

for judicial review may be filed, and shall not postpone the effectiveness of such rule or action. This action may not be challenged later in proceedings to enforce its requirements. (See section 307(b)(2).)

#### List of Subjects in 40 CFR Part 52

Environmental protection, Air pollution control, Incorporation by reference, Intergovernmental relations, Ozone, Reporting and recordkeeping requirements, Volatile organic compounds.

Dated: December 18, 2007.

**Bharat Mathur,**

*Acting Regional Administrator, Region 5.*

■ For the reasons stated in the preamble, part 52, chapter I, of title 40 of the Code of Federal Regulations is amended as follows:

#### PART 52—[AMENDED]

■ 1. The authority citation for part 52 continues to read as follows:

**Authority:** 42 U.S.C. 7401 et seq.

#### Subpart O—Illinois

■ 2. Section 52.720 is amended by adding paragraph (c)(180) to read as follows:

##### § 52.720 Identification of plan.

\* \* \* \* \*

(c) \* \* \*

(180) On January 10, 2007, Illinois submitted revisions to its rules for the Emission Reduction Market System. These revisions assure that sources in the Chicago area with potential emissions of VOC between 25 and 100 tons per year will remain subject to the program, irrespective of changes in the area's ozone nonattainment classification or designation and any associated changes in whether such sources are defined to be major sources. EPA is again deferring action on section 205.150(e).

(i) *Incorporation by reference.*

(A) The following sections of 35 Illinois Administrative Code Part 205, as effective June 13, 2005: sections 205.120, 205.130, 205.150 (except for 205.150(e)), 205.200, 205.205, 205.210, 205.220, 205.300, 205.310, 205.315, 205.316, 205.318, 205.320, 205.330, 205.335, 205.337, 205.400, 205.405, 205.410, 205.500, 205.510, 205.610, 205.700, 205.730, 205.750, and 205.760.

[FR Doc. E8-806 Filed 1-29-08; 8:45 am]

**BILLING CODE 6560-50-P**

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 180

[EPA-HQ-OPP-2005-0145; FRL-8347-3]

#### Boscalid; Denial of Objections

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final order.

**SUMMARY:** In this order, EPA denies objections filed by the Natural Resources Defense Council (“NRDC”) 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 boscalid on various leafy greens. 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.

**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](mailto:kish.tony@epa.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. General Information

###### A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. Potentially affected entities may include, but are not limited to:

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

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities that are potentially affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in

determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

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

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

###### C. How Can I Access Electronic Copies of Materials in the Docket?

EPA has established a docket for this action under docket identification (ID) number EPA-HQ-OPP-2005-0145. 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.

## II. Introduction

### A. What Action Is the Agency Taking?

In this order, EPA denies objections filed by the Natural Resources Defense Council (“NRDC”) 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 boscalid on various leafy greens. (Ref. 1). NRDC argues that EPA must retain an additional ten-fold (10X) safety factor for the protection of infants and children due to data showing that juvenile animals are more sensitive than adults. Retention of this additional safety factor, NRDC contends, shows that the tolerances are unsafe. Additionally, NRDC contends that EPA's tolerance decision was arbitrary and capricious because (1) EPA failed to explain adequately its reason for not applying a 10X safety factor for infants and children and (2) the safe dose for boscalid established by EPA is “clearly contrary to the data . . .” (Id. at 3-4, 7-8).

### 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

1. *In general.* EPA establishes maximum residue limits, or “tolerances,” for pesticide residues in food under section 408 of the FFDCA. (21 U.S.C. 346a). Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is “adulterated” under section 402 of the FFDCA and may not be legally moved in interstate commerce. (21 U.S.C. 331, 342). Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration and the U.S. Department of Agriculture. Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (“FQPA”), which added the provisions discussed below establishing a detailed safety standard for pesticides and additional protections for infants and children.

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

2. *Safety standard for pesticide tolerances.* A pesticide tolerance may only be promulgated by EPA if the tolerance is “safe.” (21 U.S.C. 346a(b)(2)(A)(i)). “Safe” is defined by the statute to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all

other exposures for which there is reliable information.” (21 U.S.C. 346a(b)(2)(A)(ii)). Section 408 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)).

Section 408(b)(2)(C) requires EPA to give special consideration to risks posed to infants and children. Specifically, this provision states that EPA “shall assess the risk of the pesticide chemical based on available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of *in utero* exposure to pesticide chemicals . . .” (21 U.S.C. 346a(b)(2)(C)(i)(II) and (III)). This provision further directs that “[i]n the case of threshold effects, . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.” (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to “use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.” (Id.). The additional safety margin for infants and children is referred to throughout this order as the “children’s safety factor.”

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

revoking the tolerance or denying the petition, any affected party has 60 days to file objections with EPA and seek an evidentiary hearing on those objections. (21 U.S.C. 346a(g)(2)). If objections are filed by a party other than the petitioner, EPA is required to serve a copy of any objections on the petitioner. (Id.). EPA’s final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

4. *Other EPA statutory authority over pesticides.* 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)).

#### B. Evaluating the Safety of Tolerances Through the Use of Risk Assessment Including the Use of Safety Factors

1. *In general.* The process EPA follows in evaluating FFDCA petitions to establish tolerances and in determining the safety of the petitioned-for tolerances 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 the statutory 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 evaluation process (choosing a tolerance value), EPA reviews 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 pages

5, 7, and Tables 1 and 5). Several samples are then gathered from each field and analyzed. (Id. at 53).

Generally, the results from such field trials show that the residue levels for a given pesticide use will vary from as low as non-detectable to measurable values in the parts per million (ppm) range with the majority of the values falling at the lower part of the range. EPA uses a statistical procedure to analyze the field trial results and identify the upper bound of expected residue values. This upper bound value is used as the tolerance value. (Ref. 4). (As discussed below, the safety of the tolerance value chosen is separately evaluated.).

