ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[OPP–2005–0190; FRL–7727–4]

Order Denying Objections to Issuance of Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final Order.

SUMMARY: On four occasions in the first half of 2002, the Natural Resources Defense Council (NRDC) and various other parties filed objections with EPA to final rules under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), (21 U.S.C. 346a), establishing pesticide tolerances for various pesticides. The objections apply to 14 pesticides and 112 separate pesticide tolerances. Although the objections raise numerous pesticide–specific issues, they all focus on the potential risks that the pesticides pose to farm children. This Order responds to NRDC's objections as to all of the challenged tolerances with the exception of the objections pertaining to the imidacloprid tolerance on blueberries which were previously denied. The objections to the other tolerances are denied for the reasons stated herein.

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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) and the following additional parties: Boston Women's Health Book Collective, Breast Cancer Action, Californians for Pesticide Reform, Commonweal, Lymphoma Foundation of America, Natural Resources Defense

Council, Northwest Coalition for Alternatives to Pesticides, Pesticide Action Network, North America, Pineros y Campesinos Unidos del Noroeste, SF-Bay Area Chapter of Physicians for Social Responsibility, and Women's Cancer Resource Center. 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:

- Industry, e.g., NAICS 111, 112, 311, 32532, Crop production, Animal production, Food manufacturing, Pesticide manufacturing.

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?

1. *Docket*. EPA has established an official public docket for this action under docket identification (ID) number OPP–2005–0190. The official public docket consists of the documents specifically referenced in this action, any public comments received, and other information related to this action. Although a part of the official docket, the public docket does not include Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. The official public docket is the collection of materials that is available for public viewing at the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1801 S. Bell St., Arlington, VA. This 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.

2. *Electronic access*. You may access this **Federal Register** document electronically through the EPA Internet under the **''Federal Register''** listings at *http://www.epa.gov/fedrgstr/*.

An electronic version of the public docket is available through EPA's electronic public docket and comment system, EPA Dockets. You may use EPA Dockets at *http://www.epa.gov/edocket/* to view public comments, access the index listing of the contents of the official public docket, and to access those documents in the public docket that are available electronically. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B.1. Once in the system, select ''search,'' then key in the appropriate docket ID number.

II. Introduction

A. What Action Is the Agency Taking?

On four occasions in the first half of 2002, the NRDC and various other parties filed objections with EPA to final rules under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), (21 U.S.C. 346a), establishing pesticide tolerances for various pesticides. [The objectors are hereinafter collectively referred to as ''NRDC.'']. The objections apply to 14 pesticides and 112 separate pesticide tolerances. This Order responds to objections as to all of the tolerances other than the objections as to the imidacloprid tolerance on blueberries. Those objections were denied previously. (69 FR 30042, May 26, 2004).

Although the objections raise numerous pesticide-specific issues, they all primarily focus on the potential risks that the pesticides pose to farm children. Further, each of the objections makes two main assertions with regard to the pesticide tolerances in question: (1) That EPA has not properly applied the additional 10X safety factor for the protection of infants and children in section 408(b)(2)(C); and (2) that EPA has not accurately assessed the aggregate exposure of farm children to pesticide residues. NRDC did not exercise the option provided in section 408(g)(2) to request a hearing on its objections, but instead asked that the Agency rule on its objections on the basis of its written objections and attached submissions.

Because the objections raised questions of broad interest, EPA published a representative copy of the objections in the **Federal Register** for comment, (67 FR 41628, June 19, 2002), and made all of the objections available for public review on its website. On May 26, 2004, EPA denied the objections as to one of the challenged tolerances (imidacloprid on blueberries) because that tolerance had expired. (69 FR 30042, May 26, 2004). At the same time EPA denied the objections to the imidacloprid tolerance on mootness grounds, EPA also established a new imidacloprid blueberry tolerance and as part of that action addressed the issues raised by the NRDC objections. (69 FR 30076, May 26, 2004). In the course of addressing these issues, EPA responded to a petition concerning farm children filed in 1998 by NRDC and various other parties. (69 FR at 30069–70, May 26, 2004). This Order relies heavily on much of the reasoning set forth in connection with the establishment of the new imidacloprid blueberry tolerance.

The body of this document contains the following sections. First, there is a background section which explains the applicable statutory and regulatory provisions, the relevant EPA science policy documents, and prior NRDC actions with regard to farm children. Second, EPA describes the objected-to tolerance actions. 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 announces its response to the objections and responds to public comments.

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)). 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. Assessing Risk Under the FFDCA

In assessing and quantifying non-cancer risks posed by pesticides under the FFDCA as amended by the FQPA, EPA first determines the toxicological level of concern and then compares 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 the lowest dose at which no adverse effects from the pesticide are seen in relevant studies (the margin of exposure (MOE) approach). How EPA determines the level of concern, chooses safety factors, and assesses risk under these two approaches is explained in more detail below. EPA's general approach to estimating exposure is also briefly discussed.

For dietary risk assessment (for risks other than cancer), the dose at which no adverse effects are observed (the ''NOAEL'') from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern. However, the lowest dose at which adverse effects of concern are identified (the ''LOAEL'') is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. A safety or uncertainty factor is then applied to this toxicological level of concern to calculate a safe dose for humans, usually referred to by EPA as an acute or chronic reference dose (RfD). The RfD is equal to the NOAEL divided by all applicable safety or uncertainty factors. Typically, a safety or uncertainty factor of 100X 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, under the FQPA, an additional safety factor of 10X is presumptively applied to protect infants and children, unless reliable data support selection of a different factor. To quantitatively describe risk using the RfD approach, estimated exposure is expressed as a percentage of the RfD. Dietary exposures lower than 100 percent of the RfD are generally not of concern.

For non-dietary, and combined dietary and non-dietary, risk assessments (other than cancer risk assessments) the same safety factors are used to determine the toxicological level of concern. For example, when 1,000X is the appropriate safety factor (10X to account for interspecies differences, 10X for intraspecies differences, and 10X for FQPA), the level of concern is that there be a 1,000–fold margin between the NOAEL from the toxicology study identified as appropriate for use in risk assessment and human exposure. To estimate risk, a ratio of the NOAEL to aggregate exposures (margin of exposure (MOE) = NOAEL/exposure) is calculated and compared to the level of concern. In contrast to the RfD approach, the higher the MOE, the safer the pesticide. Accordingly, if the level of concern for a pesticide is 1,000, MOE's exceeding 1,000 would generally not be of concern.

For cancer risk assessments, EPA generally assumes that any amount of exposure will lead to some degree of cancer risk. Using a model based on the slope of the cancer dose-response curve in relevant studies, EPA estimates risk in terms of the probability of occurrence of additional cancer cases as a result of exposure to the pesticide. An example of how such a probability risk is expressed would be to describe the risk as one in one hundred thousand (1×10^{-5}), one in a million (1×10^{-6}), or one in ten million (1×10^{-7}). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. No further discussion of cancer risk assessment is included here because NRDC's objections do not relate to cancer risks.

Equally important to the risk assessment process as determining the toxicological level of concern is estimating human exposure. As explained in more detail in Unit VII.D.5. of this document, EPA uses a tiering system to estimate exposure which attempts to minimize resources expended in exposure estimates. The first tier is generally a worst case assessment that is relatively easy to conduct because it relies on conservative (health-protective) assumptions. Only if that tier suggests

that the pesticide may pose a risk of concern are more resource-intensive tiers triggered where the focus is on obtaining more realistic exposure values. (Ref. 1).

C. Science Policies

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. Of particular interest to the NRDC objections are the science policies covering the children's safety factor, aggregate pesticide exposure, and the population percentile of exposure used in estimating aggregate exposure.

1. *Children's safety factor policy.* On January 31, 2002, EPA released its science policy guidance on the children's safety factor. (Ref. 2) [This policy is hereinafter referred to as the ''Children's Safety Factor Policy'']. That policy had undergone an intensive and extended process of public comment as well as internal and external science peer review. An EPA-wide task force was established to consider the children's safety factor in March 1998. Taking into account reports issued by the task force on both toxicity and exposure issues, EPA's Office of Pesticide Programs (OPP) released a draft children's safety policy document in May 1999. That document was subject to an extended public comment period as well as review by the FIFRA Scientific Advisory Panel. (Id. at 5). Although the January 31, 2002 policy differed in some respects from prior Agency practice, for the most part the policy statement reflected EPA's experience in implementing the children's safety factor provision since the passage of the FQPA.

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, EPA 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, EPA indicates a preference for making an individualized determination of a protective safety factor if possible. (Id. at 11). EPA 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.). EPA 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.). Concluding that individualized assessments would be able to be made in most cases, EPA indicates that ''this guidance document focuses primarily on the considerations relevant to determining a safety factor 'different' from the default 10X that protects infants and children. Discussions in this document of the appropriateness, adequacy, need for, or size of an additional safety factor are premised on the fact that reliable data exist for choosing a 'different' factor than the 10X default value.'' (Id. at 12).

In making such individual assessments regarding the magnitude of the safety factor, EPA 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, EPA 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). EPA indicates that the principal inquiry concerning missing data would center on whether the missing data would significantly affect calculation of a safe exposure level (commonly referred to as the RfD). (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, EPA indicates 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. 2 at 23). Finally, with regard to the DNT study, EPA lists several important factors addressing the weight of evidence bearing on the degree of concern when such a study has been required but has not yet been completed. (Id. at 24). Moreover, EPA reiterates that, like any other missing study, the absence of the DNT study does not trigger a mandatory requirement to retain the default 10X value, but rather requires an individualized assessment centering on the question of whether ''a DNT study is likely to identify a new hazard or effects at lower dose levels of the pesticide that could significantly change the outcome of its risk assessment . . .'' (Id.). The extent to which the policy stresses the need for EPA's evaluation of the completeness of the database to focus directly on whether missing data might possibly lower an existing RfD was a change in emphasis from past actions.

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, EPA emphasizes that the analysis should focus on whether any identified pre- or post-natal toxicity raises uncertainty as to whether the RfD 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, EPA stresses the importance of evaluating all of the data under a weight-of-evidence approach focusing on the safety of infants and children. (Id.). This attention on the overall database also indicated a shift in emphasis for EPA's implementation of the children's safety factor provision as previous decisions had often treated a finding of increased sensitivity in the young as almost necessitating some additional safety factor.

