adult animals, ''EPA must retain the full tenfold safety factor . . . .'' (Id. at 5).

3. *Inadequate and missing data*—a. *Immunotoxicity data*. NRDC argues that, because EPA has not required immunotoxicity data on pyraclostrobin, EPA cannot explain the differential immunotoxic results between males and females in the pyraclostrobin studies. Due to this lack of understanding, NRDC claims that immunotoxicity ''should be considered a serious potential risk of pyraclostrobin . . . [and] EPA must retain the full tenfold safety factor as a result.'' (Id. at 6–7). NRDC cites four studies in support of this argument. First, it references a 90–day oral toxicity mouse study in which females allegedly showed immunotoxic effects at a dose at which males only showed more generalized toxicity (e.g., reduced body weight). Second, NRDC points to a 90–day oral toxicity study in dogs in which NRDC claims females suffered body weight loss, reduced food intake, and reduced food efficiency in addition to the gastrointestinal effects that occurred in both sexes. Third, NRDC cites two neurotoxicity studies in which males were shown to be significantly more sensitive than females. NRDC claims that these studies demonstrate that males and females respond differently to pyraclostrobin and that EPA should be particularly concerned about the immunotoxic effects in females because there is ''substantial data demonstrating that females are more likely than males to develop autoimmune diseases in response to environmental stressors.'' (Id. at 6).

b. *Two-generation reproduction study*. NRDC asserts that the two-generation rat reproduction study with pyraclostrobin relied upon by EPA is ''invalid'' and that EPA cannot rehabilitate it by combining it with a one-generation rat reproduction study because that study produced results which contradict the two-generation study. (Id. at 7–8). The two-generation study is invalid, according to NRDC, because it showed no adverse effects at any of the doses tested. NRDC states that such a study ''must be considered invalid because it is unknown whether the study failed to find an effect because there really was no effect, or if it was due to a lack of statistical power, poor study design, or an endless number of potential fatal weaknesses (e.g., the test agent could have degraded through poor storage conditions; the endpoint measurements could have been reported in error; treated and control animals could have been mis-categorized, etc.).'' (Id. at 8). NRDC argues that the one-generation study contradicts the two-generation study because the former identified adverse effects at a dose lower than a dose in the two-generation study that showed no effects. NRDC concludes that ''EPA must retain the full tenfold safety factor in light of these invalid and deficient studies.'' (Id.)

c. *Other data deficiencies*. NRDC briefly mentions several other alleged data gaps or deficiencies: (1) data on anticipated pyraclostrobin residues which EPA has required to be submitted; (2) a missing 28–day inhalation toxicity study; (3) a deficient chronic toxicity study in rats due to failure to show adverse effects; (4) a deficient mouse cancer study due to failure to show adverse effects; and (5) an unacceptable dermal penetration study due to problems in administration of the test dose. Categorizing these deficiencies as ''significant,'' NRDC argues EPA must retain the children's safety factor to address them. (Id. at 8–10).

B. Arbitrary and Capricious

NRDC also argues that the tolerance decision was arbitrary and capricious ''because EPA never received or reviewed information that the agency considered necessary to review the pesticides' safety (listed above), and because EPA failed to explain adequately its departure from the required children's safety factor.'' (Id. at 10).

VI. Public Comment

A. In General

On July 19, 2006, EPA published a notice in the **Federal Register** calling attention to and requesting comments on the NRDC Objections. (71 FR 41015 (July 19, 2006)). The notice included a short summary of the objections and referenced readers to EPA's electronic docket for a full copy of the objections. EPA received three comments on the objections. Other than NRDC's comments on its own objections, the only significant comment EPA received was from BASF Corporation, the registrant under FIFRA for pyraclostrobin.

B. BASF Corporation

BASF Corporation has registered pyraclostrobin for use as a pesticide under FIFRA and petitioned for several of the tolerances that are subject to the present objections. As to the potential for pyraclostrobin to impact differently on males and females, BASF argues in its comments that differential effects on the sexes are noted in toxicology studies and taken into account in setting the RfD. (Ref. 11). Any uncertainty regarding the sensitivities of these two groups is addressed, according to BASF, by the tenfold uncertainty factor used to account for variable sensitivities in humans. Further, BASF argues that the ''issue of differential sensitivity between sexes is not relevant for evaluating the need to apply the FQPA safety factor'' because that safety factor only addresses potential differences in sensitivities between adults and children. (Id. at 1).

BASF challenges NRDC's assertion that qualitative sensitivity was demonstrated in the rat and rabbit developmental studies. BASF claims that the fetal effects seen in the rat study (dilated renal pelvis and cervical ribs with no cartilage) were not due to treatment. This is evidenced, according to BASF, by the fact that the incidence of these effects was within the historical control range for the experimental animal. As to the effects on rabbit fetuses (increased resorption and post-implantation loss), BASF argues these effects are a result of the severe effects that pyraclostrobin had on the maternal animals as opposed to any direct toxic effect on the fetuses. According to BASF, ''maternal body weight gain during the treatment period was reduced by a dramatic 77% at the high dose and 39% at the mid dose compared to controls. This substantial effect to the maternal animals would be expected to affect the dam's ability to deliver full-term fetuses and does not reflect a direct action of the test material on the fetus.'' (Id. at 2).

With regard to the two-generation reproduction study in rats, BASF contends that the results from this study are not inconsistent with the one-generation reproduction study. BASF claims that body weight changes were seen in the highest dose tested in the two-generation reproduction study. Although the body weight changes in the two-generation study were small, BASF argues that ''the effects at this dose fits along a dose-response curve with the two doses in the range-finding [one-generation] study.'' (Id. at 3).

BASF disputes NRDC's claims regarding data gaps and deficiencies. First, BASF asserts that a 28–day inhalation study has been submitted to EPA. Second, BASF contends that subsequent data submitted to EPA led EPA to conclude that the rat and mouse carcinogenicity studies were conducted at sufficiently high doses. Finally, BASF

states that a repeat dermal penetration study was conducted. (Id. at 4).

C. NRDC

In its comments, NRDC expands on its legal argument that EPA must retain the children's safety factor when data are absent. According to NRDC, when data EPA has determined are ''necessary to evaluate safety'' are not available, EPA ''by definition'' may not remove the 10X children's safety factor. (Ref. 10 at 2). NRDC also cites general statements that children can be more vulnerable than adults to pesticides and that children may have greater relative exposure to pesticides than adults and argues that this means that the children's safety factor must be retained for pyraclostrobin. (Id. at 3). Finally, NRDC listed various documents that it claims support its objections. (Id. at 4).

VII. Response to Objections

As summarized above, NRDC's objections pertain primarily to EPA's decision on the children's safety factor – in brief, NRDC's argument is that, due to evidence on pre-natal toxicity and immunotoxicity, and data deficiencies, EPA erred in removing the children's safety factor. NRDC also recasts these same allegations to claim that EPA acted arbitrarily and capriciously in promulgating the pyraclostrobin tolerances. These arguments are addressed separately below.

A. Children's Safety Factor

NRDC objects to the pyraclostrobin tolerances on the ground that it was unlawful for EPA to remove the children's safety factor. Although not stated, presumably NRDC believes that EPA should have denied the petition seeking the pyraclostrobin tolerances for this reason. A decision on the children's safety factor, however, is not outcome determinative with regard to whether a petitioned-for tolerance meets the safety standard for establishing tolerances. Retention of the children's safety standard would generally result in a tenfold lowering of the pesticide's RfD/PAD, thus decreasing by a factor of ten the amount of aggregate exposure to the pesticide that would not exceed the RfD/PAD; it would not, however, bar the establishment of the tolerance. EPA has established many tolerances for which the children's safety factor has been retained. (See, e.g., 71 FR 56369, 56372 (September 27, 2006); 70 FR 14535, 14541–14542 (March 23, 2005)). Similarly, EPA has recently denied a petition to revoke tolerances which claimed that EPA should have retained the children's safety factor where it was clear that EPA could make the reasonable certainty of no harm finding with or without retention of the additional safety factor. (72 FR 39318, 39323–39324 (July 18, 2007)). For pyraclostrobin, EPA's exposure assessment, which is partially refined, suggests that retention of the children's safety factor may raise safety concerns for the pesticide. Because it is unclear whether further refinement of the exposure assessment would render the decision on the children's safety factor irrelevant to the ultimate safety decision, EPA has chosen to address the merits of the argument presented by NRDC.