There are three main reasons for closely linking tolerance values to the maximum value that could be present from maximum label usage of the pesticide. First, EPA believes it is important to coordinate its actions under the two statutory frameworks governing pesticides. (See 61 FR 2378, 2379, January 25, 1996). It would be illogical for EPA to set a pesticide tolerance under the FFDCA without considering what action is being taken under FIFRA with regard to registration of that pesticide use. (Cf. 40 CFR 152.112(g) (requiring all necessary tolerances to be in place before a FIFRA registration may be granted)). In coordinating its actions, one basic tenet that EPA follows is that a grower who applies a pesticide consistent with the FIFRA label directions should not run the risk that his or her crops will be adulterated under the FFDCA because the residues from that legal application exceed the tolerance associated with that use. To further this goal, 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.

Once the hazard for a durational scenario is identified, EPA must determine the toxicological level of concern and then compare estimated human exposure to this level of concern. This comparison is done through either calculating a safe dose in humans (incorporating all appropriate safety factors) and expressing exposure as a percentage of this safe dose (the reference dose ("RfD") approach) or dividing estimated human exposure into an 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, 52–53; 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 added 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. To some extent, the FQPA safety factor addresses concerns related to the factors driving EPA's traditional use of additional safety factors.

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 pesticide's MOE, the safer the pesticide would be considered. Accordingly, if the target MOE for a pesticide is 1,000, MOE's for that pesticide 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 if quantitation of the risk is deemed appropriate. Rather, EPA calculates the slope of the dose-response curve for the non-threshold effects from relevant studies using a model that assumes that any amount of exposure will lead to some degree of risk. The slope of the dose-response curve can then be used to estimate the probability of occurrence of additional adverse effects as a result of exposure to the pesticide. For non-threshold cancer risks, EPA generally is concerned if the probability of increased cancer cases exceed the range of 1 in 1 million.

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:

- i. the types and amount of food that is consumed; and
  - ii. the residue levels in that food.
- Consumption is estimated by EPA based on scientific surveys of individuals' food consumption in the United States conducted by the U.S. Department of Agriculture. (Ref. 2 at 12). Information on residue levels comes from a range of sources including crop field trials; data on pesticide reduction due to processing, cooking, and other practices; information on the extent of usage of the pesticide; and monitoring of the food supply. (Id. at 17).

In assessing exposure from pesticide residues in food, EPA, for efficiency's sake, follows a tiered approach in which it, in the first instance, conducts its 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 unnecessary 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. (72 FR 52112, July 18, 2007; 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 Tolerances

Boscalid is a fungicide used both on agricultural food crops as well as turf. It has a wide variety of agricultural uses including berries, nuts, soybeans, and various vegetables. (40 CFR 180.589(a)). Tolerances have also been established to cover inadvertent residues on various other crops as a result of rotation of these crops onto fields previously treated with boscalid. (40 CFR 180.589(d)). On December 20, 2006, EPA promulgated new boscalid tolerances for residues in or on leafy greens crop subgroup 4A, except head and leaf lettuce, and leafy petioles crop subgroup 4B. (71 FR 76185, December 20, 2006).

In promulgating these tolerances, EPA assessed the risk from boscalid based on aggregate boscalid exposure. Animal studies indicated that repeat dosing with boscalid resulted in effects in the liver and/or thyroid in various species. Mechanistic studies indicated that the thyroid effects were derivative of enzymatic effects on the liver. (Ref. 8 at 4). The chronic RfD/PAD was based on the results of three studies that showed similar effects at similar levels. (Id. at

23–24). The boscalid database showed no effects that were attributable to a single dose, and thus boscalid was deemed not to pose an acute risk. Testing involving *in utero* and/or post-natal exposure of animals showed no developmental or reproductive effects; however, this testing resulted in some findings of qualitative or quantitative sensitivity with regard to body weight effects in the young. EPA concluded there was low concern regarding these sensitivity findings for various reasons including that clear NOAELs were identified for these effects and the effects were transient in nature or inconsistent. EPA assessed exposure to boscalid in food relying on the worst case assumption that boscalid residues in all crops to which boscalid may be legally applied had residues at the tolerance level.

EPA concluded that chronic exposures to boscalid did not raise safety concerns because the most highly exposed population subgroup, children 1–2 years old, had exposures below the PAD or safe dose (exposure was at 38 percent of the PAD). (71 FR 76188). Short-term exposures from golf course turf was also judged to be safe having a MOE of 1,400. (Id.). EPA concluded the cancer risk posed by boscalid was negligible given the weak evidence of carcinogenicity in animal studies. (Id. at 76189). In conducting these assessments, EPA determined that the children's safety factor could be removed because the database was complete, there was low concern for increased sensitivity in the young, and exposure had been estimated in a conservative fashion. (Id. at 76188).

#### V. NRDC's Objections

On February 20, 2007, NRDC filed objections to the December 2006 rule establishing tolerances for boscalid on various leafy greens. (Ref. 1). On May 21, 2007, NRDC supplemented and expanded its objections by filing comments during the comment period held by EPA on NRDC's initial objections. (Ref. 9).

NRDC's objections have two main thrusts: (1) that EPA erred in removing the children's safety factor given the finding of that young animals had increased sensitivity to boscalid; and (2) that EPA's decision is arbitrary and capricious due to a failure to adequately explain its reasons for removing the children's safety factor and because EPA's selection of NOAELs and the RfD/PAD "are clearly contrary to the data." (Ref. 1).

With regard to increased sensitivity in young animals, NRDC relied in its objections principally on the EPA

finding in the DNT study that rat pups had decreased body weight and decreased body weight gain at a dose of 147 milligrams/kilogram of body weight/day (mg/kg/day) whereas no effects were seen in the maternal animals even at the highest dose tested (1,442 mg/kg/day). Further, NRDC cites the rat reproduction study as evidencing increased sensitivity in rat pups. Given this sensitivity, NRDC argues that it was wrong for EPA to rely on a study on adult animals to set the RfD/PAD without retaining the children's safety factor. In addition to arguing that EPA did not give proper weight to its findings of increased sensitivity to the young, NRDC claims that EPA analyzed the data in several studies in a manner that understates the sensitivity of the young and has selected a RfD/PAD that is under-protective of the young. (NRDC's arguments on these points are presented in more detail in Unit VII.A. below.) EPA's allegedly improper analysis is cited as grounds for retaining the children's safety factor. NRDC claims that if EPA had retained the children's safety factor it could not have concluded that the boscalid tolerances are safe.