In evaluating the completeness of the exposure database, EPA 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).

Given that this policy was released at roughly the same time the challenged tolerance actions were issued and that the toxicological, exposure, and risk assessments leading up to such actions can take several months or even years, the challenged tolerance actions were not evaluated prior to being finalized under this new restatement of EPA's policy on the children's safety factor. EPA's experience in making decisions under the 2002 policy is that while for many pesticides the safety factor determination remains unchanged, for others the safety factors may go up or down. To generalize, in situations where the database is incomplete, EPA's heightened emphasis on whether the missing data may affect the assessment of risk has tended to make it more likely that EPA will retain the full 10X children's safety factor. (See, e.g., 70 FR 7876, 7882, February 16, 2005) (avermectin - 10X factor retained due to lack of DNT study and acute and subchronic neuorotoxicity studies and residual toxicological concerns as to safety of young); 70 FR 7886, 7891, February 16, 2005) (clothianidim - 10X factor retained due to lack of developmental immunotoxicity study); 69 FR 58058, 58062–58063, September 29, 2004) (fenamidone - 10X factor retained due to lack of DNT study); but see 69 FR 52182, 52187, August 25, 2004) (folpet - 10X removed despite lack of DNT study because the DNT study is unlikely to change RfD)). On the other hand, in instances where a study shows increased sensitivity in the young, the focus on whether in the context of the overall database such sensitivity indicates that EPA's risk assessment is not protective of infants and children, has frequently resulted in the removal of the factor. (See, e.g., 69 FR 63083, 63092–63093, October 29, 2004) (pyraclostrobin - 10X factor removed because additional sensitivity well-characterized); 69 FR 58290, 58295, September 30, 2004) (cyazofamid - 10X factor removed because additional sensitivity well-characterized); but see 69 FR 62602, 62610, October 27, 2004) (deltamethrin - 10X factor lowered but not removed taking into consideration level at which additional sensitivity was observed)). As these decisions evidence, the determination on the children's safety factor is heavily dependent on the results from the studies specific to the pesticide in question. (See, e.g., 70 FR 14535, 14541–14542, March 23, 2005) (dinotefuran - 10X factor retained as to some risk assessments due to the lack of a developmental immunotoxicity study; no additional factor on any risk assessment found necessary to address lack of a DNT study)).

2. *Aggregate exposure policies.* As mentioned above, the FQPA-added safety standard directs that the safety of pesticide residues in food be based on ''aggregate exposure'' to the pesticide. (21 U.S.C. 346a(b)(2)(A)(ii)). Aggregate exposure to a pesticide includes all ''anticipated dietary exposure and all other exposures for which there is reliable information.'' (Id.). The statute makes clear that in assessing aggregate exposure pertaining to a pesticide EPA must consider not only exposure to the pesticide in the food covered by the tolerance in question but exposure to the pesticide as a result of other tolerances and from ''other non-occupational sources.'' (Id. 346a(b)(2)(D)(vi)). Further, the statute directs EPA to consider aggregate exposure to other substances related to the pesticide so long as that exposure results from a non-occupational source. (Id. 346a(b)(2)(D)(vi)). In November 2001, EPA released a science guidance document entitled ''General Principles for Performing Aggregate Exposure and Risk Assessments.'' This document deals primarily with the complex subject of integrating distributional and probabilistic techniques into aggregate exposure analyses. (Ref. 3).

More relevant to the current objections is the science guidance document issued in March 2000 addressing the population percentile of exposure used in making acute exposure estimates for applying the safety standard under section 408. (Ref. 4) [hereinafter referred to as ''Percentile Policy'']. Traditionally, EPA had used the 95th percentile of human exposure in acute dietary exposure assessments as representing a reasonable worst case scenario. (Id. at 15). Due to the very conservative (health-protective) assumptions used for acute exposure assessments, the 95th percentile was viewed as a reasonable approximation of an exposure level not likely to be exceeded by any individuals. (Id. at 15–17). For these assessments EPA generally assumed that all crops for which there is a tolerance are treated with the pesticide and all treated crops have residues at the highest level legally permitted.

More recently, because of the availability of better data on residue values and new risk assessment techniques, EPA has restructured its approach to the use of population exposure percentiles in making safety determinations for acute risks under section 408. EPA has retained the 95th percentile as the starting point of analysis for worst case (tolerance level) assessments. EPA, however, generally uses higher percentiles of exposure when less conservative assumptions are made concerning residue values. (Id.). For example, beginning in the late 1990's, EPA has increasingly relied upon probabilistic assessment techniques for assessing acute dietary exposure and risk. Because EPA generally uses much more realistic exposure values (e.g., monitoring data on pesticide levels in food) in conducting probabilistic assessments, a higher population exposure percentile was generally found to be necessary to ensure that exposure for the overall population was not understated. The Percentile Policy explains and defends EPA's choice of the 99.9th percentile as a starting point for evaluating exposure and acute risk with probabilistic assessments.

EPA confirms in the Percentile Policy document that it will generally continue to use the 95th percentile of exposure for non-probabilistic, or what has been referred to as ''deterministic'' acute risk assessments that use worst case exposure assumptions.'' (Id. at 17, 29). The conservative (health-protective) nature of this approach is confirmed by data EPA cites showing that deterministic assessments of exposure at the 95th percentile assuming residues at tolerance levels regularly result in exposure predictions significantly higher than probabilistic exposure estimates of the 99.9th percentile using monitoring data. (Id. at 16–17).

Importantly, EPA's Percentile Policy makes clear that in choosing a population percentile to estimate exposure, EPA is not intending to define the portion of the population that is to be protected. The policy explicitly states that: ''OPP's goal is to regulate pesticides in such a manner that everyone is reasonably certain to experience no harm as a result of dietary and other non-occupational exposures to pesticides.'' (Id. at 28).

D. NRDC Farmworker Children Petition

On October 22, 1998, NRDC and 58 other public interest organizations and individuals submitted a petition to EPA asking that EPA ''find that farm children are a major identifiable subgroup and must be protected under FQPA when setting allowable levels of pesticide residue in food.'' (Ref. 5) [hereinafter referred to as the ''Farm Children Petition'']. The Farm Children Petition claims that ''[a]n increasing body of scientific evidence, including biomonitoring data and residential exposure studies, indicates that farm children face particularly significant

exposures and health risks from pesticides.'' (Id. at 3). In addition to requesting the ''major identifiable subgroup'' designation, the Petition also asked that EPA use the children's safety factor to protect farm children, require additional exposure data on farm children exposure and not issue any new tolerances until such data are available, deny registration for any pesticide without a validated method for detecting residues in food, increase research into issues concerning farm children exposure to pesticides, and honor the President's Executive Order on Environmental Justice.

EPA responded to the Farm Children Petition in the Imidacloprid Order. EPA declined to name farm children as a separate major, identifiable subgroup pointing out that any pesticide exposures to children as a result of proximity to agricultural fields can be fully taken into account as part of the consideration of EPA's already existing major identifiable subgroups of children. (69 FR 30069, May 26, 2004). EPA agreed with most of the other aspects of NRDC's petition. (69 FR 30076–30077, May 26, 2004).

IV. The Challenged Tolerance Decisions

Table 1 lists the tolerance actions challenged by NRDC. The tolerance actions are grouped as they were by NRDC in NRDC's four sets of objections.

TABLE 1.—CHALLENGED TOLERANCE ACTIONS

Pesticides Involved	FR Citations (respectively)
halosulfuron-methyl, pymetrozine	66 FR 66333, December 26, 2001; 66 FR 66778, December 27, 2002; 66 FR 66786, December 27, 2001
imidacloprid, mepiquat, bifenazate, zeta-cypermethrin, diflubenzuron	67 FR 2580, January 18, 2002; 67 FR 3113, January, 23, 2002; 67 FR 4913, February 1, 2002; 67 FR 6422, February 12, 2002; 67 FR 7085, February 15, 2002
2,4-D	67 FR 10622, March 8, 2002
isoxadifen-ethyl, acetamiprid, propiconazole, furilazole, fenhexamid, fluazinam	67 FR 12875, March 20, 2002; 67 FR 14649, March 27, 2002; 67 FR 14866, March 28, 2002; 67 FR 15727, April 3, 2002; 67 FR 19114, April 18, 2002; 67 FR 19120, April 18, 2002

Each of these tolerance actions, except imidacloprid, is summarized briefly below.

1. *Halosulfuron-methyl*. NRDC challenged two separate tolerance actions on halosulfuron-methyl: (1) A December 26, 2001 action establishing tolerances on the melon subgroup; (66 FR 66333, December 26, 2001), and (2) a December 27, 2001 action establishing time-limited tolerances in connection with an emergency exemption under FIFRA on asparagus, (66 FR 66778, December 27, 2002). The risk assessments for both actions yielded similar results. Given halosulfuron-methyl's exposure pattern and toxicological characteristics, EPA determined that halosulfuron-methyl potentially presented acute, chronic, short-term, and intermediate-term risks and EPA quantitatively assessed these risks in making its safety determination. (66 FR 66336–66339; 66 FR 66783–66784). All of these risks were found to be below the Agency's level of concern. (Id.). Although a DNT study was outstanding, EPA determined that the additional 10X children's safety factor was not needed to protect infants and children because the toxicological data showed no evidence of greater sensitivity to the young and indicated that the DNT study was unlikely to affect the risk assessment. EPA explained the latter conclusion by noting that:

(a) The alterations in the fetal nervous system occurred in only one species (in rats and not in rabbits); (b) the fetal effects which will be investigated in the required developmental neurotoxicity study were seen only at a dose of 750 mg/kg/day which is close to the Limit-Dose (1,000 mg/kg/day); (c) there was no evidence of clinical signs of neurotoxicity, brain weight changes, or neuropathology in the subchronic or chronic studies in rats; (d) the developmental neurotoxicity study is required only as confirmatory data to understand what the effect is at a high exposure (dose) level. (66 FR at 66782).