NRDC makes two different types of arguments as to why the children's safety factor should be retained. First, citing various issues regarding pre-natal toxicity and data completeness, NRDC essentially argues that the overall weight-of-evidence does not support EPA's conclusion that there is reliable data showing it will be safe for children to use a hundredfold margin of safety rather than a thousand-fold margin. Second, NRDC argues that each of the individual issues it raises ''compel'' EPA to retain the children's safety factor. This second argument is more fully made in the legal contentions presented in NRDC's comments on its objections.

In responding to NRDC's arguments, EPA first addresses the legal contention that various findings ''compel'' the retention of the children's safety factor. In this section, EPA explains why it fundamentally disagrees with NRDC's approach to the safety factor provision. Second, EPA examines the merits of the various factual allegations made by NRDC concerning pre-natal toxicity and data deficiencies. As EPA makes clear below, in most instances NRDC is mistaken in its factual allegations. Finally, EPA addresses whether the totality of the claims raised by NRDC alter EPA's conclusion regarding removal of the children's safety factor.

1. *Legal interpretation of the children's safety factor provision*. In its objections and its comments on its objections, NRDC claims that (1) EPA is legally compelled to retain the children's safety factor when there is a data gap; (2) EPA is legally compelled to retain the children's safety factor when there is evidence showing that the young are more sensitive to the effects of a pesticide or a pesticide causes pre- or post-natal toxicity; and (3) EPA has applied an incorrect standard in evaluating whether the presumptive tenfold children's safety factor may be modified. Following a summary of the statutory language on the children's safety provision, EPA explains why each of these assertions are incorrect.

a. *Children's safety factor provision*. The statutory requirements pertaining to the children's safety factor are contained in two sentences in section 408(b)(2)(C). The first sentence commands that as to ''threshold effects, for the purposes of [making the reasonable certainty of no harm finding], an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children.'' (21 U.S.C. 346a(b)(2)(C)). This sentence also explains that the purpose for this additional safety factor is ''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.'' (Id.). Switching course, the second sentence then countermands the mandatory language in the first sentence (''shall be applied'') and makes clear that EPA has the authority to deviate from the requirement to apply an additional 10X safety factor. The second sentence reads ''[n]othwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such a margin will be safe for children.'' (Id.).

b. *Operation of the children's safety factor provision*. EPA has interpreted the children's safety factor provision as containing a presumption in favor of retaining an additional tenfold safety factor for the protection of infants and children. That presumption may be overcome, however, when EPA has reliable data showing that use of a different safety factor will protect the safety of infants and children. Such a different safety factor may be lower or higher than the default 10X value. In making decisions about whether it has reliable data supporting a different safety factor, EPA has looked at the totality of the evidence bearing on the safety of infants and children and carefully weighed the strength of that evidence in determining whether a different safety factor would be safe. That was the approach followed with pyraclostrobin.

NRDC appears to interpret the children's safety factor provision quite differently. Repeatedly in its objections, NRDC argues that EPA ''must'' retain the children's safety factor due to some data deficiency or because of the identification of increased sensitivity in the young. NRDC affirms this view in its comments stating that the statute ''mandates application of the safety factor to account for any potential for pre- or post-natal toxicity'' and, that

where necessary studies are missing, ''EPA, by definition'' cannot make the safety finding needed to choose a different safety factor. Under NRDC's interpretation, the children's safety factor operates in a rigid and automatic fashion: upon identification of a data gap or of sensitivity in the young, EPA loses all discretion to choose a different safety factor.

i. *Data gaps*. EPA has previously rejected NRDC's interpretation as it applies to data gaps noting that the interpretation fails to take into account the entire children's safety factor provision. In responding to other tolerance objections filed by NRDC, EPA stated its disagreement with the view ''that the mere absence of a required [developmental neurotoxicity] study should, by itself, conclusively bar EPA from applying a different additional safety factor than the 10X default value.'' (70 FR at 46723). EPA pointed out that the statute ''expressly authorizes'' EPA to choose a different safety factor based solely on whether EPA determined that a different factor was safe and that EPA's policy of making children's safety factor decisions on a case-by-case basis examination of all of the data on a pesticide is in accord with this statutory provision. (Id.). EPA concluded that NRDC's outcome-determinative approach to data gaps and the children's safety factor simply did not address the statute's grant of discretion to EPA to choose a different safety factor.

In its comments on its objections, NRDC now offers the following argument as to why, when data on pesticide safety are lacking, EPA does not have the authority to choose a different safety factor. NRDC claims that, when needed safety data are missing, EPA, ''by definition,'' cannot make the reasonable certainty of no harm (i.e. safety) finding necessary to choose a different safety factor. NRDC's logic seems to be as follows: if EPA determines it needs additional data on safety, EPA has necessarily concluded that such data are ''necessary to ensure safety,'' and if data that are ''necessary to ensure safety'' are lacking, EPA cannot make the safety finding required to apply a different children's safety factor.

The main problem with this argument is that it ignores the plain language of the statute. As noted above, section 408(b)(2)(C) contains two sentences regarding application of an additional safety factor for the protection of infants and children. The first sentence requires EPA to apply an additional 10X safety factor to address, among other things, data completeness issues. Importantly, the data completeness issue mentioned by the statute is data bearing on toxicity and exposure – i.e., data on safety. In the very next sentence, however, the statute provides that ''notwithstanding such requirement'' to apply a safety factor to address safety data completeness issues, EPA may choose a different factor so long as that factor is safe for children. If there is any definitional reading of this language, it is that EPA has the authority to choose a different safety factor when safety data are incomplete. NRDC's interpretation would read EPA's grant of authority to choose a different factor when there are safety data completeness issues out of the statute.

In addition to ignoring the plain language of the children's safety provision, NRDC's argument also is inconsistent with the statutory structure in at least two ways. First, NRDC's interpretation renders the children's safety factor provision, itself, mere surplusage if data completeness issues arise. If, as NRDC has argued, a request for data means that the data are necessary to ensure safety, then EPA, in those circumstances, not only cannot make the safety (reasonable certainty of no harm) finding necessary to remove the children's safety factor but EPA cannot make the safety (reasonable certainty of no harm) finding necessary to grant the tolerance. In other words, under NRDC's argument, the entire children's safety provision becomes irrelevant if EPA has requested data, because that request, by itself, conclusively bars EPA from establishing the tolerance. NRDC has not explained why it is rational to assume that Congress drafted a provision addressing data completeness issues but made the provision inoperative if data completeness issues arise.

Second, NRDC's elevation of an EPA requirement for additional safety data to a determination that a tolerance is unsafe (i.e. that a safety determination cannot be made) is inconsistent with the structure of section 408 that permits EPA to require additional safety data on existing tolerances while at the same time commanding that tolerances that do not meet the safety standard be revoked. Under section 408(f), EPA is authorized to require the submission of data ''to support the continuation of a tolerance . . . .'' (21 U.S.C. 346a(f)). The sole criterion for the continuation of a tolerance is whether it continues to meet the reasonable certainty of no harm standard. (21 U.S.C. 346a(b)(2)(A)(i)). Thus, Congress contemplated that EPA could require safety data on existing tolerances. Yet, under NRDC's interpretation it is difficult to see how EPA could ever require submission of safety data on existing tolerances. NRDC has argued that if data bearing on the reasonable certainty of no harm finding are needed (which is the finding necessary to request data under section 408(f)), then the reasonable certainty of no harm finding cannot be made. Thus, if EPA were to determine that additional safety data are needed on an existing tolerance, it would also be concluding that that tolerance is unsafe. The statute, however, commands EPA to revoke unsafe tolerances, not request more safety data concerning them. (21 U.S.C. 346a(b)(a)(2)(A)(ii)). In other words, under NRDC's approach, if EPA determines that data were needed to support the continuation of a tolerance, EPA would have to revoke the tolerance rendering moot any decision to require submission of additional data to support the tolerance. Presumably, Congress would not have enacted such a self-defeating provision.

The underlying flaw in NRDC's argument is that it equates an EPA decision to seek additional safety data with the proposition that EPA has necessarily determined that a safety finding cannot be made in the absence of such data. NRDC does not take into account that there are many types of safety data and that the varying types of safety data have varying degrees of importance to the ultimate reasonable certainty of no harm finding. For example, the five core required toxicology studies would generally be of greater importance to the children safety factor determination than conditionally-required toxicology studies or special studies, for instance, to determine mechanism of toxicity. Similarly, as to pesticide exposure data, residue data on major crops will be of more significance than data on minor crops, and even for major crops the importance of the first 15 geographically-distributed residue studies will be of more value than the next five such studies. Further, not only are some studies more important or necessary to the safety determination than others, but, in the absence of a study, information from one study, or a group of studies, or the assumptions made to compensate for the missing study, may significantly diminish any uncertainty raised by the study's absence. For example, in the absence of dermal absorption data, EPA generally assumes 100 percent of a pesticide is dermally absorbed. Given all of these considerations and the range of data that can be required, it is apparent that a request for additional data is not synonymous with a determination that

a safety finding cannot be me made. Thus, it is reasonable not to adopt NRDC's absolutist approach but to evaluate on a case-by-case basis whether the safety data that are available on a pesticide show that a different safety factor is safe.