NRDC makes no new arguments to justify its claim that EPA's decision is arbitrary and capricious; rather, NRDC merely cross-references its earlier assertions regarding EPA's interpretation of science data.

In its comments on its objections, NRDC expands on these arguments. First, it argues that EPA erred in discounting the seriousness of the increased sensitivity in the DNT and rat reproduction studies. NRDC claims that EPA's analysis is based on nothing more than speculation. (Ref. 9 at 2–4). Second, NRDC cites a third study as showing sensitivity in young animals, the rabbit developmental study, and argues similarly that EPA has relied on nothing more than speculation to conclude that the demonstrated sensitivity is of low concern. Finally, NRDC provides greater detail in support of its argument that EPA's selection of a RfD/PAD for boscalid is not protective of children and does not justify removal of the children's safety factor.

## VI. Public Comments

Upon receipt of the objections, EPA provided a copy of the objections to the tolerance petitioner, BASF Corporation, as required by the statute. Further, on March 28, 2007, EPA published a notice of the availability of the objections and established a 60-day comment period. (72 FR 14551, March 28, 2007). Other than from BASF, EPA received

significant comments only from NRDC – commenting on its own objections.

BASF's comments stressed that a complete database had been submitted on boscalid including neurotoxicity studies that went beyond the core toxicology database requirements. In addition, BASF asserted that these studies showed “no toxicologically meaningful effects [in young animals] were observed at a dose below one that produced toxicity to the parental animals.” (Ref. 10 at 2). BASF contended that effects in rat pups in the DNT and the two-generation reproduction study that occurred at doses lower than effects in maternal animals were small and/or transient decreases in pup body weight. (Id.).

Because NRDC's comments on its own objections were a supplementation of its objections, these comments were provided to BASF and BASF was given a 30-day period for response. (Ref. 11). As to NRDC's new arguments concerning sensitivity in the young, BASF asserts that the data did not support that conclusion. As regards the two-generation reproduction study and the DNT, BASF notes that, although toxicity in the parental animals was not seen in the DNT study and was seen only at the high dose in the reproduction study, in the chronic/carcinogenicity study in rat, where systematic toxicity is examined more thoroughly, adverse effects were seen at doses corresponding to the mid and high doses in the DNT and reproduction studies. Thus, BASF concludes that the findings of adverse effects in the young at the mid and high doses in the DNT and reproduction studies do not show increased sensitivity in the young. As to the rabbit developmental study, BASF argues that, because the effects on the fetuses (increased number of abortions) occurred at a dose that showed the maternal animals were under stress (decreased weight gain), the study does not show increased sensitivity in the fetuses. According to BASF, “[t]he rabbit is prone to spontaneously abort as a response to maternal stress, and feed restriction alone during the gestational period may trigger abortions in rabbits.” (Id. at 3). Finally, BASF defends EPA's use of the NOAEL from the chronic dog study as the Point of Departure for setting the cRfD/PAD by presenting a “benchmark dose” analysis of the relevant studies. Benchmark dose analysis involves fitting a mathematical model to the dose response data for the purpose of estimating the threshold effect level (i.e., the no adverse effect level) reflecting a selected benchmark response (e.g., 5%, 10%). BASF's benchmark dose analysis revealed that

the NOAEL from the chronic dog study was lower than the benchmark dose from DNT and two-generation reproduction studies.

## VII. EPA's Response to the Objections

For the reasons stated below, EPA denies each of NRDC's objections.

### A. NRDC's Challenge to EPA's Children's Safety Factor Determination

NRDC contends that EPA's decision to remove the children's safety factor was erroneous based on (1) the legal argument that whenever EPA identifies increased sensitivity in the young it is required to retain the full 10X children's safety factor; and (2) the scientific claim that EPA did not have a reasoned basis for its conclusion that the sensitivity identified in animal studies was of low concern in evaluating whether the 10X children's safety factor should be retained or a different factor selected.

Before reaching the merits of these arguments, one preliminary matter needs to be addressed. In a prior order on an objection to EPA's removal of the children's safety factor as to different pesticides, EPA denied the objection where retention of the children's safety factor would not have altered EPA's conclusion on the pesticide's safety (72 FR 39318, 39323–39324, July 18, 2007). For boscalid, the retention/removal decision appears to be critical to the safety determination because EPA concluded that chronic exposure to boscalid for the highest exposed population subgroup is at 38 percent of the RfD/PAD. If no other change is made to the boscalid risk assessment other than retaining the 10X children's safety factor, then the calculation that boscalid exposure uses 38 percent of the RfD/PAD for the most highly-exposed subgroup would increase by a factor of 10. Because of the conservativeness of the exposure assessment for boscalid (assuming all foods that may be legally treated bear tolerance level residues), however, EPA strongly suspects that a more realistic exposure assessment will not show a risk of concern. Exposure refinements from the worst case assumptions of all foods containing tolerance level residues generally reduce exposure estimates by an order of magnitude or more. (70 FR 46706, 46732, August 10, 2005). Nonetheless, because EPA has not completed a revised risk assessment for boscalid at this time, it will address in this order the substance of NRDC's challenge to EPA's decision on the children's safety factor. It should be noted that EPA's decision on the children's safety factor for boscalid relied in part on the conservativeness of EPA's exposure

assessment. This consideration continues to be relevant, even if, at this point, it does obviate NRDC's objection entirely.

1. *NRDC's legal argument.* NRDC argues that, because section 408 "requires that the additional FQPA tenfold safety factor 'shall be applied' to 'take into account' 'potential pre- and post-natal toxicity,'" . . . [t]he clear evidence that juveniles are significantly more vulnerable than adults compels EPA to retain or increase the default FQPA tenfold safety factor for boscalid." (Ref. 1 at 3).