2. *Pymetrozine*. NRDC challenged a December 27, 2001 action establishing tolerances for pymetrozine on cotton seed, cotton gin byproducts, the fruiting vegetables crop group, the cucurbit vegetables crop group, the leafy vegetables crop group (except Brassica), head and stem Brassica, leafy Brassica, turnip greens, dried hops, and pecans. (66 FR 66786, December 27, 2001). Given pymetrozine's exposure pattern and toxicological characteristics, EPA determined that pymetrozine potentially presented acute, chronic, short-term, and cancer risks and EPA quantitatively assessed these risks in making its safety determination. (66 FR at 66791–66792). All of these risks were found to be below the Agency's level of concern. (Id.). Although a DNT study was outstanding, EPA determined that the additional 10X children's safety factor could generally be reduced to 3X because the toxicological data showed no evidence of greater sensitivity to the young and there was no evidence of abnormalities in the development of the fetal nervous system. (64 FR 52438, 52444, September 29, 1999). Because the endpoint used for assessing acute dietary and short-term risk for the general population, including infants and children, was based on a LOAEL a second 3X safety factor was used for these risk assessments. (Id.).

3. *Mepiquat*. NRDC challenged a January 23, 2002 action establishing tolerances for mepiquat on cotton gin byproducts and meat byproducts of cattle, goats, hogs, horses and sheep. (67 FR 3113, January, 23, 2002). Given mepiquat's exposure pattern and toxicological characteristics, EPA determined that mepiquat potentially presented acute and chronic risks and EPA quantitatively assessed these risks in making its safety determination. (67 FR at 3116). All of these risks were found to be below the Agency's level of concern. (Id.). Although a DNT study was outstanding, EPA determined that the additional 10X children's safety factor was not needed to protect infants and children because the toxicological data showed no evidence of greater sensitivity to the young and the evidence signaling a need for a DNT study did not show ''some special concern for the developing fetuses or young'' such as ''neuropathy in adult animals; [central nervous system] malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring.'' (65 FR 1790, 1794, January 12, 2000)).

4. *Bifenazate*. NRDC challenged a February 1, 2002 action establishing tolerances for bifenazate on wet apple pomace, undelinted cotton seed, cotton gin byproducts, the pome fruit crop group, grapes, raisins, dried hops, nectarines, peaches, plums, strawberries and the fat of cattle, goats, hogs, horses, and sheep. (67 FR 4913, February 1, 2002). Given bifenazate's exposure pattern and toxicological characteristics, EPA determined that bifenazate potentially presented a chronic risk and EPA quantitatively assessed this risk in making its safety determination. (67 FR at 4919). As assessed, chronic risk was below the Agency's level of concern. (Id.). Because there was no outstanding toxicity data, the existing toxicity data showed no evidence of increased sensitivity of the young, and exposure data were deemed unlikely to understate exposure, EPA determined that it was safe for infants and children to remove the children's safety factor. (67 FR at 4918–4919).

5. *Zeta-cypermethrin*. NRDC challenged a February 12, 2002 action establishing tolerances for zeta-cypermethrin on the podded legume vegetable crop group; the succulent, shelled peas and beans crop group; dried shelled peas and beans crop group; soybeans; the fruiting vegetables crop group; grain sorghum; sorghum stover; sorghum forage; wheat grain; wheat forage; wheat hay; wheat straw; aspirated grain fractions; and meat of cattle, goats, hogs, horses and sheep. (67 FR 6422, February 12, 2002). Given zeta-cypermethrin's exposure pattern (including the exposure pattern of a toxicologically similar pesticide, cypermethrin) and toxicological characteristics, EPA determined that zeta-cypermethrin potentially presented acute, chronic, short-term, intermediate-term, and cancer risks and EPA quantitatively assessed these risks in making its safety determination. (67 FR at 6426–6429). All of these risks were found to be below the Agency's level of concern. (Id.). Although a DNT study was outstanding, EPA determined that the additional 10X children's safety factor was not needed to protect infants and children because the toxicological data showed no evidence of greater sensitivity to the young and the evidence signaling a need for a DNT study did not show ''some special concern for the developing fetuses or young'' such as ''neuropathy in adult animals; [central nervous system] malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring.'' (Id. at 6426).

6. *Diflubenzuron*. NRDC challenged a February 15, 2002 action establishing a tolerance for diflubenzuron on pears. (67 FR 7085, February 15, 2002). Given diflubenzuron's exposure pattern and toxicological characteristics, EPA determined that diflubenzuron potentially presented a chronic risk and EPA quantitatively assessed this risk in making its safety determination. (Id. at 7089–7090). As assessed, chronic risk was below the Agency's level of concern. (Id.). EPA determined that the additional 10X children's safety factor was not needed to protect infants and children because the toxicological data showed no evidence of greater sensitivity to the young, there was no missing toxicological data, and the exposure assessments were unlikely to understate exposure. (Id. at 7089).

7. *2,4-D*. NRDC challenged a March 8, 2002, action establishing a time-limited tolerance for 2,4-D on soybeans. (67 FR 10622, March 8, 2002). Given 2,4-D's exposure pattern and toxicological characteristics, EPA determined that 2,4-D potentially presented acute, chronic, and short-term risks and EPA quantitatively assessed these risks in making its safety determination. (Id. at 10628–10629). All of these risks were found to be below the Agency's level of concern. (Id.). Although a DNT study was outstanding, EPA determined that the additional 10X children's safety factor could be reduced because the toxicological data showed no evidence of greater sensitivity to the young and all other required toxicological data was complete. (Id. at 10627–10628). A factor of 3X was retained because the DNT study was triggered based on a finding of neuropathology (retinal degeneration) and was applied to all population subgroups for all durations of exposure.

8. *Isoxadifen-ethyl*. NRDC challenged a March 20, 2002, action establishing tolerances for isoxadifen-ethyl on corn commodities. (67 FR 12875, March 20, 2002). Given isoxadifen-ethyl's exposure pattern and toxicological characteristics, EPA determined that isoxadifen-ethyl potentially presented acute and chronic risks and EPA quantitatively assessed these risks in making its safety determination. (Id. at 12876-12877; 66 FR 33179, 33184–33185, June 21, 2001). All of these risks were found to be below the Agency's level of concern. (Id.). Although the data showed evidence of increased pre-natal sensitivity, EPA determined that the additional 10X children's safety factor could be reduced to 3X because the toxicological data were complete (i.e., there were no outstanding studies such as a DNT study). (Id. at 33184). This additional factor was applied to the acute dietary risk assessment for females aged 13–50 because the increased sensitivity resulted from *in utero* exposure. (Id.).

9. *Acetamiprid*. NRDC challenged a March 27, 2002, action establishing tolerances for acetamiprid on dried citrus pulp, the citrus fruit crop group, cotton gin byproducts, cotton undelinted seed, grapes, the fruiting vegetable crop group, the leafy brassica vegetable crop group, the leafy vegetable crop group, the pome fruit group, tomato paste, as well as various animal products. (67 FR 14649, March 27, 2002). Given acetamiprid 's exposure pattern and toxicological characteristics, EPA determined that acetamiprid potentially presented acute, chronic, short-term, and intermediate-term risks and EPA quantitatively assessed these risks in making its safety determination. (Id. at 14656–14657). All of these risks were found to be below the Agency's level of concern. (Id.). Although the data showed qualitative evidence of increased pre-natal sensitivity and a DNT study was outstanding, EPA determined that the additional 10X children's safety factor could be reduced to 3X because two of the three toxicological studies bearing on effects on the young showed no increased sensitivity in the young, the evidence of increased sensitivity was only qualitative and not quantitative, and the DNT study was not requested based on evidence indicating a special concern for developing fetuses or the young. (Id. at 14656). This additional factor was applied for all population subgroups for all exposures other than acute dietary exposure because the increased sensitivity resulted from chronic exposure. (Id.).

10. *Propiconazole*. NRDC challenged a March 28, 2002, action re-establishing a time-limited tolerance for propiconazole on blueberries in connection with an emergency exemption under FIFRA. (67 FR 14866, March 28, 2002). Given propiconazole's exposure pattern and toxicological characteristics, EPA determined that propiconazole potentially presented acute, chronic, short-term, intermediate-term, and cancer risks and EPA quantitatively assessed these risks in making its safety determination. (64 FR 2995, 2999–3001, January 20, 1999). All of these risks were found to be below the Agency's level of concern. (Id.). Based on the completeness of the toxicity database and the lack of any evidence showing increased pre- or post-natal sensitivity, EPA determined that removing the additional 10X children's safety factor

would be protective of infants and children. (Id. at 3000).

11. *Furilazole*. NRDC challenged an April 3, 2002, action establishing tolerances for furilazole on corn commodities. (67 FR 15727, April 3, 2002). Given furilazole's exposure pattern and toxicological characteristics, EPA determined that furilazole potentially presented acute, chronic, and cancer risks and EPA quantitatively assessed these risks in making its safety determination. (Id. at 15732–15733). All of these risks were found to be below the Agency's level of concern. (Id.). Although EPA was lacking a chronic toxicity study in dogs for furilazole, EPA determined that the additional 10X children's safety factor could be removed and that a 3X additional factor would be protective of infants and children because otherwise the database was complete, there was no evidence of pre- or post-natal sensitivity, and the subchronic toxicity studies in rats and dogs show that the toxicity of furilazole is similar, both qualitatively and quantitatively, in both species. The 3X factor was applied to the chronic risk assessment because the missing study was a chronic study. (Id. at 15730).

12. *Fenhexamid*. NRDC challenged an April 18, 2002, action establishing tolerances for fenhexamid on the caneberry crop subgroup, the bushberry crop subgroup, juneberry, lingonberry, salal, and pistachio. (67 FR 19114, April 18, 2002). Given fenhexamid's exposure pattern and toxicological characteristics, EPA determined that fenhexamid potentially presented a chronic risk and EPA quantitatively assessed this risk in making its safety determination. (Id. at 19118). As assessed, chronic risk was found to be below the Agency's level of concern. (Id.). Although the data showed qualitative evidence of increased pre-natal sensitivity, EPA determined that the additional 10X children's safety factor could be reduced to 3X because the toxicological data were complete, two of the three toxicological studies bearing on effects on the young showed no increased sensitivity in the young, and the evidence of increased sensitivity was only qualitative and not quantitative. (Id. at 19117).