At bottom, the decision on the children's safety factor turns on whether a safety finding can be made, not on whether any particular study is available. If data are absent, EPA may still examine the existing reliable data to determine if a factor different than 10X is safe. NRDC is incorrect to the extent it argues that EPA is statutorily barred from making this inquiry.

ii. *Increased sensitivity in the young.* In the current objections, NRDC also argues that EPA ''must'' retain the children's safety factor because ''[j]uveniles are qualitatively more sensitive than adults to pyraclostrobin toxicity.'' (Ref. 1 at 7). NRDC criticizes EPA for examining whether there is ''substantial evidence'' of sensitivity. (Id. at 5). Presumably, NRDC's view is that any evidence of sensitivity automatically requires EPA to retain the children's safety factor.

This rigid interpretation of the children's safety provision, however, fails for the same reason NRDC's argument for automatic retention of the children's safety factor for data deficiencies fails – it is not in accord with the plain language of the statute. The statute does direct EPA to consider ''susceptibility of infants and children'' to pesticides. (21 U.S.C. 346a(b)(2)(C)(i)(II)). It also states that an additional safety factor to protect infants and children shall be applied ''to take into account potential pre- and post-natal toxicity . . . .'' (21 U.S.C. 346a(b)(2)(C)). Nonetheless, in clear and unmistakable language, Congress decreed that, ''[n]otwithstanding such requirement for an additional margin of safety'' to take into account potential pre- and post-natal toxicity, EPA is authorized to choose a different safety factor if EPA has reliable data showing a different factor is safe. (Id.). Interpreting the statute as creating a rigid, per se rule that the identification of sensitivity in the young removes EPA's discretion to choose a different safety factor is inconsistent with this language and the flexibility granted to the Agency. On the other hand, EPA's policy, and the approach it followed with pyraclostrobin, of examining the entire database to determine if, despite a finding of sensitivity, there are reliable data showing a different factor to be safe, is in full accord with the statutory provision.

c. *The standard for choosing a different safety factor.* Alternatively, NRDC argues that even if the statutory language does not compel EPA to retain the children's safety factor whenever there is a data gap or evidence of sensitivity in the young, EPA's interpretation of the standard for choosing a different safety factor ''frustrates congressional policy.'' (Ref. 10 at 2). NRDC asserts that the language EPA offered in summarizing its decision to remove the children's safety factor demonstrates the unlawfulness of EPA's interpretation: ''[EPA] has concluded that there are reliable data to support reducing the FQPA SF [safety factor] to 1X for all potential pyraclostrobin exposure scenarios because the toxicity and exposure databases are adequate, there are no residual uncertainties for pre- or postnatal toxicity, and there is no substantial evidence of increased sensitivity of infants and children to pyraclostrobin.'' (Id.). NRDC claims that ''requiring 'substantial evidence' of 'increased sensitivity of infants and children,' along with merely 'adequate' data regarding toxicity and exposure'' is not true to the reasonable certainty of no harm standard. (Id.).

NRDC's view here is not well-founded. Contrary to NRDC's argument, EPA does not apply the reasonable certainty of no harm standard in some sort of formalistic fashion using fixed rules that provide minimal protection to children. Rather, EPA applies the reasonable certainty of no harm standard in the children's safety factor provision, just as it does with the overall reasonable certainty of no harm provision for tolerances, using a comprehensive, weight-of-the-evidence approach that is designed to protect fully the safety of children.

EPA, as well as FDA, has applied a reasonable certainty of no harm standard in administering various provisions of the FFDCA for many years. Since its enactment in 1958, the ''safety'' standard in FFDCA section 409 has been interpreted by FDA as imposing a reasonable certainty of no harm standard. (21 C.F.R. 170.3(i)). EPA was governed by this standard in implementing section 409 as to pesticides in processed foods for the period between 1970 and 1996. In 1996, when Congress enacted the FQPA, the reasonable certainty of no harm safety standard was codified in section 408. (7 U.S.C. 346a(b)(2)(A)(ii)). In brief, EPA has applied that standard using a complex risk assessment process which involves careful weighing of scientific evidence at each step along the way. (62 FR 62961, 62962–62963 (November 26, 1997)). First, a thorough evaluation of hazard and exposure data is conducted to determine the adequacy of that data to address the potential risks posed by a pesticide and the significance of any data gaps that are identified. Hazard data are examined using a weight-of-the-evidence approach for the purpose of identifying a safe dose for humans. Derivation of a safe dose generally requires use of safety factors to address any uncertainties in knowledge. Exposure data are carefully weighed in estimating potential human exposure. Finally, human exposure estimates are compared to the safe dose to determine if there is a reason for concern. (Ref. 2; 5; and 6).

A similar, if slightly more narrowly focused, inquiry is involved in determining if there are reliable data showing that a safety factor different than the presumptive 10X factor will ensure that there is a reasonable certainty of no harm to children. (Ref. 5 at 8–18; 50–53). This inquiry examines the risks to children guided by the three factors mentioned in the statute – completeness of the toxicity database; completeness of the exposure database; and the potential for pre- and post-natal toxicity. (21 U.S.C. 346a(b)(2)(C)). In other words, EPA focuses on the completeness or adequacy of the databases regarding the hazard a pesticide poses to children and children's potential exposure to that pesticide. This completeness inquiry identifies and evaluates the significance of any data gaps. It also examines evidence bearing on pre- and post-natal toxicity with particular emphasis on whether there is evidence indicating that children may be more sensitive than adults to the toxic effects of a pesticide. (21 U.S.C. 346a(b)(2)(C)(i)(II)). As in the broader reasonable certainty of no harm evaluation, the children's safety factor determination involves an examination of uncertainties and a determination as to whether these uncertainties are addressed by adequate safety factors or other aspects of the risk assessment such as the levels that adverse effects occur in adults. Each step involves a careful weighing of the scientific evidence and a characterization of what the data show. That is precisely what was done with pyraclostrobin – examining the adequacy of the hazard and exposure data; and evaluating the evidence on pre- and post-natal toxicity, the evidence on increased sensitivity in the young, and the degree to which any pre- or post-natal toxicity was addressed by basing safety determinations on effects seen at similar or lower doses in adults. EPA did not apply any rigid tests in

determining if there was reasonable certainty of no harm supporting the removal of the additional safety factor for pyraclostrobin but rather considered all of the relevant data and weighed its significance to the safety of children. This approach is consistent with (1) the statutory language itself – reasonable certainty of no harm; (2) EPA's historic interpretation and implementation of that language; and (3) protection of infants and children.

The language from the pyraclostrobin decision cited by NRDC (adequate safety data and no substantial evidence of sensitivity) was intended as a summary of EPA's weight-of-the-evidence evaluation in making its reasonable certainty of no harm finding on the children's safety factor. Considerations of data adequacy and the substantiality of evidence on harmful effects are a routine part of the weight-of-the-evidence analysis used to make reasonable certainly of no harm determinations. Surely, Congress did not intend to remove EPA's discretion to choose a different safety factor when data on infants and children are adequate to evaluate safety and evidence of sensitivity in the young is insubstantial.

Accordingly, EPA denies NRDC's objection to the extent they rely on these flawed interpretations of the statute or a misreading of EPA's tolerance decision.

2. *Individual factual findings bearing on the children's safety factor*—a. *Pre-natal sensitivity*. As indicated above, NRDC relies on evidence of qualitative pre-natal sensitivity (i.e., effects more severe in the young as compared to adults) as grounds for retaining the children's safety factor for pyraclostrobin. NRDC's objections appear to argue that the mere indication of increased qualitative sensitivity requires EPA, as a legal matter, to retain the children's safety factor. That legal interpretation is without merit as explained above. NRDC may, however, have been asserting that the evidence bearing on pre-natal sensitivity for pyraclostrobin is so significant to the evaluation of the safety of pyraclostrobin that EPA erred in concluding that there was reliable data to determine that removing the children's safety factor would be protective of the safety of children.