On repeated occasions EPA has rejected the interpretation that the children's safety factor provision mandates that the absence of a particular study or a finding of pre- or post-natal toxicity or increased sensitivity in the young removes EPA's discretion to choose a different safety factor. (72 FR 52108, 52115–52117, September 12, 2007; 71 FR 43906, 43919, August 2, 2006). EPA explained its rationale recently in responding to NRDC objections which made precisely the same argument in this case:

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.

(72 FR at 52117). NRDC has raised no arguments in its current objections which convince EPA to vary from its long-held interpretation.

2. *NRDC's scientific argument.* NRDC makes five claims as to why the evidence on increased sensitivity in the young is of such significance that it was inappropriate for EPA to remove the children's safety factor. NRDC also argues that an alleged lack of reliable data supporting EPA's derivation of the boscalid RfD/PAD demonstrates that it was unlawful to remove the children's safety factor. Each claim is addressed in turn below.

a. *The degree of increased sensitivity seen in the DNT.* NRDC claims that adverse effects on auditory startle reflex were seen at all doses in the offspring

in the DNT study and thus the dose EPA identified as a NOAEL for the offspring (14 mg/kg/day) is actually a LOAEL. According to NRDC, this demonstrates a higher degree of sensitivity in the offspring. NRDC notes that a draft EPA assessment of the DNT study concluded that there were adverse effects on the auditory startle reflex in offspring at all tested doses. The final EPA review of the DNT study took the opposite position: that there was not a significant effect on the auditory startle reflex at any dose. NRDC argues that EPA's final review is flawed because EPA misused data on the historical level of the auditory startle reflex in rat controls in other studies ("historical control data"). According to NRDC, EPA erred by comparing historical control data to the results in the treated animals in the boscalid DNT study to determine if the treated animals varied from control animals generally. NRDC argues that the only valid use of historical control data is as a check on whether there is a problem with the controls in a particular study.

EPA disagrees with NRDC's analysis and reaffirms its conclusion that boscalid did not elicit an adverse effect on auditory startle reflex in the DNT study. In its initial analysis of the DNT, an EPA reviewer concluded that there were treatment-related decreases in auditory startle reflex at all doses on post-natal-day ("PND") 24. This finding was based on a statistically significant decrease in auditory startle reflex in males at both the low and high doses in the first block of five trials and for the average effect over all trials. The average decrease was greater in the low dose group (24%) than the high dose group (19%). The mid-dose group had a slightly lower decrease of 15%. In females, a statistically significant effect was only seen in the second block of the low and mid-dose groups but no such effect was seen for the average across blocks. Again, there was no dose-response effect in that greater decreases were seen at the low dose than at the mid or high dose. No statistically significant effects on auditory startle reflex were seen on PND 60. Noting the "limitations" in the data, the EPA reviewer nonetheless tentatively found a treatment-related effect at all doses.

In response to this tentative conclusion, the boscalid registrant submitted historical control data on auditory startle reflex and data concerning one male pup that died on PND 25. After examining the historical control data, EPA concluded that the auditory startle reflex of the controls from the boscalid DNT study were similar to historical controls and thus

the controls from the boscalid study "should be considered the primary source for analysis and consideration" for this study. (Ref. DER at 30). As to the rat which died, EPA concluded that it was suffering from an underlying illness unrelated to treatment and removed its data from the study. As a result, none of the individual block trials nor the average from all trials for males evidenced a statistically significant decrease in auditory startle reflex at PND 24. EPA also reanalyzed the statistical significance of the results for the females and found a statistically significant effect only at the low dose for the second block. Given the revised finding of a statistically significant effect in only one block trial (out of five) at one dose (out of three) in one sex on one day of testing (out of two) and the lack of a dose response (effects only at the low dose), EPA concluded that there was no treatment-related effect on auditory startle reflex.

NRDC's objection here is denied. As a preliminary matter, EPA would note that it disagrees with NRDC's claim that historical control data can only be used for the narrow purpose of evaluating the fitness of a study's controls. (Refs. 12a, 12b, and 12c). This disagreement, however, is beside the point because for the boscalid DNT study EPA used historical control data in precisely the manner that NRDC argues they should be used. EPA's review of the DNT specifically found that "[h]istorical control data provided indicated that the mean startle amplitude on PND 24 for the current study of [boscalid] was similar to the control means of the submitted studies on PND 24. Therefore the analysis of this group's relation to treatment groups is valid and should be considered the primary source for analysis and evaluation." (Ref. 13 at 30). Finally, EPA's conclusion that the DNT study showed no treatment-related effect on auditory startle reflex was based upon a reasonable evaluation of the data, as demonstrated above.

b. *The sensitivity of DNT Study.* NRDC claims that the DNT study is an insensitive study because it involves examination of only one male and one female pup per litter and that therefore EPA should have attached more significance to the finding of increased sensitivity in the young in that study. NRDC also criticizes the statistical analysis of the DNT study for only including probability values ("p-values") representing confidence levels of 95 percent (p-value of 0.05) and 99 percent (p-value of 0.01). (Basically, a p-value defines the probability that an observed difference between a control group and a treatment group is based on

chance alone.). NRDC argues that rather than analyze the data against the p-values of 0.05 and 0.01, EPA should calculate the “actual p-value statistic,” and thus EPA could use its “expert judgment on the significance of the findings, given the limitations of the study.” (Ref. 1 at 5).

EPA believes that the significance attached to findings of sensitivity in a DNT study should be driven primarily by an evaluation of the results of the study itself. EPA would note that the development and design of the DNT study underwent an exhaustive independent scientific peer review as well as public comment process. (Ref. 14). This process included multiple reviews by EPA’s FIFRA Scientific Advisory Panel and public comment opportunities as well as a scientific workshop involving outside experts organized expressly to evaluate developmental neurotoxicity testing issues. (Id.). NRDC’s criticisms of use of reporting statistical significance at the 95 and 99 percent confidence levels are misplaced. Use of p-values of 0.01 and 0.05 to document statistically significant differences between treated and control animal groups is a long-established practice in the scientific community. (Refs. 15a, 15b, 15c, 15d, and 15e). EPA can calculate different levels of statistical confidence if for some reason the data suggest that may be valuable; however, in EPA’s judgment no such reasons were present in the circumstances of the boscalid DNT study.

c. *Weight-of-the-evidence evaluation of the two-generation reproduction study in rats.* NRDC argues that EPA undervalues the importance of increased sensitivity identified in the two generation reproduction study in rats based on nothing more than speculation. According to NRDC, EPA was just “guess[ing]” when it stated that: “The degree of concern is also low for the quantitative evidence of susceptibility seen in the 2-generation reproduction study in rats because the decreases in body weight and body weight gains were seen primarily in the [second] generation. These *may have been* due to exposure of the parental animals to high doses (above the Limit Dose).” (Ref. 9 at 2 (citing to 76 FR 76188) (emphasis added by NRDC)). NRDC also suggests that EPA’s “speculation” is “nonsensical” because if the second generation pups had effects due to high dose exposures of the parents, then these effects should have been seen in the first generation pups because their parents had the same high dose exposures.