13. *Fluazinam*. NRDC challenged an April 18, 2002, action establishing a tolerance for fluazinam on the wine grapes. (67 FR 19120, April 18, 2002). Given fluazinam's exposure pattern and toxicological characteristics, EPA determined that fluazinam potentially presented acute and chronic risks and EPA quantitatively assessed these risks in making its safety determination. (Id. at 19127–19128). All of these risks were found to be below the Agency's level of concern. (Id.). Because the data showed qualitative evidence of increased pre-natal sensitivity and a DNT study had been required (but not yet submitted) based on evidence of neurotoxic lesions, EPA retained the additional 10X safety factor for acute dietary exposure to the population subgroup females aged 13–50. For other populations and exposures the additional 10X factor was reduced to 3X because the increased sensitivity had only been seen with *in utero* exposure. (Id. at 19126–19127).

V. NRDC Objections

A. In General

As mentioned above, NRDC submitted four separate sets of objections on various pesticide tolerances during the first half of 2002. The objections were received on February 25, 2002; March 19, 2002; May 7, 2002; and May 20, 2002. (Refs. 6, 7, 8, and 9). NRDC was joined in the objections concerning 2,4-D by the following public interest and/or advocacy organizations: Boston Women's Health Book Collective, Breast Cancer Action, Californians for Pesticide Reform, Commonweal, Lymphoma Foundation of America, Northwest Coalition for Alternatives to Pesticides, Pesticide Action Network North America, Pineros y Campesinos Unidos del Noroeste, SF-Bay Area Chapter of Physicians for Social Responsibility, and Women's Cancer Resource Center.

B. Generic Issues

NRDC raises a myriad of claims in its objections. Most of the claims fall fairly neatly into three categories: (1) Children's safety factor issues; (2) aggregate exposure issues; and (3) issues regarding use of findings from hazard studies in calculating safe exposure levels - the''no observed effect level'' (NOEL) versus ''no observed adverse effect level'' (NOAEL) and the ''lowest observed adverse effect level'' (LOAEL) questions.

1. *Children's safety factor issues*. For each of the pesticides included in the objections, NRDC asserts that EPA used an additional safety factor for the protection of infants and children that is different from the default 10x value. NRDC claims that EPA erred in doing so due to the ''significant toxicity and exposure data gaps'' corresponding to the tolerances established. (See, e.g., Ref. 7 at 3). Three types of data gaps are cited by NRDC. First, NRDC notes that as to certain of the pesticides EPA has required a developmental neurotoxicity study but such study has not yet been submitted. Pointing to various EPA documents recommending that this study be widely required and EPA's specific finding that this study is required as to the pesticides in question, NRDC argues that use of a factor different than the default 10X is precluded. Second, NRDC claims EPA lacks ''pesticide-specific data on water-based exposure'' to the pesticides. (Id. at 6). NRDC argues that exposure estimates EPA calculated through the use of models cannot qualify as the ''reliable data'' needed to vary from the default 10X value. (Id.). Third, NRDC claims that ''EPA failed to consider important exposure routes for millions of infants and children, including exposure to children living on farms and who accompany their parents into farm fields [], and exposure from spray drift.'' (Ref. 9 at 5).

2. *Aggregate exposure issues*. NRDC raises several issues relating to whether EPA properly estimated ''aggregate exposure'' for the pesticides in question. First, NRDC argues that farm children are a ''major identifiable subgroup'' and that EPA has failed to consider information concerning the sensitivities and exposures of farm children as a major identifiable subgroup'' in conducting its aggregate exposure assessment. According to NRDC, farm children have unique exposures to pesticides ''from their parents' clothing, dust tracked into their homes, contaminated soil in areas where they play, food eaten directly from the fields, drift from aerial spraying, contaminated well water, and breast milk.'' (Ref. 7 at 12). Further, NRDC asserts farm children's exposure is increased because they ''often accompany their parents to work in the fields . . . .'' (Id.). NRDC cites various studies collected in its ''Farm Children Petition'' as well as more recent studies in support of these claims. (Ref. 7 at 12–13). Second, NRDC argues that EPA's aggregate exposure assessment is flawed for these pesticides because EPA did not consider the added exposure to pesticides that farmworkers receive as a result of their occupation. (Id. at 14). NRDC states that EPA's interpretation of the statute as excluding occupational exposure is incorrect. (Id.). Third, NRDC claims that EPA has underestimated aggregate exposure for several of the pesticides because EPA used ''anticipated residues'' for estimating exposure rather than assuming residues would be at the tolerance level. NRDC argues that ''EPA must ensure that the legal level of pesticide chemical residue - the established tolerance levels - are themselves safe.'' (Ref. 9 at 20). Additionally, NRDC asserts that using

''anticipated residues'' does not take into account the ''significant number of consumers who purchase produce at farmers markets, farm stands, and 'pick-your-own' farming operations.'' (Id. at 19). These ''potentially millions of consumers,'' NRDC contends, are exposed ''to residues of these pesticides at the tolerance level.'' (Id. at 20). Fourth, NRDC argues that for several of the pesticides EPA has, in effect, underestimated aggregate exposure by using the 95th population percentile of exposure instead of the 99.9th percentile in determining whether exposure to the pesticide meets the safety standard. (Ref. 7 at 19). NRDC claims that this is inconsistent with existing Agency policy. (Id.).

3. *Reliance on LOAELs and NOAELs.* NRDC asserts that, in the absence of identifying a NOEL in relevant animal studies, EPA cannot make a safety finding under section 408(b)(2). In support of this argument, NRDC cites to legislative history using the term NOEL. NRDC calls particular attention to the instances where EPA determined safety relying on a LOAEL: Use of acute neurotoxicity LOAEL to evaluate oral exposure for pymetrozine; (Ref. 6 at 9), use of reproductive toxicity LOAEL for mepiquat; (Id.), use of developmental toxicity LOAEL for zeta-cypermethrin; (Ref. 7 at 19), use of LOAEL for dermal toxicity for fluazinam; (Ref. 9 at 18), and reliance on rat and mouse dietary studies for fluazinam that identified only a LOAEL. (Id.). NRDC, however, also objects to several pesticide tolerances for use of a NOAEL in making the safety determination. (Ref. 9 at 17–18).

C. Pesticide-specific Issues

NRDC's pesticide-specific objections to some extent build upon the more general objections described immediately above. As to each of the pesticides, NRDC identifies allegedly missing toxicity or exposure data and argues that these missing data necessitate retention of the default 10X children's safety factor. Additionally, for several of the pesticides, NRDC raises specific issues regarding the aggregate exposure estimate. One aggregate exposure issue raised repeatedly is EPA's reliance on allegedly arbitrary processing factors for estimating residues in processed food. These objections are addressed in detail in Unit VIID.7.b. and f. below, respectively.

Finally, NRDC objects to the 2,4-D tolerance on soybeans arguing that EPA relied upon a human exposure study ''in an arbitrary departure from the Agency's stated policy on considering human tests and a violation of international and federal law.'' (Ref. 8 at 22). Also with regard to 2,4-D, NRDC discusses various toxicological studies that according to NRDC show that 2,4-D is a carcinogen, an endocrine disruptor, and a neurotoxicant. (Id. at 4–7). NRDC did not link these toxicological claims to its specific objections.

VI. Public Comment

A. In General

On June 19, 2002, EPA published a notice in the **Federal Register** calling attention to and requesting comments on the NRDC Objections. (67 FR 41628, June 19, 2002). As part of that notice, EPA published the full text of one set of objections in the **Federal Register**. A period of 60 days was initially allowed for comment but that period was extended twice and was closed on October 16, 2002. (See 67 FR 58536, September 17, 2003; 67 FR 53505, August 16, 2002). In addition to a large number of form letters (principally supporting the objections) and the NRDC's comments mentioned above, EPA received roughly 20 sets of substantive comments. These comments were for the most part from pesticide manufacturers and each requested denial of the objections. The most significant of these comments are summarized below. EPA has not repeated comments in instances where they were made by more than one commenter.

B. Individual Comments

1. *The FQPA Implementation Working Group.* Extensive comments were filed by the FQPA Implementation Working Group (IWG), an organization comprised of associations representing pesticide manufacturers, growers, and food processors. (Ref. 10) [hereinafter cited as ''IWG comments'']. The IWG comments provided two alternative approaches as to why the NRDC's objections should be denied. First, the IWG asserted that EPA has misinterpreted the concept of ''aggregate exposure'' ever since passage of the FQPA, and once this interpretation is corrected, it becomes clear that the objections, for the most part, are flawed. These comments by IWG were thoroughly described and responded to in the Imidacloprid Order. (69 FR at 30072–30073, May 26, 2004).

Second, in the alternative, the IWG, assuming the EPA's aggregate exposure interpretation is retained, explained that the NRDC objections are factually flawed. IWG's comments concerning pesticide exposure to farm children and exposure to pesticides in drinking water were discussed in the Imidacloprid Order. (69 FR at 30049, 30069). One issue not addressed was IWG's comments on pesticide exposure from food purchased at farm stands. The IWG challenges the NRDC's assertion that levels of pesticide residues in foods purchased at farm stands are higher than residue levels in food purchased at other retail outlets. The IWG notes that ''NRDC does not provide information to support its allegations, and we are not aware of any credible data to suggest that this is the case.'' (Ref. 10 at 16). The IWG cites two demonstrable reasons undermining NRDC's claim: first, label directions and restrictions on pesticide use apply equally to food grown for sale at farmstands and food grown for distribution through broader channels of trade; and second, ''[t]he various circumstances (weather, pest pressure, etc.) that affect residue levels resulting from a given treatment regimen are the same for those who grow crops to market through wholesale channels and for those who grow crops to sell at retail.'' (Id.). Finally, the IWG notes that assuming residue levels are at the tolerance value would vastly overstate exposure amounts given that FDA data has shown ''no pesticide residues in 41 percent and 73.5 percent of fruit and vegetable samples and either no residues or below tolerance residues in 99.5 percent and 98.9 percent of fruit and vegetable samples.'' (Id. at 17).

2. *Inter-Regional Research Project Number 4 (IR-4).* The IR-4 is a program sponsored by the US 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. In its comments, the IR-4 notes that several of the pesticides covered in the objections - diflubenzuron, halosulfuron-methyl, and fenhexamid - are both ''critical to minor crop growers'' and safer, reduced risk pesticides. (Ref. 11). The IR-4 asserts that diflubenzuron provides an alternative to the organophosphate pesticides and that halosulfuron-methyl is a methyl bromide alternative. (Id.).