NRDC claims two pyraclostrobin studies show that pyraclostrobin causes increased qualitative pre-natal sensitivity: the developmental study in rats and the developmental study in rabbits. The developmental study in rats found that pre-natally exposed fetuses had adverse effects at 50 milligrams/kilogram of body weight/day (mg/kg/day) and that the maternal animals had adverse effects at the lower dose of 25 mg/kg/day. The NOAELS in fetuses and maternal animals respectively were 25 mg/kg/day and 10 mg/kg/day. (Refs. 9 at 4; and 12). NRDC contends that the study showed qualitative pre-natal sensitivity because the effects in the fetuses (incidences of dilated renal pelvis and cervical ribs with no cartilage) were more severe than the effects in the maternal animals (reduced body weight, reduced body weight gain, food intake, and food efficiency). The developmental study in rabbits showed adverse effects in fetuses and the maternal animals at the same level (LOAEL – 10 mg/kg/day; NOAEL – 5 mg/kg/day). (Refs. 9 at 5–6; and 13). NRDC asserts that effects in the fetuses (increased resorption and post-implantation loss) however, are more severe than in the maternal animals. (Ref. 1 at 7).

BASF in its comments disputes NRDC's claims of qualitative sensitivity. First, BASF claims that effects seen in the rat fetuses were not caused by exposure to pyraclostrobin. To support this assertion BASF argues that adverse effects were within the level to be expected based on historical information on this species of rat. Second, BASF claims that the rabbit developmental study does not evidence qualitative sensitivity because the effects in the fetuses were derivative of the effects on the maternal animals. Noting that decreased weight gain in the maternal animals was dramatic (39% at the LOAEL and 77% and the next higher dose), BASF argues that it is to be expected that ''the dam's ability to deliver full-term fetuses [would be affected] and does not reflect a direct action of the test material on the fetus.'' (Ref. 11 at 2).

In the pyraclostrobin rulemaking, EPA characterized the effects in the rabbit, but not the rat, study as evidencing qualitative sensitivity in the young. EPA further determined that there was a low degree of concern as to the sensitivity seen in the rabbit study because the effects in the rabbit fetuses occurred at the same dose that adverse effects occurred in the maternal animals and a clear NOAEL for the effects seen in the fetuses was identified and taken into account in assessing potential risk to humans. In light of NRDC's objections and BASF's comments, however, EPA has re-examined its earlier conclusions both as to the presence or absence of qualitative sensitivity in the rat and rabbit fetuses and the degree of concern raised by the studies regarding the protection of infants and children.

i. *Rat developmental study*. To recap, in the rat developmental study, pyraclostrobin exposure resulted in dilated renal pelvis and cervical ribs with no cartilage in the rat fetuses at 50 mg/kg/day (with a NOAEL of 25 mg/kg/day) and reduced body weight in the maternal animals at the lower dose of 25 mg/kg/day (with a NOAEL of 10 mg/kg/day). EPA does not believe that these findings support retention of the children's safety factor for four reasons.

First, there is substantial evidence indicating that the effects seen at the high dose in the fetuses (dilated renal pelvis and cervical ribs with no cartilage present) were not treatment-related. These effects occur with some frequency in rats. Historical data from the lab conducting the study showed that, for rat controls in other studies, dilated renal pelvis was seen in between 8.8 and 28.8 percent of rat fetuses, and cervical ribs with no cartilage present was seen in between 0.5 and 6.6 percent of rat fetuses. (Ref. 14 at 2–3). In the pyraclostrobin rat study, dilated renal pelvis was detected in 18.8 percent of the fetuses and cervical ribs with no cartilage present was found in 5.1 percent. (Id.). Because these effects appeared at a rate consistent with those seen in control groups, this study outcome carries little weight.

Second, the effects in fetuses are not more severe than the reduced body weight seen in maternal animals. Dilated renal pelvis and cervical ribs with no cartilage present are relatively common effects in rat fetuses and are regarded as reversible developmental variations in that they often disappear as the animal matures. Dilated renal pelvis involves an enlargement of the portion of the kidney referred to as the pelvis. The renal pelvis is a funnel-shaped region that collects urine before it is discharged through the ureter. When the renal pelvis becomes dilated or enlarged there may be difficulties in discharging urine. As the historical control data cited above shows, this is a fairly common event in rats. The enlargement is related to rapid renal growth late in the gestation period and it generally is resolved following birth so long as no other abnormalities are present in the kidney. (Ref. 15). A cervical rib without cartilage is a supernumerary (or extra) rib that commonly disappears after birth as ossification of the bone is unlikely to occur in the absence of cartilage. Because these effects are generally reversible post-natally, were seen with pyraclostrobin at the high dose only, and were within the range of historical controls, it was reasonable for EPA not to treat them as a severe effect. On the

other hand, reduced body weight, while not one of the more severe effects seen in animal studies, is nonetheless a sign of generalized toxicity that merits concern. Thus, the effects in the fetuses are not properly characterized as more severe than the effects in maternal animals.

Third, reduced body weight in the maternal animals was found at a lower dose than the dose which resulted in dilated renal pelvis and cervical ribs with no cartilage present in the fetuses. Thus, on a quantitative basis, adult animals proved more sensitive than the fetuses.

Fourth, and probably most important, a clear NOAEL was identified for the effects seen in the fetuses. That NOAEL was taken into consideration in setting the RfD/PAD for pyraclostrobin as EPA examined all of the NOAELs from relevant studies to identify the lowest NOAEL. Accordingly, the RfD/PAD for pyraclostrobin was set at least 100–fold (10X for inter-species sensitivity and 10X for intra-species variability) below the safe level (NOAEL) for rat fetuses in the rat developmental study. In fact, as to the NOAEL for the fetal effects seen in the rat developmental study, there was a greater than 100–fold margin because the NOAEL in the rat developmental study for maternal animals was lower than the fetal NOAEL, and a still lower NOAEL from another study was used to set the RfD/PAD. (Ref. 8 at 12–13).

Accordingly, after re-evaluating the rat developmental study, EPA concludes that (1) the study does not show increased qualitative sensitivity in rat fetuses; and (2) given the results of the study and the manner in which those results were incorporated into EPA's risk assessment for infants and children, there is reliable data to show, with regard to developmental effects in rats, that it is safe to remove the children's safety factor.

ii. *Rabbit developmental study*. As noted above, the findings in the rabbit developmental study were that, at the same dose level, pyraclostrobin caused reduced body weight and reduced body weight gain in maternal animals, and increased resorption of fetuses. EPA concluded that, because fetal resorptions were more serious than body weight effects, this study shows increased qualitative sensitivity in rabbit fetuses; however, EPA concluded that the traditional safety factors provide sufficient protection for infants and children. (Ref. 9 at 7). NRDC argues that because the study shows qualitative sensitivity the children's safety factor must be retained. Taking a different tack, BASF does not contend that fetal resorptions are not more serious than body weight effects but instead claims that the resorptions are derivative of the effects on the maternal animals and thus not evidence of qualitative sensitivity.

EPA disagrees with BASF that the fetal resorptions are derivative of the body weight effects. To the extent either effect is derivative of the other, it is the decreased body weights in maternal animals that is the result of the fetal resorptions, not the other way around. Body weight decreases in the maternal animals were due, in large part, to decreases in the weight of the gravid uterus (a uterus containing a fetus or fetuses). In turn, weight loss in the gravid uterus was a result of the fetal resorptions. (Ref. 14 at 7). In light of this finding, as well as the other evidence of gestational effects (e.g. blood in the bedding), EPA concludes there is insufficient evidence to classify the resorptions as a derivative effect.

EPA, however, also disagrees with NRDC regarding the significance of the finding of qualitative sensitivity based on fetal resorptions and reaffirms its conclusion that there is low concern that traditional safety factors are not protective of the fetal effects seen in the rabbit developmental study. Not only were the fetal effects seen at the same quantitative levels as the maternal effects but clear NOAELs were identified for both the fetal and maternal effects in that study. These NOAELs (which were identical) formed the basis for the RfD/PAD for pyraclostrobin. Specifically, EPA used the NOAELs in establishing the RfD/PAD by dividing the NOAELs by 10X safety factors for inter- and intra-species variability (total of 100X). Having clearly defined the threshold for the qualitatively more sensitive effects in the young, and applied a 100X safety factor to the NOAEL below the threshold, EPA concludes it is safe for infants and children not to retain an additional 10X factor.

b. *Immunotoxicity* . NRDC claims various studies show that males and females have different levels of sensitivity to pyraclostrobin. According to NRDC, some of the studies indicated males were more sensitive and others indicated females were more sensitive. NRDC calls particular attention to alleged heightened female sensitivity to immunotoxic effects in the 90–day oral toxicity study in the mouse and claims that this sensitivity ''is supported by substantial data demonstrating that females are more likely than males to develop autoimmune diseases in response to environmental stressors.'' (Ref. 1 at 6). Based on this alleged sensitivity of females to immunotoxic results, NRDC then argues that ''[b]ecause EPA does not routinely test pesticides for immunotoxicity, the full repercussions of these results for female mortality and morbidity (i.e. autoimmune disease, compromised immune response, etc.) should be considered a serious potential risk of pyraclostrobin'' and merits retention of the children's safety factor. EPA interprets this argument as essentially a claim that EPA cannot remove the children's safety factor because it has inadequate data on the immunotoxic effects of pyraclostrobin.