In comments on NRDC’s objections, BASF argues that young animals are not more sensitive to boscalid than adult animals given that adult animals in the chronic/carcinogenicity study in the rat experienced adverse effects at similar dose levels as the pups in the two generation rat study. BASF makes the same contention with regard to the DNT study. (See Unit VII.A.2.d., below).

EPA does not believe that the sensitivity evidenced in the pups in the two-generation reproduction requires retention of the 10X children’s safety factor. As discussed in detail in Unit VII.A.2.f., the NOAEL from the chronic dog study used for the Point of Departure in setting the chronic RfD/PAD for the liver effects is protective of the body weight effects seen in the second generation male pups at mid and high doses in the two-generation reproduction study. EPA disagrees with NRDC that it was somehow improper to take into account that the body weight effects in the pups in the two-generation reproduction study were only seen in males and only in the second generation. These factors bear on significance of the effects seen. Effects seen in only one sex and only after dosing for two generations are generally regarded as less significant than effects seen in both sexes and in both generations of a two-generation study. Moreover, there is other evidence from the study suggesting that body weight effects in the young were not entitled to great weight in EPA’s weight-of-the-evidence analysis. First, absolute body weight and bodyweight gain of the male F<sub>2</sub> offspring of treated dams were similar to those of the offspring of the control dams at birth. Birth is a more sensitive time point to indicate susceptibility than subsequent time periods. (Refs. 16a, 16b, and 16c). Second, there was a lack of consistency in the observed body weight decreases (i.e., decreased on days 7 and 21 but not on days 4 and 17). (Ref. 17 at 20). EPA believes these factors are important to informing its expert judgment regarding the level of concern regarding, or the significance of, the increased sensitivity observed in this study. In any event, EPA’s determination that the chronic RfD/PAD is protective of the pup effects seen in the reproduction study is alone sufficient to allay any concerns regarding increased sensitivity and pre- and post-natal toxicity raised by the two-generation reproduction study.

NRDC places special emphasis on EPA’s suggestion that the body weight effect may be due to the very high dose given the maternal animals. EPA’s statement on this issue was in error because, as noted, the body weight

effects were seen at both the mid and high doses in the study in the second generation pups. Nonetheless, for the reasons described above, identification of a clear NOAEL for body weight effects and limited nature of the body weight effects (e.g., one sex only, inconsistent findings at the mid dose), EPA concludes that the chronic RfD/PAD based on a safety factor of 100X is safe for infants and children.

EPA does not agree that BASF has made an appropriate comparison of the results of the two-generation reproduction study and the chronic/carcinogenicity study given the substantial difference in time of exposure to boscalid in the two studies.

d. *Weight-of-the-evidence evaluation of the DNT Study.* NRDC argues that EPA errs in downplaying the significance of the decreased weight gain in pups seen in the DNT. NRDC states that EPA found there to be low concern for the decreases in pup body weight on post-natal days 1–4 because no effects on body weight were seen at any other time and the effects only occurred when the maternal animals were receiving an extremely high dose (above the Limit Dose) suggesting that pup effects were derivative of effects on the maternal animals. This reasoning is attacked by NRDC as mere speculation. NRDC claims that “the Agency does not and cannot assert that inadequate weight gain on days 1–4 is an insignificant adverse effect. Any significant reduction in weight gain during early development is potentially harmful and may cause permanent adverse effects.” (Ref. 9 at 3). Further, NRDC states that EPA has presented no empirical evidence to support its conclusion that the high dose to the maternal animals might have been the reason for the pup effect.

For similar reasons to those relied upon in rejecting NRDC’s arguments concerning the two-generation reproduction study, EPA does not believe that the sensitivity evidenced in the pups in the DNT study requires retention of the 10X children’s safety factor. As discussed in detail in Unit VII.A.2.f., the NOAEL from the chronic dog study used for the Point of Departure in setting the chronic RfD/PAD for the liver/thyroid effects is protective of the transient body weight effects seen in the pups at mid dose and the more severe pup body weight effects at the high dose in the DNT study. EPA disagrees with NRDC that it was somehow improper to take into account that the body weight effects in the mid-dose pups were transient in nature – i.e., statistically significant decreases in body weight were seen on post-natal



days 1–4 but the animals had recovered by day 11. The severity of an effect aids in evaluation of the dose response curve for a pesticide; in this case, it indicates that mid dose was not far from the actual no adverse effect level. In any event, EPA's determination that the chronic RfD/cPAD is protective of the pup effects seen in the DNT study is alone sufficient to allay any concerns regarding increased sensitivity and pre- and post-natal toxicity raised by the DNT study.

NRDC challenges EPA's reasoning that the effects on pups' body weight may be due to the maternal animals being exposed above the Limit Dose. The Limit Dose is regarded as the highest dose possible that can be given an animal without overwhelming its defense mechanisms. As a general matter, EPA does not believe NRDC's argument is well-founded because discounting the weight of effects seen only at or above the Limit Dose is a well-accepted scientific precept. Here, however, EPA erred by mentioning the Limit Dose because effects were present in the pups at the mid dose as well as at the dose that exceeded the Limit Dose. Nonetheless, for the reasons described above, identification of a clear NOAEL for body weight effects and limited nature of the body weight effects (e.g., one sex only, transient nature of effects at the mid dose), EPA concludes that the RfD/PAD based on a safety factor of 100X is safe for infants and children.