3. *ISK Biosciences - Fluazinam.* ISK Biosciences is the owner of the data used to support the fluazinam tolerance on wine grapes. (Ref. 12). ISK Biosciences notes that this is an import tolerance for wine grapes meaning that as to this use there will be no exposure in the United States other than through the consumption of wine. (Id. at 4). ISK Biosciences also points out that children do not usually consume wine. (Id.). ISK Biosciences notes several factors that contributed to the conservativeness of EPA's risk assessment, including (1) use

of tolerance level residues; (2) assumption of 100 percent crop treated even though fluazinam can be at most used on wine imported to the United States (22 percent of the wine); and (3) use of a default processing factor for wine of 1.0 even though wine processing studies show significant reductions in residue levels. (Id. at 5–7). As regards reliance on a LOAEL, ISK Biosciences states that EPA did indicate the 21–day dermal toxicity study did not identify a NOAEL for dermal irritation but that EPA did find a systemic NOAEL from that study which was used for aggregate risk assessment. According to ISK Biosciences, NOAELs were used for dietary risk. (Id. at 7).

4. *Bayer CropScience - Isoxadifen-ethyl.* Bayer CropScience claims that EPA assigned a 3X children's safety factor to isoxadifen-ethyl due to concerns regarding a rat teratology study and EPA requested historical control information pertaining to the study. (Ref. 13). Bayer states that that information has been submitted and should alleviate any concerns EPA has with regard to the study regarding potential increased sensitivity of the young. With respect to the conservativeness of EPA drinking water exposure estimates Bayer CropScience cites a study which it asserts demonstrates that EPA models typically overstate exposures by 100- to 10,000-fold. (Id. at 2 (citing Ref. 14)). Finally, as to EPA's use of default processing factors, Bayer CropScience argues they are not arbitrary because they assume a worst case concentration of residues in the processed food based on the ratio of the weights of the raw and processed foods. (Ref. 13 at 6).

5. *Aventis CropScience - Acetamiprid.* Aventis CropScience asserts ''there was no specific concern on the part of [EPA with regard to acetamiprid] that would give concern for the developing fetuses or young. The developmental neurotoxicity study was required by EPA to expand knowledge, not for reasons of specific concerns.'' (Ref. 15). Further, Aventis CropScience claims that ''[t]here is no reason to expect that a lower NOEL than previously determined will be found for acetamiprid in a developmental neurotoxicity study.'' (Id.).

6. *FMC Corporation - Zeta-cypermethrin.* FMC Corporation argues that no DNT study has been required for zeta-cypermethrin because no data call-in has been issued. (Ref. 16). If a DNT study has not been required, FMC Corporation reasons, then the absence of a DNT study cannot make the database incomplete. Further, FMC asserts that even if such a study was requested any decision on the children's safety factor would have to be based on whether the data ''give rise to concerns for potential developmental effects.'' (Id.). Challenging claims by NRDC, FMC contends that the DCVA degradates of zeta-cypermethrin were considered by EPA, (Id. at 3–4), and the residential exposure due to cypermethrin was taken into account in the aggregate risk assessment for zeta-cypermethrin. (Id. at 6). As to the DCVA metabolites, FMC asserts that EPA considered them and decided not to include them in an aggregate assessment due to their lack of toxicological significance. (Id. at 3).

7. *Crompton Corporation - Diflubenzuron and Bifenazate*—a. *Diflubenzuron.* Crompton Corporation argues that NRDC's criticisms of the adequacy of the residential exposure assessment for diflubenzuron are misplaced given that an exposure assessment for agricultural workers showed minimal exposure under conditions much more likely to result in exposure than the sole registered residential use for diflubenzuron on trees and shrubs limited to professional application only. (Ref. 17).

b. *Bifenazate.* Crompton Corporation asserts that NRDC has misconstrued a statement in **Federal Register** notice establishing the bifenazate tolerances in question. (Id. at 4). In a table summarizing toxicological studies, EPA at one point states that ''a clear assessment of developmental toxicity was not possible.'' (67 FR at 4915,). Crompton Corporation contends that this statement only applied to a range-finding study and that once the main study was completed developmental toxicity could be clearly assessed. Crompton Corporation acknowledges that the database does not include, as NRDC has noted, several inhalation studies; however, Crompton argues this does not render the database incomplete because ''significant toxicity by this exposure route would not be expected'' given data from short-term inhalation studies and information pertaining to the particle size of bifenazate formulations. (Ref. 17 at 4). In response to NRDC's claim that arbitrary processing factors were used for estimating bifenazate residues on processed apples and grapes, Crompton points out that, at least in part, actual processing data from bifenazate-treated grapes and apples were used to derive processing factors. (Id. at 7–8).

8. *Syngenta Crop Protection - Propiconazole and Pymetrozine*—a. *Propiconazole.* Syngenta Crop Protection responds to NRDC's claim that drinking water models cannot be relied upon to provide reliable data on exposure by citing to a study done to evaluate the residue levels of propiconazole in drinking water reservoirs. (Ref. 18). According to Syngenta,''[i]n 312 samples of raw water, propiconazole was detected in only one, and that at the limit of detection. Propiconazole was not detected in ANY finished water samples analyzed. (Id.). As to exposure to farm children, Syngenta notes that:

> [m]any of the exposure scenarios depicted in the NRDC objections are the result of poor hygiene (contaminated work clothing being worn inside the home instead of being washed after use, . . .) substandard living conditions due to poverty, and lack of information on safe pesticide handling. These kinds of issues cannot be managed within the constraints of a risk assessment based on labeled use of a pesticide, but rather must be addressed through appropriate stewardship, education, and outreach. Recognizing this as an issue, particularly in the growing Latino community of North Carolina, Syngenta has sponsored and actively participated in projects with the Department of Family and Community Medicine at Wake Forest University to develop safety videos in Spanish for pesticide handlers. These modules include a discussion of proper hygiene for pesticide handlers/field workers once inside the home. (Id. at 3–4).

b. *Pymetrozine.* Syngenta defends the use of a LOAEL reduced by a factor of 3X for assessing the acute dietary risk of pymetrozine by noting that the effects observed at the LOAEL ''were reversible and not of severe magnitude (for example, body temperature was decreased at the LOEL, but only by about 2 percent compared to controls).'' (Id. at 5). Syngenta cites to reports indicating that a very high percentage of toxicity studies have a ratio between LOAELs and NOAELs of 5X to 6X or less. (Id.). Syngenta notes that ''Dourson et al. (1996) conclude that when faced with a LOEL and not a NOEL, the choice of uncertainty factor should generally depend on the severity of the effect at the LOEL.'' (Ref. 18 at 5).

9. *BASF Corporation - Mepiquat.* BASF Corporation disputes NRDC's claim that a NOEL was not identified by EPA for the mepiquat reproductive toxicity study in rats. Citing to EPA's Reregistration Eligibility Document for mepiquat chloride, BASF Corporation concludes that ''this study established a NOEL for all parameters investigated, both for parents and pups.'' (Ref. 19).

10. *Industry Task Force II on 2,4-D Research Data.* A good portion of the 2,4-D Industry Task Force II's comments pertain to NRDC statements regarding the toxicity of 2,4-D. (Ref. 20). Because NRDC did not directly relate these statements to its objections, neither its allegations nor the Industry Task Force's

rebuttal is repeated in any detail here. In sum, the Industry Task Force disagreed with NRDC's conclusions asserting that NRDC had focused on a few studies of questionable reliability without considering the extensive database on 2,4-D. The Task Force noted that ''[i]t is difficult to understand the toxicological arguments put forth by NRDC as many are simply threads of ideas that have been only loosely woven into a fabric.'' (Id. at 2). To the extent necessary, toxicological issues concerning 2,4-D are discussed below in EPA's response to the objections.

On the children's safety factor for 2,4-D, the Industry Task Force defends EPA's selection of a 3X factor based on the assertion that it would be '''double counting''' to ''require both a database uncertainty factor for the lack of a DNT study and an FQPA safety factor for neurological sensitivity.'' (Id. at 15). The Industry Task Force also notes that the neurological sensitivity was only found at a high dose. (Id. at 14). As to regulation of farm children as a major identifiable subgroup, the Industry Task Force protests that ''NRDC did not define farm children as a subgroup by their type of living situation, food consumption, and other population characteristics that would discriminate them from children generally.'' (Id. at 16). The Industry Task Force also challenges NRDC's claims regarding high exposures for farm children noting that in three recent biomonitoring studies of farm applicators, spouses, and their children ''only a small fraction of the spouses and children have levels of 2,4-D detectable at 1 part per billion.'' (Id.). Studies cited by NRDC in support of its claims regarding high exposure to farm children, the Industry Task Force asserts, ''fail to concurrently demonstrate a measurable internal dose of 2,4-D to the home residents.'' (Id. at 20). Finally, as to the human testing data relied upon by EPA in evaluating the safety of 2,4-D, the Industry Task Force points out that they were biomonitoring studies conducted by a provincial Canadian government agency and not ''third-party clinical trials [conducted by the pesticide industry] to determine effects in humans.'' (Id. at 25).

VII. Response to Objections

As summarized above, NRDC's Objections can be grouped into a few main categories and EPA has organized its response to the objections around these categories instead of by pesticide. Further, even among these categories, one consistent theme emphasized by NRDC is the potential heightened exposure of ''farm children'' to pesticides. For that reason, EPA begins its substantive response in Unit VII.B. below with an analysis of the data bearing on children's exposure to pesticides in agricultural areas. Then EPA turns to NRDC's specific objections. Unit VII. C. below addresses the objections raising issues regarding the children's safety factor. Unit VII.D. below covers aggregate exposure questions. Unit VII.E. below responds to claims regarding use of LOAELs and NOAELs. Finally, Unit VII.F. below addresses the human study issue.

Prior to addressing these substantive issues, EPA responds in Unit VII.A. below to the objections as to several tolerances which have now expired.