BASF responds to NRDC by asserting that the children's safety factor was not intended to address differential sensitivities between males and females. Further, BASF asserts that any differences in sensitivity are taken into account in the risk assessment because the lowest NOAEL from male or female is used in selecting a safe dose and, in addition, a tenfold safety factor is applied to this NOAEL to address any lingering uncertainty as to differential male/female sensitivity.

While EPA agrees generally with BASF's comments, EPA does not believe that they address NRDC's core concern here which is the adequacy of the data pertaining to pyraclostrobin's immunotoxic potential. EPA has identified the immune system as a target of pyraclostrobin; however, EPA believes that pyraclostrobin's immunotoxic effects have been well-characterized and that no additional data is needed to protect against immunotoxic risks.

Currently, EPA does not routinely require that pesticides be tested specifically for immunotoxicity. Toxicology data requirements for a food-use pesticide, however, typically contain data that provide information for evaluating potential hazard to the immune system. For example, examination (in varying degrees) of the macro- and/or microscopic structural anatomy of immune system organs and tissues is performed in a number of toxicity studies, including the 90–day subchronic studies in multiple species, the chronic and carcinogenicity studies, the prenatal developmental toxicity studies (rats and rabbits), acute inhalation toxicity study, and the two-generation reproduction and fertility effects study. Additionally, non-specific indicators of a diseased state in the animal (e.g., clinical behavior which is evaluated by detailed observations throughout the conduct of all guideline animal studies) can also be useful in discerning perturbations in immune system function. If these toxicity studies show findings indicative of possible

immunotoxicity, they are given due consideration in the risk assessment. (Ref. 16 at 3).

EPA is considering requiring specific immunotoxicity testing for pesticides in the future. If the toxicity studies are inconclusive regarding immunotoxicity, there is concern, depending on the pesticide, that potential immunotoxic effects may not have been identified. Accordingly, the Agency has proposed that the pesticide toxicity data requirements be amended to require adult immunotoxicity testing for all pesticides. (70 FR 12277 (March 11, 2005). The proposed immunotoxicity testing would improve the likelihood that pesticides which have potential immunotoxic effects will be identified. If these proposed amendments are adopted, EPA will have to make determinations as to the timing of requiring these tests for existing pesticides and what the implications are for application of the children's safety factor of this new data requirement. The Children's Safety Factor policy recommends that this safety factor is more appropriate in situations when a study is requested ''for cause'' as opposed to a request based on more general considerations. EPA is likely to apply a similar approach to broadly-imposed new data requirements for immunotoxicity testing: although the requirements may apply to all pesticides, only those pesticides for which immunotoxicity is a specific concern would require retention of the children's safety factor. Important considerations in this analysis are likely to be the sensitivity of any immunotoxicity effects seen in the existing database (i.e., is the RfD/PAD based on the immunotoxic responses or do such effects only occur at higher doses), the degree to which any immunotoxicity effects are seen across studies and across species, and the nature and severity of the immunotoxic effects.

For pyraclostrobin, EPA's analysis of the existing data identified the immune system as a target organ but not the primary target. Effects were seen in the thymus, an important gland in the immune system, in terms of thymus atrophy and lymph node apoptosis. The thymus effects were seen in the 90–day study in mice at high doses (NOAEL/LOAEL of 30.4/119 mg/kg/day in males and NOAEL/LOAEL of 12.9/40.4 mg/kg/day in females). In a chronic/carcinogenicity study in mice, these effects were not seen at the highest dose tested (17.2 mg/kg/day for males and 32.8 mg/kg/day for females). Similar findings were not seen in available data with rats and dogs. Although decreased thymus weights were found at the highest dose (29–36 mg/kg/day) in the pups in the two-generation rat reproduction study, EPA does not interpret this effect as an immunotoxic response because total pup weights were reduced and ''relative'' thymus weights (the ratio of thymus weight/body weight) was normal. (Ref. 16 at 2). Similarly, in a recently submitted inhalation study, apparent thymus weight effects were seen, but again EPA concluded this was not an immunotoxic response given the lack of any confirming histopathological findings in the thymus and the excessively toxic level of the dose at which the thymus effects were seen. (Refs. 16 at 2 and 17).

EPA believes that the immunotoxic potential of pyraclostrobin has been well-characterized; that no additional data is needed taking into account all of the evidence bearing on potential immunotoxic effects; and that identification of immunotoxic effects in the 90–day mouse study does not support retention of the children's safety factor to protect the safety of infants and children. Most important to these findings are the facts that (1) immunotoxic effects were only seen at high doses in one study in the mouse – no immunotoxic effects were seen in other mouse studies or in studies in other species; and (2) combining the data from the 90–day mouse study and the chronic/cancer study in mice shows a NOAEL for immunotoxic effects for both male and female mice (30.4 mg/kg/day for males from the 90–day mouse study and 32.8 mg/kg/day for females in the chronic/cancer study) that is approximately 10X higher than the NOAEL used to set the RfD/PAD (3.4 mg/kg/day from the rat chronic study).

Although EPA has required the submission of developmental immunotoxicity data for two pesticides, those pesticides have a markedly different toxicological profile than pyraclostrobin. The two pesticides in question, clothianidin and dinotefuran, caused immunotoxic effects in multiple studies and species, and rat pups in the two generation rat reproduction study appeared to be more sensitive to these immunotoxic effects than adult animals. Further, the immunotoxic effects for these pesticides were the most sensitive effects seen in the database and were used to set the RfD/PAD for the pesticides. These circumstances are markedly different from pyraclostrobin where an immunotoxic effect was seen at a high dose in only one study.

c. *Two-generation reproduction study*. NRDC claims that the two-generation reproduction study in rats is invalid because it did not show adverse effects at any dose and that it cannot be rehabilitated by reference to the one-generation reproduction study because that study is contradictory in that it showed adverse effects at levels below levels tested in the two-generation study. BASF disputes NRDC's contention, arguing that the two-generation study did show some adverse effects at the highest dose tested and these effects were consistent with the one-generation study and ''fit along a dose-response curve with the two doses in the [one-generation] range-finding [reproduction] study.'' (Ref. 11 at 3.)

EPA disagrees with NRDC. An examination of all of the data from the two reproduction studies indicates that the reproduction effects of pyraclostrobin have been adequately characterized and no further data is needed.

The two-generation reproduction study and the one-generation reproduction study both tested the same strain of male and female Wistar rats from the same source. Using the same batch and purity of pyraclostrobin (BAS 500 F; Batch No. J.-No. 27882/199/b or /c; 98.7%), the two-generation study tested 0, 25, 75 or 300 ppm and the one-generation study tested 200, 400 and 600 ppm of Pyraclostrobin. This corresponds to 0, 2.5/2.6, 7.4/7.8 and 29.0/30.4 mg/kg/day (males/females (''M/F'')) for the two-generation reproduction study and 0, 20.5/21.3, 39.9/42.5 and 59.1/60.4 mg/kg/day (M/F) for the one-generation reproduction study. (Ref. 14 at 7–8).

In evaluating the results of these studies, EPA concluded that the one-generation reproduction study resulted in statistically significant, adverse body weight effects in parental animals at the mid (39.9/42.5 mg/kg/day) and high (59.1/60.4 mg/kg/day) doses and in pups at the low (20.5/21.3 mg/kg/day) as well as the mid and high doses. On the other hand, EPA determined that none of the doses used in the two-generation reproduction study (2.5/2.6, 7.4/7.8 and 29.0/30.4 mg/kg/day) caused statistically significant adverse effects in the parental animals or the offspring. Further, EPA initially classified the two-generation reproduction study as unacceptable due to its failure to identify statistically significant adverse effects and indicated that the study should be repeated at higher doses.