For the same reason as stated in Unit VII.A.2.c., EPA disagrees with BASF's comparison of the DNT study and the chronic/carcinogenicity study.

e. *Weight-of-the-evidence evaluation of the rabbit developmental study.* NRDC claims that EPA wrongfully disregards the qualitative evidence of increased sensitivity seen in the rabbit developmental study. According to NRDC, EPA expressed a low degree of concern for increased abortions or early delivery effects on the young because they were seen only at the Limit Dose and may have been caused by maternal stress. NRDC faults EPA for not providing empirical evidence to support this conclusion and argues that the Limit Dose might not be the maximum tolerated dose for boscalid in rabbits. This type of "speculation," NRDC claims, cannot meet the "reliable data" requirement for choosing a different children's safety factor.

NRDC's claims as to the rabbit developmental study, have even less merit than its arguments as to the two-generation reproduction and DNT studies. Not only is the chronic RfD/PAD for the thyroid effects protective of

the qualitative sensitivity seen in the rabbit developmental study but the chronic RfD/cPAD is protective by an order of magnitude of an effect seen only at a "limit dose." The chronic RfD/PAD is based on a NOAEL from the chronic dog study of 21.8 mg/kg/day as compared to the NOAEL for the fetal effects in the rabbit developmental study of 300 mg/kg/day. The fetal effects (abortions and early delivery) were seen only at the Limit Dose. (Unlike in the two-generation reproduction and DNT studies, adverse effects were only seen in the young at the high dose.) Moreover, the fetal effects were seen only in the presence of adverse effects in the maternal animals. The primary adverse effects in the maternal animals were abortions and early delivery (considered an adverse effect on both maternal animals and fetuses) but the study evidenced decreased food consumption and decreased body weight in the maternal animals as well. Although a definitive conclusion was not reached on whether the food consumption effects were treatment-related, evaluation of the individual animals showed that three of the four does that aborted or delivered early experienced dramatic reductions in food consumption. Given these results, it was reasonable for EPA to take into account its scientific expertise with rabbit toxicology studies which indicated that maternal animals put under stress had a tendency to abort or deliver early. Based on all of this evidence, EPA rejects NRDC's arguments concerning the rabbit developmental study and concludes that the qualitative sensitivity evidenced in the fetuses in the rabbit developmental study does not require retention of the 10X children's safety factor. (Refs. 18 and 19).

f. *Derivation of the chronic RfD/PAD.* NRDC claims that EPA erred in its selection of a NOAEL to calculate the chronic RfD/PAD by not relying on the lowest NOAEL from the applicable chronic studies. (Ref. 1 at 5–6). NRDC argues that, because EPA's justification for the RfD/PAD is allegedly nothing more than speculation, EPA lacks the reliable data necessary to remove the children's safety factor. (Ref. 9 at 4–5).

EPA relied on three co-critical studies in selecting a NOAEL for the chronic RfD/PAD: chronic toxicity in the rat, carcinogenicity in the rat, and chronic toxicity in the dog. Each of these studies showed liver effects and the rat studies also evidenced secondary effects on the thyroid. The NOAELs for the studies tightly bunched between 21.8 and 30 mg/kg/day. EPA selected the 21.8 mg/kg/day NOAEL from the chronic dog study to calculate the chronic RfD/PAD.

EPA considered but rejected lower NOAELs from three other studies: the 90-day subchronic toxicity study in the dog; the two-generation reproduction study in the rat; and the developmental neurotoxicity study. EPA's rationale for not using the NOAELs from these studies was that the lower NOAELs from these studies were an artifact of dose selection given the wide range between NOAEL and LOAEL in the studies and the minimal effects seen at the LOAEL.

NRDC challenges EPA's conclusion claiming that EPA has ignored "effects at significantly lower doses in juvenile animals (2-gen repro and DNT)." (Ref. 1 at 4). NRDC also argues that EPA's decision is speculative because (1) "EPA does not identify any reliable data to support its theory that a 10x differential between NOAELs and LOAELs – as occurred [with the three studies with lower NOAELs] – can never result from well designed and conducted studies;" and (2) "EPA offers no reliable data to support its assumption that the relationship between the LOAELs and NOAELs across studies with different designs and with different test species must always be the same . . ." (Ref. 9 at 4).

NRDC's arguments are without merit. First, NRDC is wrong to contend that EPA, in setting the chronic RfD/PAD, ignored "effects at significantly lower doses in juvenile animals" in the two-generation reproduction study and the DNT. EPA based the chronic RfD/PAD on the chronic dog study. In that study the lowest dose in which adverse effects were seen was 57.4 mg/kg/day. On the other hand, in the two-generation reproduction study and the DNT, the lowest doses at which adverse effects were seen were 101.2 mg/kg/day and 147 mg/kg/day, respectively. (Ref. 18 at 17). Second, EPA is not contending, nor does its analysis depend on, the supposition that a "10x differential between NOAELs and LOAELs . . . can never result from well designed and conducted studies." The differential between a study's NOAEL and LOAEL depends on the dose spacing in the study – studies with more and closely-spaced doses are likely to yield a lower differential than studies with fewer and widely-spaced doses. EPA is not arguing that it is inappropriate to design a study with a factor of 10 between doses. Third, EPA is not contending that the relationship between NOAELs and LOAELs across studies must always be the same. Rather, EPA concluded that the data for boscalid indicated that the NOAEL it selected as the Point of Departure for calculating the chronic

RfD/PAD would be protective of all effects.

In making this conclusion, EPA relied on several factors. First, EPA compared the NOAELs and LOAELs of the six chronic studies that had NOAELs that were relatively close. This exercise is appropriate because the NOAEL from any one study is, in part, an artifact of the dose selection process, and does not

identify the no adverse effect level just the level at which no effects were observed in the particular study. In animal testing, animals are generally dosed at three or four different levels. The dose levels are fairly widely spread (generally 2X – 10X) so that there is a good chance of identifying both a NOAEL and a LOAEL. The actual no adverse effect level or lowest adverse

effect level will be somewhere between the identified NOAEL and LOAEL. When multiple studies produce results in a similar range, they often can provide valuable information about where the true no adverse effect and lowest adverse effect levels are. The NOAELs and LOAELs for the six studies are presented in Table 1.