A. Expired Tolerances

The following time-limited tolerances that were objected to by NRDC have now expired and are, therefore, no longer in effect: halosulfuron-methyl on asparagus, (66 FR 66778, December 27, 2001) (expired on December 31, 2003); 2,4-D on soybeans, (67 FR 10622, March 8, 2002) (expired on December 31, 2004); and propiconazole on blueberries, (67 FR 14866, March 28, 2002) (expired December 31, 2003). Because these tolerance actions are without legal force, NRDC's objections are denied as moot. Other halosulfuron tolerances objected to by NRDC have not expired and are included in the response below. Additionally, because EPA has already, or may in the future, undertake tolerance actions as to propiconazole and 2,4-D, EPA's analysis to the specific issues raised by propiconazole and 2,4-D are included in this notice.

B. Children's Exposure to Pesticides in Agricultural Areas

Children can be exposed to pesticides through multiple sources and pathways. The Agency currently considers children's exposure to pesticides by three broad pathways: food, drinking water, and residential use. NRDC, however, has asserted that children residing in agricultural communities also are significantly exposed to agricultural pesticides through additional exposure pathways.

Children in agricultural areas may be exposed to agricultural pesticides through pathways such as contact with treated fields, roadsides and other areas; contact with residues on clothing of parents who work in agriculture; contact with moving spray drift while near application areas; contact with spray drift residues left by any spray drift that may reach their homes, yards or other areas they frequent, such as schools and schoolyards; and contact with pesticide residues that have volatilized after application. In addition, some of these children may also be exposed to agricultural pesticides in their homes via other pathways.

In analyzing the potential exposure of children in agricultural areas, EPA first focused on data from studies relied upon by NRDC or otherwise known to EPA that attempted: To measure levels of pesticides in the homes of children in agricultural areas; to measure levels of pesticide metabolites in body fluids of children in agricultural areas; and/or to compare levels of pesticide exposure of farm children to those experienced by non-farm children, based on similar types of measurements. In addition, EPA examined data NRDC submitted relating to airborne levels of pesticides (stemming from spray drift or post-application volatilization drift) in farm communities. Finally, EPA reviewed data it has concerning the potential for pesticides to drift offsite during application.

1. *Studies focusing on exposure to children in agricultural areas.* In response to objections filed by NRDC with regard to the imidacloprid tolerance on blueberries, EPA discussed various studies focusing on exposure to children in agricultural areas (other than the data cited by NRDC regarding airborne residues). In brief, EPA found that the data concerning levels of pesticides in homes or children's bodily fluids are limited and inconclusive, and do not demonstrate that children in agricultural areas as a group receive more pesticide exposure than children in non-agricultural areas. (In fact, some data suggest that pesticide residues in houses in urban or non-agricultural areas may be higher than those in houses in agricultural areas.) EPA incorporates that discussion into this response. (69 FR at 30050–30054, May 26, 2004).

Since issuing its response to the imidacloprid objections, EPA has received several additional studies bearing on exposure of farm children. First, EPA has received a study it funded investigating, among other things, aggregate exposure of children to persistent pollutants, including pesticides. (Ref. 21). Pesticides in the study included chlorpyrifos, diazinon, permethrin, and 2,4-D. The Pilot Study of Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) was designed to investigate the relative contribution of various routes of exposure (dietary, indirect oral exposure, and inhalation) and to determine if there are differences in exposure due to such factors as income

level, child care location, and regional location. CTEPP was conducted in two states, Ohio and North Carolina, and involved 257 children in both urban and rural (farmland) areas of these states. What the results of CTEPP show are that (1) the dietary route is the dominant route of exposure for the pesticides and other pollutants in the study (ranging from 55 to 95 percent for the six pesticides studied); (Id. at 9-75), and (2) although there were some differences in exposure for some pesticides for some routes of exposure, where differences were present it was the urban children that received higher exposures than rural children (e.g. exposure of urban children in North Carolina to 2,4-D through indirect ingestion exceeded exposure of rural children to 2,4-D by the same route by a factor of 3), (Id. at 9-66, 9-67).

A second source of information bearing on farm children exposure is a partial report from the Agricultural Health Study (AHS), which is a prospective epidemiologic study of pesticide applicators and their spouses in Iowa and North Carolina. (Ref. 22). Exposure to 2,4-D was measured in conjunction with agricultural applications for a subset of applicators in the AHS Pesticide Exposure Study. Urinary Biomarker levels were measured in pre-and post-application samples collected from applicators and their spouses and children using 2,4-D in broadcast and hand spray applications. The results indicated applicator exposure increased approximately 3-fold between the pre- and post-application periods. For spouses and children exposure increased but in smaller increments, approximately 50 percent and 25 percent, respectively. The values, however, are questionable due to the fact that one of the spouses admitted using a 2,4-D product, there were a low number (9) of children participating, and it is not clear whether any of the children assisted in farm work.

The final study, the Farm Family Exposure Study (FEES), which was funded by a group of pesticide manufacturers, was designed to quantify real world pesticide exposures in farmers and family members around the time of a single pesticide application. (Ref.23). Pesticides involved in the study included 2,4-D, chlorpyrifos, and glyphosate. The farm families were randomly selected from a public list of licensed private pesticide applicators from Minnesota and South Carolina. Exposures were measured in applicators, spouses and children by collection of 24 hour urine samples on the day of and for three days following a pesticide application. Urine samples were also collected prior to application. With regard to children, the study concluded that exposure levels of chlorpyrifos and glyphosate increased marginally on post-application days and that these marginal increases were caused by children who directly assisted in pesticide application or who were around the application process. Greater increases were seen between pre-application and post-application exposure levels of children in connection with use of 2,4-D. The study found that the highest levels of exposure were seen in children who assisted with application although increases were seen in some children not directly involved in the application process. Specifically, the study concluded:

> Exposure related to chemical application was also higher in children when compared to spouses. Unlike the spouses, the children were more often present during the application process and some assisted their parent with the application. These opportunities for direct exposure accounted for the higher concentrations of the chemicals in the urine. While the children did exhibit an overall positive change from baseline, the geometric mean differences in urine concentration were very small (2 µgL for 2,4-D). Not all children who had measurable changes in urine concentration were directly involved with the application process, yet identifying a potential route of exposure will be difficult as the exposures are subtle.

(Ref. 23 at 28). Comparisons of the exposure levels in this study with other population-based exposure data showed mixed results. To evaluate the significance of the exposures measured in the study, EPA compared the exposure levels for children aged 4-15 to the dose level of concern. Children in that range were chosen because fewer children of this age would be expected to directly assist or otherwise participate in agricultural activities. All exposure levels for this group were found to be well below safe levels with margins of exposure ranging from 4,000 to 2.6 million and averaging 42,000. (Ref. 24). Thus, although there were increases in exposure for some children, these increases were not meaningful in terms of risk.

The CTEPP study further confirms EPA's conclusions in the Imidacloprid Order regarding differential exposures of urban and rural (farm) children. The other two studies suggest that some farm children may be exposed to pesticides as a result of living in proximity to fields treated with pesticides; however, these exposures for farm children are generally a result of occupational-type exposures from the children participating in the application of pesticides or otherwise assisting in or being present in the field during agricultural operations. Occupational source exposure to pesticides is not appropriately considered under FFDCA section 408. 21 U.S.C. 346a(b)(2)(D)(vi). Importantly, even as to the increases in 2,4-D exposure in the FFES, the only pesticide as to which increased exposure could not be definitively tied to occupational-type exposures, the data did not indicate that children were receiving any exposures that were even close to levels of concern. Moreover, these studies did not indicate EPA's risk assessment process was under-protective. For example, EPA's risk assessment for 2,4-D, both as presented in the tolerance document and as described in Unit VII.B.2.a., predicts significantly higher risks (i.e., lower margins of exposure) for children from exposure to 2,4-D. Thus, EPA reaffirms its earlier finding that data concerning levels of pesticides in homes or children's bodily fluids are limited and inconclusive, and do not demonstrate that children in agricultural areas as a group receive significantly more non-occupational pesticide exposure than children in non-agricultural areas.

2. *Information bearing on exposure levels as a result of spray drift and post-application drift of volatilized residues.* Although the epidemiology data mentioned above and discussed in the Imidacloprid Order generally do not indicate that pesticide exposures to children in agricultural areas differ significantly from such exposures to children in urban or suburban areas, EPA has examined whether data on the drift of pesticide during applications (spray drift) and the transport of volatized pesticide residues following application (post-application drift) suggest that these sources of exposure should be included in EPA calculations of aggregate exposure.

a. *Pesticide spray drift during application.* EPA defines spray drift as the movement of droplets off-target during or shortly after application, which is independent of the chemical properties of the pesticide being sprayed. EPA has gathered substantial data on the potential of pesticides, as applied, to drift offsite through the work of the Spray Drift Task Force (SDTF). The SDTF is a group of pesticide registrants who have worked collaboratively to develop a database to meet the majority of their collective spray drift data requirements under 40 CFR 158.440. The group was chartered on April 17, 1990. (Ref. 25). Since its formation, the SDTF has generated standardized data on spray drift levels resulting from different application

methods under varying meteorological conditions. The data developed by the SDTF was reviewed by EPA internally, through external peer review workshops, and through FIFRA Scientific Advisory Panel meetings. The reviews generally identified the data set associated with aerial applications to be the most robust, followed by the data sets from ground boom applications, orchard/vineyard airblasting, and chemigation, respectively. After the spray drift data were available, the SDTF worked with EPA's Office of Research and Development, as well as the USDA's Agricultural Research Service and Forest Service to use the data in the development/evaluation of the AgDRIFT model. (See generally Refs. 26, 27, and 28).

The AgDRIFT model has been incorporated to a limited extent in EPA exposure assessments. It is used most prominently in environmental assessments in estimating potential exposure of offsite animals and plant life to pesticide residues. The AgDRIFT model has also been used in the context of FFDCA risk assessment through use of model estimates as an input to the various models used to estimate potential exposure in drinking water. Importantly, EPA has regarded its drinking water models as screening models and not as realistic predictors of actual exposure. For that reason, until recently EPA has not directly summed exposure estimates from its drinking water models with estimates of exposure from food in calculating aggregate exposure. Rather, EPA has used water model estimates more indirectly by comparing them to Drinking Water Levels of Comparison which are estimates of the amount of safe exposure that can occur taking exposure through residues in food into account. This indirect approach to the use of water model estimates of pesticide exposure keeps distinct the screening nature of water model estimates.