Upon reevaluation, EPA concluded that, when taken together, the two reproduction studies fulfilled the requirement for a two-generation reproduction study and a second reproduction study did not have to be conducted. Importantly, the two-generation study did show treatment-

related effects on body weight; these effects, however, were not judged significant enough to be considered adverse. Body weight decrements of 5 percent or less were consistently seen in both maternal and paternal animals at the high dose in the two-generation study and slightly greater weight decrements were seen in the first and second generation pups. (Refs. 14 at 8; 18). Specifically, the first and second generation pups of the high dose group (29.0/30.4 mg/kg/day) had decreased body weights on days 14 and 21 and on day 7 as well in second generation pups. The decreases were slightly more pronounced in the second generation (9 to 13%) than in the first (4 to 10%). In the one-generation study, the body weight decrease in pups between days 7 and 21 for the low (20.5/21.3 mg/kg/day), mid (39.9/42.5 mg/kg/day), and high (59.1/60.4 mg/kg/day) doses groups pups were 7 to 14 percent, 11 to 20 percent, and 24 to 37 percent, respectively. (Ref. 14 at 8). As Table 1 indicates, a comparison of the percentage weight loss from the pups in the two studies shows that the studies are complementary because the dose response curve when comparing the lowest two doses in the one-generation study with the highest dose in the two-generation study only slightly deviates from what might be expected. EPA concludes that this slight deviation in the dose response curve is likely due to normal variability in mammalian response and variability in human and instrumental measurements rather than any defect in the two-generation study.

TABLE 1.—BODY WEIGHT LOSS IN PUPS IN THE ONE- AND TWO-GENERATION RAT REPRODUCTION STUDIES

Dose (mg/kg/day) for Males/Females	Study	Weight Loss (days 7–12)
20/21	One-generation	7–14%
29/30	Two-generation	4–10% (first generation)* 9–13% (second generation)
40/42	One-generation	11–20%

*Days 14 - 21 only.

The consistency of effect and response from the two studies refute NRDC's claims regarding the contradictory nature of the findings from the two studies.

Moreover, although the body weight effects seen at the highest dose in the two-generation reproduction study were not significant enough to be judged adverse, a new study would not provide any additional data for risk assessment purposes. The concern with that study is not that it did not test at a low enough dose, but the opposite. Repeating the two-generation study at doses similar to and above 29 mg/kg/day (the highest dose tested in the two-generation study) is very unlikely to change the Point of Departure for pyraclostrobin which is currently a NOAEL of 3.4 mg/kg/day from the rat chronic/carcinogenicity study. The conclusion not to request a repeat study is in accord with the decisions made by the Agency's Pesticide Rejection Rate Analysis - Toxicology which states that a study should not be rejected provided that NOAELs are established in other studies that can be used to estimate a reference dose. (Ref. 19). In the case of pyraclostrobin, acute and chronic reference doses for dietary risks as well as doses for non-dietary risks were based on other studies.

d. *Other data deficiencies*. NRDC also claims there are several other significant data deficiencies which necessitate retention of the children's safety factor. For the reasons explained below, EPA does not find merit in this contention.

i. *Anticipated residue data*. NRDC notes that EPA is issuing a data call-in for information bearing on anticipated residues and asserts that this means there is a database deficiency. NRDC cites to page 17016 of the **Federal Register** to support this assertion. In fact, however, there is no data deficiency. If EPA relies on anticipated residue information in establishing a tolerance, it must require, pursuant to section 408(f)(1), that data be provided five years after the tolerance is established demonstrating that the residue levels in food are not above the levels anticipated. 21 U.S.C. 346a(b)(2)(E). Page 17016 of the pyraclostrobin **Federal Register** notice merely notes that EPA is subject to this obligation with regard to pyraclostrobin because it did rely on anticipated residue data in setting the tolerance.

ii. *28–day inhalation study*. NRDC notes that in 2004 a 28–day inhalation study in rats was outstanding and argues that this is a significant data gap. The 28–day inhalation study, however, is used to assess worker risk in connection with application of pyraclostrobin. Inhalation is not a significant exposure pathway for residential post-application exposure due to pyraclostrobin's very low volatility. In any event, this study has now been submitted and reviewed. The study established a NOAEL of 0.001 milligrams/liter (mg/L) based on hyperplasia of the duodenum, alveolar histiocytosis in the lungs, and olfactory atrophy/necrosis in the nasal tissues at 0.030 mg/L (LOAEL). (Ref. 17). This endpoint will be taken into account in the future in an updated occupational risk assessment for pyraclostrobin.

iii. *Rat chronic toxicity study*. NRDC claims the chronic toxicity study in rats was unacceptable due to failure to test at a dose high enough to produce significant toxicity. NRDC cites an October 2004 rulemaking for pyraclostrobin, (67 FR 63083, 63086 (October 29, 2004)), in support of this claim. The October 2004 **Federal Register** statement, however, was an error because EPA had determined in 2003 that the dosing in the rat chronic study was adequate. Specifically, EPA concluded in an October 2003 memorandum that ''[u]pon reevaluation at the September 10, 2003 meeting, the [Cancer Assessment Review Committee] concluded that female rats were tested adequately at the top dose of 200 ppm.'' (Ref. 20 at 23). The re-evaluation was based on additional data and statistical analysis bearing on the rat chronic study. EPA found that ''[t]here was a statistically significant decrease in cumulative body weight gain compared to controls across study intervals from Day 147 to study termination in the 200 ppm group females.'' (Id.). It had been previously determined that male rats were tested at a high enough dose. (Id. at 22).

iv. *Mouse carcinogenicity study*. NRDC claims the mouse carcinogenicity study was unacceptable due to failure to test at a dose high enough to produce significant toxicity. EPA originally concluded that this study had to be re-conducted at a higher dose; however, based on interim reports from a second study, using a higher dose, EPA found the dosing in the first mouse carcinogenicity study to be adequate. (Ref. 21). The second study involved a dose of 360 ppm which is double the high dose in the first study. Within a short period the study evidenced severe reductions in body weight and body weight gain at the 360 ppm dose. (Ref. 22). After 6 months of the study, EPA agreed that the 360 ppm dose was excessive and permitted the study to be terminated concluding that based on both studies, it had sufficient information to determine that the dosing in the first study was high enough to adequately characterize any cancer potential of pyraclostrobin. Following formal submission of the data, EPA confirmed that, compared to control

animals, there was a large decrease in the body weight/ body weight gain of female mice at 360 ppm up to the end of the study. Mean body weight of treated females was significantly decreased by 4–24% compared with that of controls during the study and was 21% less than that of controls when the study was terminated at 7 months. Weight gain, relative to controls, was reduced by 37% ($p \leq 0.01$) during the first 91 days of the study and by 40% ($p \leq 0.01$) over the entire study. (Ref. 23).

v. *Dermal absorption study*. NRDC claims the dermal absorption study was inadequate. NRDC notes that EPA described the study as unacceptable but nonetheless used it to calculate the percentage of dermal absorption by pyraclostrobin. EPA acknowledges that there were difficulties with the dermal absorption study; however, EPA was ultimately able to use the data obtained from this study to calculate pyraclostrobin's dermal absorption rate. (Ref. 9 at 15–16). The difficulty with the study was that most of the pyraclostrobin intended to be applied to the skin of the animal, remained in the dressing used to cover the skin where pyraclostrobin was applied. Because, however, the amount of pyraclostrobin that remained in the dressing was measured, it was possible to calculate what amount of pyraclostrobin was applied to the skin and hence, by comparing this amount to the amount absorbed by the animal, to derive the dermal absorption rate. In the underlying science memorandum, EPA initially characterized the study as unacceptable without expressly noting that its ability to derive a dermal absorption rate despite the flaws in the study made the study acceptable. EPA's initial characterization of the study was mistakenly cited in the 2004 **Federal Register** notice relied upon by NRDC. EPA notes that BASF claims to have submitted a new dermal absorption study but EPA has not received such a study from BASF.

e. *Conclusion with regard to NRDC's factual allegations*. For the reasons described above, EPA rejects each of NRDC's claims regarding the need for additional data or alleged deficiencies in submitted data.

B. NRDC's Claim that EPA's Tolerance Decision was Arbitrary and Capricious

NRDC also claims that it was arbitrary and capricious for EPA to establish the challenged pyraclostrobin tolerances because EPA did not review needed safety data and because ''EPA failed to explain adequately its departure from the required children's safety factor.'' (Ref. 1 at 10). As to the first contention, NRDC relies on its prior allegations regarding missing or deficient data. Because EPA has above rejected each of these claims regarding missing or deficient data, EPA also disagrees that its tolerance decision was arbitrary or capricious due to a failure to consider needed data.