TABLE 1.—SELECTED CHRONIC AND SUBCHRONIC STUDIES FOR BOSCALID

Study	NOAEL male/female (m/f) in mg/kg/day	LOAEL m/f in mg/kg/day
Chronic toxicity in rats	21.9/30	110/150.3
Carcinogenicity in rats	23/29.7	116.1/155.6
Chronic toxicity in dogs	21.8/22.1	57.4/58.3
Subchronic toxicity in dogs	7.6	78.1
Two-generation reproduction study in rats	10.1/12.3 (offspring)	101.2/123.9 (offspring)
DNT in rats	14 (offspring)	147 (offspring)

Just based on the dose spread alone, the chronic dog study appears to provide valuable information because it has the tightest spread between NOAEL and LOAEL.

Second, EPA considered the effects seen in the studies. The NOAEL/LOAELs for the chronic rat, carcinogenicity rat, and chronic dog studies were all based primarily on effects on the liver and/or thyroid. The other three studies had NOAEL/LOAELs based on decreased body weight and decreased body weight gain. The first three studies also demonstrated body weight effects but at the same or higher doses than the organ effects. Organ effects are generally judged to be of more serious concern than systemic toxicity as shown through body weight effects. Given the heightened concern with the liver and thyroid effects and the fact that body weight effects only occurred at the same or higher doses, evaluation of the effects seen in the studies also supported reliance on the NOAEL from the chronic dog study.

Finally, EPA undertook a one-to-one comparison of the chronic dog study with the three studies that had a lower NOAEL. Given that the subchronic dog study was conducted in the same species as the chronic dog study and that the results of the subchronic dog study were fully consistent with the chronic dog study (i.e., based on the chronic dog study it would be expected that 7.6 mg/kg/day would be a NOAEL and 78.1 a LOAEL), the subchronic dog study supported reliance on the NOAEL from the chronic dog study. Further, the strength of the findings at the LOAEL in

the two-generation reproduction study and the DNT study, did not suggest that the actual no adverse effect level for the effects seen in these studies is far below the identified LOAEL. In the two-generation reproduction and DNT studies, the body weight effects at the LOAEL were either transient in nature (DNT study), not seen in both sexes (two-generation reproduction study), or not consistently seen post-natally (DNT and two-generation reproduction studies). (See Units VII.A.2.c., VII.A.2.d., and VII.A.2.e.)

Given the weight-of-the-evidence, EPA concludes it was reasonable to choose the NOAEL from the chronic dog study in calculating the chronic RfD/PAD. Contrary to NRDC's contention, this decision is not based on speculation but on careful consideration of the entire database – a complete database that provides reliable data on which to choose a safety factor that is protective of the safety of infants and children. In any event, EPA would note that selecting the NOAEL from the DNT study or the two-generation reproduction study would not change the safety conclusion on the boscalid tolerances even without any further refinement of the worst case exposure assumptions relied upon in the tolerance document. EPA estimated exposure was at 38 percent of the chronic RfD/PAD and a lowering of the chronic RfD/PAD by a factor of two due to reliance on the two-generation reproduction study (i.e. using a NOAEL of 10.1 mg/kg/day instead of 21.8 mg/kg/day) would still show worst case

exposure to be below the chronic RfD/PAD.

BASF, in its comments, presents a benchmark dose analysis of the DNT and two-generation reproduction studies in support of EPA's selection of 21.9 mg/kg/day as the Point of Departure. The benchmark dose calculated by BASF is supportive of EPA's decision in that all of the benchmark doses covering various endpoints in these two studies were higher than 21.8 mg/kg/day. Although BASF's description of the method it used for calculating these benchmark doses appears scientifically appropriate, BASF has not submitted supporting documentation for its calculation and EPA has not independently verified it.

3. *Conclusion on children's safety factor.* EPA disagrees both with NRDC's legal claim that a finding of sensitivity always requires retention of the children's safety factor and factual assertion that the particular evidence of increased sensitivity on boscalid requires such a result. NRDC's legal argument ignores the plain language of the statute. NRDC's factual argument fails to take into account the entire database.

EPA has a complete toxicity database for boscalid. The toxicity studies for boscalid show it generally to have low mammalian toxicity and the database reveals no reproductive or developmental concerns, including no developmental neurotoxic concerns. Data involving the testing of young animals did show increased quantitative sensitivity in the young with regard to body weight effects and qualitative

sensitivity in one developmental study. Clear NOAELs were identified for all of these effects. Moreover, the body weight effects at the LOAELs in these studies were either transient or inconsistent and qualitative sensitivity occurred at the Limit Dose in the presence of maternal toxicity. EPA reasonably concluded that using the NOAEL from the chronic dog study was protective of all of the effects seen in the developmental and reproduction studies. That the chronic dog study only involved the testing of adult dogs does not raise concerns for the young because, as noted, EPA found the NOAEL from that study to be protective of the effects seen in all studies with the young, and the effects of concern in the dog study, increased liver weights and hepatic enzyme induction, are not common developmental concerns. In any event, when rats were exposed to boscalid pre- and post-natally as well as into adulthood in the two generation reproduction study, increased liver weights were only seen at the Limit Dose. Thus, increased sensitivity to liver effects in the young is not a concern. Finally, EPA has conservatively estimated human exposure to boscalid, relying on worst case exposures in food (assuming all registered crops contain residues at the tolerance level), and conservative models as well as pesticide-specific data in estimating exposure from residues in drinking water and from residential uses. Based on consideration of all of these data, EPA reasonably concluded it had reliable data showing that infants and children would be safe without application of an additional 10X safety factor.