In estimating pesticide exposure from various pathways EPA is careful to avoid relying on maximum values from every input because such an approach can grossly overestimate exposure. As EPA's exposure guidelines note: ''When constructing this [exposure] estimate from a series of factors [environmental concentrations, intake rates, individual activities, etc.], not all factors should be set to values that maximize exposure or dose, since this will almost always lead to an estimate that is much too conservative.'' (Ref. 29). Given that EPA's approach to estimating pesticide exposure from food, water, and residential uses already tends to be very conservative (health-protective), EPA has been cautious about simply adding in yet another screening level value in calculating aggregate exposure. Certainly, the epidemiology data discussed above and in the Imidacloprid Order does not strongly suggest that EPA exposure estimates have been ignoring a major pathway of exposure.

That does not mean that the AgDRIFT model does not have a role to play in considering aggregate exposure to pesticides. It may prove useful in designing buffer zones for pesticides that otherwise have potentially high exposures. Alternatively, as data on exposure expands and modeling improves, some aspect of AgDRIFT modeling may be meaningfully incorporated into probabilistic modeling of exposure. However, as the analysis below shows, exposure as a result of spray drift is unlikely to be a significant contributor to any substantial number of individuals.

To evaluate potential exposures from spray drift, EPA: (1) Compared potential spray drift exposures to exposures from residential lawn uses; and (2) computed MOE's for each of the 13 pesticides assuming spray drift exposure is a component of residential exposure. Both exercises confirm EPA's view that spray drift is unlikely to be a significant contributor to risk.

1. *Comparison of AgDrift model estimates of exposure with exposure from residential lawn use generally.* AgDRIFT version 2.01 is a computer model that can be used to estimate downwind deposition of spray drift from aerial, ground boom, and orchard and vineyard airblast applications. The model contains ''Toolbox'' screens that can be used to estimate deposition levels in terrestrial and aquatic environments and estimate concentrations in water bodies. The model contains three tiers of increasing complexity for aerial application. In Tier 1, the user can estimate downwind deposition resulting from each of the application methods under several predefined scenarios. In higher tiers more options are available. AgDRIFT only allows Tier 1 level analyses for ground boom and airblast application methods. The aerial portion of the model is based on a mechanistic U.S. Forest Service model, (Ref. 30). The SDTF field trial data were used to validate the aerial portion of AgDRIFT, (Refs. 31 and 32). The ground boom and orchard airblast portions use data collected by the Spray Drift Task Force (SDTF) to empirically calculate spray drift deposition. AgDRIFT was developed under a cooperative research and development agreement between EPA, USDA, and the SDTF.

The AgDRIFT model can provide a picture for each of the three application techniques (aerial, groundboom, and airblast) of what amount of an agriculturally-applied pesticide may drift onto areas ranging from 10 feet to 210 feet from the treated field. In the following Table 2, high-end spray drift deposition as modeled by AgDrift is presented in terms of deposition rate offsite as a percentage of the pesticide application rate. (Ref. 33).

TABLE 2.—HIGH-END DOWNWIND SPRAY DRIFT DEPOSITION LEVELS BY APPLICATION METHOD

Lawn placement relative to application area	Spray drift deposition (percent of application rate)				
	aerial	ground boom	airblast		granular
			dormant orchards	dense or tall canopies	
10 to 60 ft downwind	34.1	9.3	25.0	8.4	0
20 to 80 ft downwind	31.6	6.4	16.1	6.0	0
40 to 90 ft downwind	27.9	4.1	8.0	3.7	0
80 to 130 ft downwind	22.0	2.4	3.0	1.9	0
160 to 210 ft downwind	14.9	1.3	0.8	0.9	0

As Table 2 shows, the highest off-target deposition levels from agricultural applications occur adjacent to the treated area and those levels decrease with increasing distance from the treatment area. Importantly, in EPA's experience, application rates for residential uses are generally equal to or greater than the levels allowed for agricultural applications. Thus, deposition on residential lawns from spray drift is generally a small fraction of deposition from direct residential treatment and, unless the residential lawn is relatively close to the treated agricultural field, the ratio of spray drift deposition to deposition from direct treatment is exceedingly low.

2. *Evaluation of MOE's based on AgDrift Model for the pesticides in the objections.* Another way of evaluating the potential significance of application drift exposure is by calculating potential high-end application drift for each pesticide for areas adjacent to treated fields and combining these values with other exposure values for the pesticide. Due to the high-end nature of the estimates from the AgDrift model and the limited number of persons that would be exposed at the field boundary, EPA does not believe it is reasonable to simply add these values to other high-end exposure values in determining pesticide safety. Nonetheless, in the context of these objections, EPA has performed this calculation to show how even making such low probability exposure assumptions does not result in any safety concerns.

The exposure/risk scenario deemed most appropriate for evaluating application drift exposures is the short-term exposure scenario. Short-term exposures are those likely to occur over a 1– to 7–day window. This is the exposure window most commonly used with assessing exposure from residential turf use of a pesticide and the turf use is the residential use that most closely approximates the exposure that may result from application drift. To estimate potential exposure to application drift, EPA first calculated the amount of deposition that may drift to an area 10–60 feet downwind of the application site using the combination of permitted application technique and rate that yielded the highest deposition. Then EPA used the predicted deposition amount as an input in its model for estimating post-application exposure to toddlers on turf. EPA focused on toddlers because toddlers have the greatest post-application turf exposure to pesticides of any population subgroup due to their behavior patterns (i.e., crawling, rolling on turf; hand-to-mouth activity; soil ingestion). As is done with evaluating aggregate short-term post-application exposures to turf uses, predicted post-application exposure from drift was then summed with background exposures to the pesticide from residue-containing food and water. If the pesticide has residential exposures, those predicted exposures were summed as well. After combining all of these exposures, the overall exposure value was divided into the safety endpoint used to evaluate short-term exposure to quantify the Margin of Exposure (MOE). To ensure that this assessment was conservative, EPA combined oral and dermal exposure where appropriate. Where combining oral and dermal exposures was not supported by the data, EPA calculated separate MOEs for dermal and oral exposures and then combined the MOEs. (Ref. 33 at 3-5).

The following Table 3 presents estimated MOEs for the 13 pesticides for background food and water exposure, residential exposure (where applicable), application drift exposure, and combined exposure. Table 3 also lists the Level of Concern (LOC) for each pesticide. The LOC is the minimum level that a MOE must obtain to ensure that the MOE includes adequate safety factors, including the children's safety factor. As can be seen, even when assessing risk using this unrealistic exposure approach, the MOEs for these pesticides remain above their respective LOC.

TABLE 3.—COMBINING APPLICATION DRIFT SHORT-TERM EXPOSURES WITH OTHER EXPOSURES OF TODDLERS

Pesticide	Food and Water Background MOE		Residential MOE		Appl. Drift MOE		Combined MOE	LOC
	food	water	oral	dermal	oral	dermal		
halosulfuron-methyl	140,000	300,000	60,000	3,100	2,500,000	110,000	2,800	100
pymetrozine	220,000	63,000	2,200	na	15,000	na	1,800	1,000
mepiquat	29,000	550,000	na	na	180,000	27,000	13,000	100
bifenazate	2,500	880,000	na	na	3,700	1,100	650	100
zeta-cypermethrin	710	22,000	4,400	na	40,000	na	570	100
diflubenzuron	13,000	220,000	na	na	1,600	15,000	1,300	100
2,4-D	17,000	17,000	970	1,100	2,500	1,600	330	300
isoxadifen-ethyl	5,600	3,500	na	na	33,000	9,100	1,600	300
acetamiprid	1,000	38,000	na	na	12,000	1,800	610	300
propiconazole	18,000	3,300,000	na	na	19,000	1,800	1,500	100
furilazole	330,000	130,000	na	na	200,000	19,000	15,000	300
fenhexamid	3,500	300,000	na	na	13,000	14,000	1,300	300
fluazinam	93,000	4,300	na	na	3,800	370	310	300

Table 3 has been compiled based on analyses and data in existence at the time of the tolerance action. Since the tolerance actions, EPA has received new information or conducted new analyses as to these pesticides. That data and analyses has resulted in changes, or potential changes to the assessment of the risk posed by these pesticides. The changes come in the form of adjusted safety factors, more realistic exposure estimates, and new toxicity endpoints. EPA has not incorporated that information into this objection response because consideration of this new information was not needed to address NRDC's objections. EPA would have considered expanding its response to address new information if NRDC's objections had convinced EPA that its prior analysis was flawed or EPA had a completed risk assessment showing risks of concern.

EPA cautions that it would be inappropriate to focus on any one aspect of the underlying risk assessment variables and conclude that based on a change in that one variable alone the risk of a particular pesticide is unacceptable. Not only must EPA assess all of the variables in combination, but EPA's risk assessment process is tiered such that more elaborate techniques to predict realistic exposure values are not used if use of worst case default exposure assumptions suggest there is not a risk of concern. (Refs. 29 at 22922; 1 at 11). For example, NRDC has argued that for some of the pesticides in the objections, use of a different safety factor would demonstrate that the objected-to tolerances are unsafe. Given, however, the very conservative exposure assumptions for many of these pesticides, such arguments are likely to be incorrect even if NRDC could support its argument for a greater safety factor.

b. *Volatilization of applied pesticides.* On June 19, 2003, NRDC supplemented its submission to the Agency with several pieces of additional information. Included was a report by the Californians for Pesticide Reform generally addressing the issue of spray drift from pesticide applications in California. (Ref. 34) [hereinafter referred to as the ''CFPR Report'']. Although EPA defines spray drift as the movement of droplets off-target during or shortly after application, which is independent of the chemical properties of the pesticide being sprayed, the CFPR Report looked more broadly at atmospheric pesticide transport including pesticide volatilization as a potential mechanism by which pesticides travel beyond treated fields. Also included in NRDC's supplemental information was a research article containing an analysis and ranking of the degree of inhalation risk posed by certain migrating pesticides in California, based on ambient air monitoring data gathered, in part, by the California Air Resources Board and the California Department of Pesticide Regulation. (Ref. 35) [hereinafter referred to as the ''Ranking Study'']. The Ranking Study conducted screening level assessments for many of the pesticides regarded as having the highest potential as toxic air contaminants by the California Department of Pesticide Regulation as well as several pesticides categorized as hazardous air pollutants by EPA. This screening level assessment, using conservative (health-protective) assumptions, only identified three soil fumigants (MITC, methyl bromide, telone) and one heavily-used non-fumigant pesticide (chlorpyrifos) as potentially presenting non-cancer acute or chronic risks of concern. (Id. at 1179). The study concluded that ''vapor pressure is a significant predictor of [] ranking of inhalation risks. (Id. at 1182). The CFPR Report examined the potential health risks from air levels of three pesticides characterized as moderate to highly volatile (chlorpyrifos, diazinon, and molinate) measured at the field boundary and at more distant locations. The Report concluded that in many instances the measured air levels of these pesticides posed risks of concern. The Report also concluded that drift due to volatilization was not a concern for pesticides that are not highly volatile. (Ref. 34 at 40).