NRDC provides no further elaboration with regard to its claim that EPA did not provide an adequate explanation of its decision on the children's safety factor. EPA explained its reasoning in both the preamble to the final rule promulgating the challenged pyraclostrobin tolerances, (71 FR at 17018), and in an earlier tolerance rulemaking on pyraclostrobin, (69 FR at 63092–63093), that was cross-referenced in the later action. EPA's regulations require that the basis for objections be stated with ''particularity,'' (40 C.F.R. 178.25(a)(2)), and NRDC's failure to provide any basis for its lack of explanation contention is alone grounds for denial of this objection. Nonetheless, EPA reiterates below its reasoning for removal of the children's safety factor.

In determining whether there are reliable data showing that a different safety factor would be safe for evaluating the risks of pyraclostrobin to infants and children, EPA has focused primarily on three issues: (1) The completeness of the toxicity database; (2) the completeness of the exposure database; and (3) what the data show with regard to pre- and post-natal toxicity.

This analysis did not occur in isolation but in the context of the overall risk assessment for pyraclostrobin. Before it makes any children's safety factor decision, EPA analyzes the toxicity and exposure databases. EPA's process with regard to toxicity data is described in its Children's Safety Factor policy:

> Before any decisions are made on the appropriate FQPA safety factor applied to ensure the safety of infants and children from the use of a particular pesticide, all of the relevant submitted data for the pesticide should be assembled and reviewed by Agency scientists. The toxicology database is evaluated to identify potential adverse effects, to determine the adequacy of the available data to characterize potential human risks, and to analyze the relationship between dose and response, that is, the levels at which the chemical causes adverse effects in test animals. The assessment of the potential for adverse health effects in infants and children is part of the overall hazard and dose-response assessment for a chemical. Available data pertinent to children's health risks are evaluated along with data on adults and the NOAEL (no-observed-adverse-effect-level) or benchmark dose (BMD) for the most sensitive critical effect(s) based on consideration of all health effects. By doing this, protection of the health of children will be considered along with that of other sensitive populations. (Ref. 5 at 7).

A similar process is undertaken to estimate exposure for all exposed population subgroups. Once these toxicity and exposure analyses are complete, EPA turns to the three critical factors pertaining to the children's safety factor described above and conducts a weight-of-the-evidence analysis to identify any concerns regarding the safety of infants and children. Finally, each of these factors are considered together in ''an integration step wherein the weight-of-evidence analyses for the completeness of the toxicity database, the degree of concern for pre- and postnatal toxicity, and results of the exposure assessments are combined by decisionmakers in evaluating whether the presumptive 10X safety factor should be retained or reliable data justify a different factor that could range from a level of 1X to 10X, and possibility greater than 10X.'' (Id. at 50).

In assessing the completeness of the toxicity database, EPA considers first whether the core five toxicology studies are available (chronic toxicity study in two species, two-generation reproduction study, and developmental toxicity study in two species) and next whether there are data gaps for any other studies, ''particularly those that pertain to evaluating risk to children and other sensitive subpopulations.'' (Id. at 24.) If data gaps are identified, then ''the risk assessor should consider the general, overall value of the particular type of study to the risk assessment.'' For pyraclostrobin, the toxicity database was adequate because no data gaps pertaining to infants and children have been identified. As explained in Unit VII.A.2., EPA disagrees with each of NRDC's claims regarding the existence of data gaps or data deficiencies.

In assessing the completeness of the exposure database, EPA uses a weight-of-the-evidence approach to ''address all important sources, routes, and pathways of exposure for the pesticide and include both the expected exposure duration as a consequence of each use and the expected pathway(s) of exposure.'' (Id. at 36). The object of this analysis is to determine the level of confidence that ''the assessment is either highly accurate or based upon sufficiently conservative input that it does not underestimate those exposures that are critical for assessing the risks to infants and children.'' (Id.). For pyraclostrobin, there is high confidence that the exposure assessment does not

underestimate exposure. EPA examined three pathways of exposure: food, drinking water, and exposure from use on residential turf. As explained in Unit III.B.3.b., EPA follows a tiered approach in estimating pesticide residues in food, first conducting a simple, very conservative assessment (assuming all registered crops contain tolerance level residues) that grossly overestimates exposure from residues in food and then refining that analysis in steps if needed. For pyraclostrobin, EPA conducted a slightly refined analysis. For the acute exposure assessment, EPA assumed all pyraclostrobin-registered crops were treated with pyraclostrobin and that 65 of 73 crops had residues at the tolerance level. For the other crops (various leafy greens and dried beans), EPA assumed residues would be at the highest average value from residue field trials designed to produce maximum residues. For the chronic exposure assessment, EPA used data on percent crop treated for most of the registered crops and assumed tolerance level residues for all registered crops other than apple and pear. For apple and pear, EPA used the average value from residue field trials designed to produce maximum residues. Although these exposure assessments are somewhat refined, they remain very conservative in comparison to estimates based on monitoring data gathered from food distribution channels. To estimate exposure to pyraclostrobin through residues in drinking water and from treated residential turf EPA used exposure models that incorporate pesticide specific information and are designed to produce high-end estimates of exposure. (Ref. 8 at 30; 69 FR at 30058–30064). Because of this conservative approach to estimating exposure, EPA has very high confidence that its exposure assessment does not underestimate exposure to pyraclostrobin. In all likelihood, it substantially overestimates exposure.

Finally, in examining a pesticide's potential pre- and post-natal toxicity, EPA also conducts a weight-of-the-evidence analysis focusing on whether data show increased sensitivity in the young, how well the dose-response relationship of any pre- or post-natal effects are understood, and, to the extent available, information on a pesticide's toxicokinetics and mode of action. For pyraclostrobin, the key studies on pre- and post-natal toxicity were the rat and rabbit developmental toxicity studies and the one and two generation rat reproduction studies. The rat developmental study showed no increased sensitivity in the rat fetuses (see discussion in Unit VII.A.2.a.i.) and, in any event, the effects seen in the fetuses occurred at higher doses than the effects in maternal animals. Qualitatively more severe effects were seen in the fetuses in the rabbit developmental study (fetal resorptions compared to body weight effects); however, these effects occurred at the same dose as the adverse effects in the maternal animals and a clear NOAEL level was identified for both the maternal and fetal effects. Finally, the one generation rat reproduction study indicated that rat pups may be quantitatively more sensitive than parental animals in that marginal body weight effects were seen at a lower dose in pups than in parental animals. The two generation rat reproduction study, however, failed to replicate this quantitative sensitivity instead showing that marginal body weight effects occurred in both pups and parental animals at the same dose (see discussion in Unit VII.A.2.c.). Moreover, the two generation study established a clear NOAEL for the body weight effects in both pups and parental animals. Based on this evidence, EPA concluded that the effects on the young were well understood/characterized and that there were no residual concerns that reliance on the traditional 10X intra-species safety factor, when applied to the NOAELs for effects in fetuses and pups, would not be protective of infants and children. (71 FR 17014, 17018 (April 5, 2006); 69 FR 63083, 63092–63093 (October 29, 2004)).

Taking into account that (1) there is a complete toxicity database; (2) the exposure estimate is a likely overestimate of pyraclostrobin exposure; and (3) pyraclostrobin's pre- and post-natal effects are well-defined by the database and there are no residual concerns regarding potential increased sensitivity – EPA concludes that it has reliable data showing that it is safe for infants children to conduct its risk assessment using a 100–fold safety factor without use of the additional 10X children's safety factor.

C. Conclusion on Objections

For the reasons stated above, all of the NRDC's objections are hereby denied.

VIII. Response to Comments on NRDC's Objections

In comments on its own objections, NRDC made two additional arguments. First, NRDC cited general statements that children can be more vulnerable than adults to pesticides and that children may have greater relative exposure to pesticides than adults. These two points, according to NRDC, make it ''especially important that EPA apply the required FQPA safety factor for pyraclostrobin.'' (Ref. 10 at 3). EPA does not believe that this general information is particularly helpful in making the specific determination for pyraclostrobin under the children's safety provision. Concerns about children's vulnerability and exposure led to passage of the children's safety factor provision; yet that provision expressly allows EPA to choose a factor different than the presumptive additional 10X safety factor if such different factor is safe for children. NRDC's argument here essentially reads EPA's authority to choose a different factor out of the statute not just for pyraclostrobin but for all pesticides. Further, EPA would note that it has taken into account, in making a decision on the children's safety factor for pyraclostrobin, data estimating children's exposure to pyraclostrobin and data evaluating the relative sensitivity of the young vis-a-vis adults to pyraclostrobin.