#### *B. NRDC's Claim That EPA's Decision is Arbitrary and Capricious*

NRDC argues that EPA's tolerance decision on boscalid was arbitrary and capricious because (1) EPA failed to adequately explain its safety factor decision; and (2) "[t]he NOAELs and cPAD established by EPA for boscalid are clearly contrary to the data . . ." (Ref. 1 at 7-8). In the section of its objections addressing this claim, NRDC provides nothing in support of its assertion that EPA provided insufficient explanation for its children's safety factor determination. Presumably, NRDC is referring to the aspects of the children's safety factor determination challenged in an earlier portion of its objections and addressed by EPA in Unit VII.A. of this order. Thus, EPA relies on Unit VII.A. as responsive to NRDC's arbitrary and capricious claim as to the children's safety factor decision, and denies the objection for

the reasons there stated. Similarly, to the extent NRDC is arguing that EPA's selection of a NOAEL in the DNT study or its selection of the NOAEL from the chronic dog study as the Point of Departure for deriving the chronic RfD/PAD were arbitrary and capricious, EPA denies this objection for the reasons contained in Units VII.A.2.a. and VII.A.2.f.

#### **VIII. 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.

#### **IX. Submission to Congress and the Comptroller General**

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

#### **X. References**

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3. U.S. EPA, "Residue Chemistry Test Guidelines: OPPTS 860.1500 Crop Field Trials" (August 1996).
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5. Office of Pesticide Programs, U.S. EPA, "Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment" (January 31, 2002).
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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 Yan Donovan to Dennis McNeilly/R.Keigwin, "PP#

1F06313 —Human Health Risk Assessment for New Fungicide BAS 510 F (Common Name: Boscalid) — Proposal for Tolerances for Residues in/on Numerous Crops and Livestock Commodities" (September 8, 2003).

9. NRDC, "Objection to the Establishment of Tolerances for Pesticide Chemical Residues of Boscalid" (May 21, 2007).

10. BASF, "Docket ID Number EPA-HQ-OPP-2005-0145: BASF Response to NRDC Objection to Boscalid Pesticide Tolerances" (May 29, 2007).

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12c. J.K. Haseman. 1995. "Data Analysis: Statistical Analysis and Use of Historical Control Data." *Regulatory Toxicology and Pharmacology*, Vol. 21, pages 52-59.

13. Health Effects Division, Office of Pesticide Programs, US EPA, "Data Evaluation Record: Developmental Neurotoxicity Study - Rat; BAS 910 F" (Date) (EPA Reviewer: William F. Sette).

14. U.S. EPA, "Response to Petition to Compel the U.S. EPA to Repeal Its Test Guidelines for Developmental Neurotoxicity" (January 3, 2005) (available at "<http://docket.epa.gov/edkpub/do/EDKStaffCollectionDetailView?objectId=0b0007d480525f44>").

15a. H.L. Adler and E. B. Roessler 1977. "Introduction to Probability and Statistics." 6th ed. H. Freeman. New York. 1977.

15b. S. Gad and C.S. Weil. "Statistics and Experimental Design for the Toxicologist." Telford Press, NJ. 1986.

15c. M. Hollander and D.A. Wolfe. "Non parametric Statistical Methods." John Wiley & Sons. New York. 1973.

15d. R.R. Holson et al., 2007. "Statistical Issues and Techniques Appropriate for Developmental Neurotoxicity Testing." *Neurotoxicology and Teratology*.

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16a. U.S. Environmental Protection Agency. "Guidelines for Reproductive

Toxicity Risk Assessment.” **Federal Register** 61: 56274–56322.

16b. U.S. Environmental Protection Agency. “Guidelines for Developmental Toxicity Risk Assessment.” **Federal Register**. 56: 63798–63826.

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18. Office of Prevention, Pesticides and Toxic Substances, U. S. EPA, Memorandum from Alan Levy to Yan Donovan, “BAS 510 F - Report of the Hazard Identification Assessment Review Committee” (March 7, 2003).

19. Health Effects Division, Office of Pesticide Programs, US EPA, “Data Evaluation Record: Prenatal Developmental Toxicity Study – Rabbit; BAS 910 F” (March 23, 2002) (EPA Reviewer: Alan Levy).

#### List of Subjects in 40 CFR Part 180

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

Dated: January 17, 2008.

**Debra Edwards,**

*Director, Office of Pesticide Programs.*

[FR Doc. E8–1523 Filed 1–29–08; 8:45 am]

BILLING CODE 6560–50–S

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 180

[EPA–HQ–OPP–2006–0481; FRL–8341–6]

#### Fluopicolide; Pesticide Tolerance

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final rule.

**SUMMARY:** This regulation establishes a tolerance for residues of fluopicolide, 2,6-dichloro-N-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl]benzamide, as an indicator of combined residues of fluopicolide and its metabolite, 2,6-dichlorobenzamide (BAM), in or on grape at 2.0 parts per million (ppm); grape, raisin at 6.0 ppm; vegetable,

cucurbit, group 9 at 0.50 ppm; vegetable, fruiting, group 8 at 1.6 ppm; vegetable, leafy, except brassica, group 4 at 25 ppm; and vegetable, tuberous and corm, subgroup, except potato, 1D at 0.02 ppm. Valent U.S.A. Corporation requested this tolerance under the Federal Food, Drug, and Cosmetic Act (FFDCA).

**DATES:** This regulation is effective January 30, 2008. Objections and requests for hearings must be received on or before March 31, 2008, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

**ADDRESSES:** EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2006–0481. To access the electronic docket, go to <http://www.regulations.gov>, select “Advanced Search,” then “Docket Search.” Insert the docket ID number where indicated and select the “Submit” button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic docket at <http://www.regulations.gov>, or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

#### FOR FURTHER INFORMATION CONTACT:

Janet Whitehurst, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 305–6129; e-mail address: [whitehurst.janet@epa.gov](mailto:whitehurst.janet@epa.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. General Information

###### A. Does this Action Apply to Me?

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

pesticide manufacturer. Potentially affected entities may include, but are not limited to those engaged in the following activities:

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

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

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

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

###### C. Can I File an Objection or Hearing Request?

Under section 408(g) of FFDCA, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA–HQ–OPP–2006–0481 in the subject line on the first page of your submission. All requests must be in writing, and must be mailed or delivered to the Hearing Clerk