An additional claim included in NRDC's comments is that its objections are supported by six documents referenced in the objections. These documents include a letter to EPA, a report from EPA's Office of Inspector General, several law review articles, and the National Academy of Sciences' 1993 report on pesticides and children. Other than listing the documents, NRDC did not explain how these documents support its objections. All of the documents address, at least in part, application of an additional safety factor for the protection of children. None of the documents, however, mentions pyraclostrobin. EPA does not believe that the mere listing of documents, particularly such general documents as these, trigger any obligation upon the Agency to respond to the substance of the documents. Further, the failure of NRDC to offer any substantive explanation as to why these documents were included in its comments means that NRDC has not presented or exhausted any issues, questions, or conclusions contained in these documents before the Agency. The reason for the exhaustion requirement in section 408 as to tolerance issues is so that EPA may make a full record on an issue and bring its experience to bear on it. (Nader v. EPA, 859 F.2d 747, 754 (9th Cir. 1988)). Because NRDC has not presented any issues, questions, or conclusions contained in these documents to EPA, it cannot, should it challenge this Order in court, cite matters in these documents to the court as supporting its objections. For the

same reason, EPA will not include these documents in the record for this action.

IX. Regulatory Assessment Requirements

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

X. 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).

XII. References

1. Natural Resources Defense Council, ''Objection to the Establishment of Tolerances for the Pesticide Chemical Residues of Pyraclostrobin'' Docket Id No. EPA-HQ-OPP-2004-0292 (June 5, 2006).

2. Office of Pesticide Programs, U.S. EPA, Available Information on Assessing Pesticide Exposure From Food: A User's Guide (June 21, 2000).

3. U.S. EPA, Residue Chemistry Test Guidelines: OPPTS 860.1500 Crop Field Trials (August 1996).

4. Office of Pesticide Programs, U.S. EPA and Pest Management Regulatory Agency, ''Health Canada, NAFTA Guidance Document for Guidance for Setting Pesticide Tolerances Based on Field Trial Data'' (September 28, 2005).

5. Office of Pesticide Programs, U.S. EPA, ''Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment'' (January 31, 2002).

6. Office of Pesticide Programs, U.S. EPA, ''The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides'' (August 18, 2000).

7. Office of Pesticide Programs, U.S. EPA, Versar Corporation, ''Standard Operating Procedures (SOPs) for Residential Exposure Assessments'' (Draft, December 19, 1997).

8. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Barry O'Keefe to John Bazuin/Cynthia Giles-Parker, ''Pyraclostrobin Human Health Risk Assessment to Account for Revised Tolerances on Succulent Beans, Dried Shelled Peas and Beans, and Strawberries, and to Establish Tolerances on Mangos and Papayas'' (November 30, 2005).

9. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Ghazi Dannan to William Wassell, ''PYRACLOSTROBIN - 3rd Report of the Hazard Identification Assessment Review Committee'' (February 10, 2003).

10. Natural Resources Defense Council, Re: ''Objection to the Establishment of Tolerances for Pesticide Chemical Residues of Pyraclostrobin,'' Docket ID No. EPA-HQ-OPP-2004-0292 (September 9, 2006).

11. BASF Corporation, Docket ID [EPA-HQ-OPP-2004-0292; FRL-8076-81 ''Pyraclostrobin; Objections to Pesticide Tolerances; Notice of Availability;'' Federal Register, Vol 71, No. 138, July 19, 2006 (September 12, 2006).

12. Health Effects Division, Office of Pesticide Programs, U.S. EPA, Data Evaluation Record (TXR#: 0051615): ''Prenatal Developmental Toxicity Study'' (*Teratology*); Species: Rat; Guideline: OPPTS 870.3700; OPP 83-3a; ''Pyraclostrobin'' (April 29, 2003).

13. Health Effects Division, Office of Pesticide Programs, US EPA, ''Data Evaluation Record (TXR#: 0051615): Prenatal Developmental Toxicity Study'' (*Teratology*); Species: Rabbit; Guideline: OPPTS 870.3700; OPP 83-3b; ''Pyraclostrobin'' (April 29, 2003).

14. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Ghazi Dannan to Cynthia Giles-Parker/Tony Kish, ''HED Response to NRDC Objection to the Establishment of Tolerances for Pesticide Chemical Residues of Pyraclostrobin.'' Docket ID No. EPA-HQ-OPP-2004-0292. (PC Code 099100) (July 16, 2007).

15. Woo, David C. and Hoar, Richard M., '''Apparent Hydronephrosis' as a Normal Aspect of Renal Development in the Late Gestation of Rats: The Effect of Methyl Salicylate'' (*Teratology*; 1972 Oct;6(2):191-6).

16. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Yung Yang to Cynthia Giles-Parker/Tony Kish,''HED Response to NRDC Objection to the Establishment of Tolerances for Pesticide Chemical Residues of Pyraclostrobin.'' Docket ID No. EPA-HQ-OPP-2004-0292. TXR # 0054635, DP Barcode: D341293, PC Code: 099100. (July 24, 2007).

17. Health Effects Division, Office of Pesticide Programs, US EPA, Data Evaluation Record: Subchronic Inhalation Toxicity - [rat]; OPPTS 870.3465 [82-4]; OECD 413. ''Pyraclostrobin; methyl [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]methyl] phenyl]methoxycarbamate'' (August 21, 2007).

18. Office of Pesticide Programs, U.S. EPA, Data Evaluation Record, Multigeneration Reproductive Toxicity Species: Rat; Guideline: OPPTS 870.3800; OPP 83-4; EPA MRID No. 45118327, EPA Pesticide Chemical Code: 099100, EPA DP Barcode D269669, D267732, EPA Submission No. S583112, HED TXR#:0051615, Test Material: BAS 500 F (January 16, 2003).

19. Office of Pesticide Programs, U.S. EPA, ''Pesticide Rejection Rate Analysis Toxicology,'' 738-R-93-005, pp. 82-83, (July 1993).

20. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Jessica Kidwell to Ghazi Dannan and Barry O'Keefe, ''PYRACLOSTROBIN: Report of the Cancer Assessment Review Committee (Second Evaluation);'' PC Code: 099100 (October 22, 2003).

21. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Jessica Kidwell to Ghazi Dannan and Paula Deschamp, ''PYRACLOSTROB IN: Third Report of the Dose Adequacy Review Team (DART)'' (July 19, 2005).

22. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Jessica Kidwell to Ghazi Dannan, ''PYRACLOSTROBIN: Second Report of the Dose Adequacy Review Team (DART)'' (March 7, 2005).

23. Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, Memorandum from Jessica Kidwell to Ghazi Dannan and Barry O'Keefe, PYRACLOSTROBIN: Report of the Cancer Assessment Review Committee (Third Evaluation); PC Code: 099100 (February 15, 2007).

List of Subjects

Environmental protection, Pesticides and pests.

Dated: September 4, 2007.

Debra Edwards,

Director, Office of Pesticide Programs.

[FR Doc. E7–18025 Filed 9–11–07; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPP–2007–0675; FRL–8145–3]

Pesticide Registration Review; New Docket Opened for Review and Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has established a registration review docket for the following pesticide: Zinc Borate (3ZnO•2BO3•3.5H2O; mw 434.66), PC Code 128859, Case number 5025. With this document, EPA is opening the public comment period for this registration review. Registration review is EPA's periodic review of pesticide registrations to ensure that each pesticide continues to satisfy the statutory standard for registration, that is, the pesticide can perform its intended function without unreasonable adverse effects on human health or the environment. Registration review dockets contain information that will assist the public in understanding the types of information and issues that the Agency may consider during the course of registration reviews. Through this program, EPA is ensuring that each pesticide's registration is based on current scientific and other knowledge, including its effects on human health and the environment.

DATES: Comments must be received on or before December 11, 2007.

ADDRESSES: Submit your comments identified by the docket identification (ID) number for the specific pesticide of interest provided in the table in Unit III.A., 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.

Instructions: Direct your comments to the docket ID numbers listed in the table in Unit III.A. for the pesticide you are commenting on. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov website is an ''anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the docket index available at regulations.gov. 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 web site to view the docket index or access available documents. Although listed in the index, some information is not publicly available, e.g., 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 electronically 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 hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: For information about the pesticide included in this document, contact the specific Chemical Review Manager for this pesticide as identified in the table in Unit III.A.

For general questions on the registration review program, contact Kennan Garvey, Antimicrobials Division (7510P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 305–7106; fax number: (703) 308–8090; e-mail address: *garvey.kennan@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including environmental, human health, farmworker, and agricultural advocates; the chemical industry; pesticide users; and members of the public interested in the sale, distribution, or use of pesticides. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. 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. What Should I Consider as I Prepare My Comments for EPA?

1. *Submitting CBI*. Do not submit this information to EPA through regulations.gov or e-mail. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in