(1) *Analysis of CFPR report and ranking study.* In terms of volatility, pesticides can be broadly grouped into three categories: (1) Those of high volatility (vapor pressure of 10^{-1} to 10^{-3} millimeter of mercury (mmHg)); (2) those of moderate volatility (vapor pressure of 10^{-4} to 10^{-5} mmHg); and (3) those of low volatility (vapor pressure of 10^{-6} mmHg and below). EPA and NRDC seem to be in general agreement regarding the exposure potential from the first and third groups. Both EPA and NRDC believe that significant airborne exposures may occur as a result of the application of pesticides of high volatility and that exposure through volatilization is unlikely for pesticides of low volatility. Where EPA and NRDC differ is regarding the middle group. NRDC argues, based on the CFPR Report, that pesticides in this group can result in exposures that raise levels of concern. EPA believes the evidence NRDC has presented on this point is open to question. Although there is a greater possibility for volatilization of residues of pesticides of moderate volatility than those of low volatility, EPA is not convinced that volatilization exposure from the former group is likely to be meaningful. In any event, as discussed below, there is no reason to expect any meaningful exposure due to volatilization from any of the 13 pesticides involved in these objections.

In the CFPR Report, CARB data is presented and analyzed for two pesticides that fall in the middle group: Diazinon and chlorpyrifos. The CFPR Report concludes that exposure to volatilized residues alone from these two pesticides raise risks of concern. The risks of concern were due to acute, not chronic exposures, and occurred primarily as a result of exposure in areas immediately adjacent to treated fields within a day or two of treatment. EPA questions the validity of this determination due to various assumptions made in the Report that tend to exaggerate exposure and risk. First, the CFPR Report estimates exposure based on the amount of air breathed in a 24–hour period. The field studies analyzed in the report, however, show that volatilization exposures peak in a relatively narrow time window that is significantly shorter than 24 hours.

Second, the measured residues in the field studies were sampled in an outdoor location just a few feet from the field. Yet, it is unlikely that any individual would remain stationary outdoors in such a location for a 24–hour period. Moreover, even if an individual did stay in that same location for a 24–hour period, it is unlikely that he or she would be outdoors the entire time. Thus, the Report's exposure estimate rests on the assumption that indoor air concentrations are the same as concentrations measured in outdoor air. This assumption is reportedly based on a pilot study supporting the prospective Agricultural Health Study of American farmers and their families. (Ref. 36). These data suggested higher air concentrations were found inside the residences of farmers than were measured outdoors. The outdoor measurements were collected either on the farmer's lawn or porch. However, it is not clear either when the actual pesticide applications were made with respect to the timing of the air concentration data collection or their location with respect to the distance from the treated field. Meteorological details were not provided. In one example from this study (lindane), indoor concentrations were traced to work clothing while the application of lindane was made to hogs situated inside a separate production facility.

In EPA's view, it is more likely that indoor levels of pesticides would be lower in homes situated near agricultural sites or other sites of pesticide application than levels that might be measured outdoors. This is particularly the case in situations involving acute exposures where airborne levels rapidly peak and dissipate. For example, Segawa et al. reported in 1991 that, when malathion was sprayed in Southern California for Mediterranean fruit fly control, indoor levels of malathion were 4 to 5 times lower than outdoor air concentrations. (Ref. 37). In a study evaluating the impact of track-in following applications of 2,4-D to lawns (Ref. 38), it was suggested that spray drift and particle intrusion had little effect on indoor carpet dust concentrations. Likewise, Solomon et al. (Ref. 39) have reported minimal impact on indoor air measurements of bystander homes adjacent to treatment areas (2,4-D applications to lawns). Therefore, the assumption that indoor air concentrations are equivalent to outdoor air concentrations appears to exaggerate risk. Consistent with this view, California DPR measurements of indoor air versus outdoor air following methyl bromide structural fumigations indicated that, within the first hour, outdoor air concentrations of methyl bromide (first 50 feet from treatment site) are approximately 5 to 8 times higher than those in indoor air, and up to 13 times higher than indoor air at distances equal to or greater than 100 feet. Only after 24 hours, when the majority of the plume had passed by the house, were indoor air measurements roughly the same as outdoor measurements.

Third, the CFPR compares these exposure estimates to reference doses from subchronic inhalation studies. With chlorpyrifos, the reference dose is based on lack of effects in two 90–day rat inhalation studies at the highest dose tested and incorporates a 1,000–fold safety factor. For diazinon, the reference dose is from a LOAEL in a 21–day inhalation study and incorporates a 300–fold safety factor. Use of reference doses from subchronic studies to assess what, in the case of the field trials, are at most short-term exposures (1 to 7 day duration) - and more likely acute exposures (single event) - is a very conservative approach. This factor should be taken into account in characterizing any risk estimation.

Finally, an EPA report on pesticide exposure to children along the United States/Mexico border (discussed in the Imidacloprid Order, (69 FR at 30052)) presents a vivid contrast to conclusions reached in the CFPR report. (Ref. 40). This report concluded that both indoor and outdoor air concentrations had a minimal impact on the exposed population. The pesticides diazinon and chlorpyrifos are two chemicals widely used in that region. Thus, this report casts doubt on the conclusions in the CFPR Report.

(2) *Vapor pressure.* As noted, EPA is in general agreement that vapor pressure is a key factor in predicting whether a pesticide has the potential to volatilize and drift offsite in significant amounts. Because soil fumigants traditionally have very high vapor pressures, and thus are highly volatile, EPA is now accounting for potential exposure due to volatilization of these pesticides in calculating their aggregate exposure. The CFPR Report concludes that post-application volatilization exposures are not of concern for pesticides with a low vapor pressure - i.e., less than or equal to 10^{-6} mmHg - but can be for pesticides with a moderate vapor pressure - i.e. between 10^{-4} and 10^{-6} mmHg. In Table 4 below, EPA has listed, according to vapor pressure, the five non-fumigant pesticides examined by the CFPR Report (including the CFPR's characterization of the vapor pressure) as well as the 13 pesticides in these objections. (Ref. 41).

TABLE 4. —VAPOR PRESSURE OF SELECTED PESTICIDES

Pesticide	Reason Included	Vapor Pressure (mmHg)
molinate	CFPR (high vapor pressure)	5.3×10^{-3}
diazinon	CFPR (moderate vapor pressure)	1.4×10^{-4}
chlorpyrifos	CFPR (moderate vapor pressure)	1.87×10^{-5}
fluazinam	Subject of objection	8×10^{-6}
mepiquat	Subject of objection	2.3×10^{-6}
propiconazole	Subject of objection	4.2×10^{-7}
2,4-D	Subject of objection	1.4×10^{-7}
paraquat	CFPR (low vapor pressure)	1×10^{-7}
halosulfuron	Subject of objection	1×10^{-7}
bifenazate	Subject of objection	1×10^{-7}
pymetrozine	Subject of objection	3×10^{-8}
isoxadifen-ethyl	Subject of objection	1.65×10^{-8}
acetamiprid	Subject of objection	7.5×10^{-9}
fenhexamid	Subject of objection	7×10^{-9}
propargite	CFPR (low vapor pressure)	4.4×10^{-9}
zeta-cypermethrin	Subject of objection	3.07×10^{-9}

TABLE 4. —VAPOR PRESSURE OF SELECTED PESTICIDES—Continued

Pesticide	Reason Included	Vapor Pressure (mmHg)
diflubenzuron	Subject of objection	9×10^{-10}
furilazole	Subject of objection	6.63×10^{-10}

As Table 4 illustrates, all but two of the pesticides in these objections have a low vapor pressure and thus, on this basis alone, are unlikely to result in significant exposures due to post-application volatilization. Two pesticides, fluazinam and mepiquat, have vapor pressures in the 10^{-5} to 10^{-6} mmHg range, but nonetheless below the vapor pressure of chlorpyrifos, the pesticide with the lowest vapor pressure that the CFPR Report concluded had significant levels of post-application drift. (A form of 2,4-D (2,4-D(BEE)) has a vapor pressure of 2.4×10^{-6} mmHg; however, whatever potential to volatize exists for this form of 2,4-D is significantly lowered by its method of application (agitation into the water profile at aquatic sites)). Traditionally, general scientific opinion has been that substances with a vapor pressure of between 10^{-4} and 10^{-6} mmHg are relatively non-volatile and thus unlikely to result in significant exposures due to volatilization. (Ref. 42). NRDC contends otherwise based on the CFPR Report. Even assuming NRDC is correct, however, there are several characteristics of fluazinam and mepiquat in addition to their lower vapor pressure, that distinguish them from chlorpyrifos and make it unlikely that they have any significant post-application drift exposures either in the acute or chronic exposure time-frame.

In terms of acute exposure, it is first worth re-emphasizing that EPA has substantial questions as to whether the CFPR Report overstates the exposure that can be expected with regard to chlorpyrifos. Second, the maximum single application rates for fluazinam (0.8 lbs/acre) and mepiquat (0.25 lbs/acre) are much lower than chlorpyrifos (6 lbs/acre - this rate was used in the CFPR study) - factors of 7.5 and 24, respectively. (Refs. 43, 44 and 45). Finally, the acute inhalation endpoints of concern, adjusted by safety factors, for fluazinam (0.0046 mg/kg/day) and mepiquat (0.584 mg/kg/day) are much higher than for chlorpyrifos (0.0001 mg/kg/day) - factors of 46 and 5,840, respectively. (Refs. 46, 47 and 48).

As to chronic exposure, although a high enough vapor pressure appears to be a necessary condition to significant ambient air concentrations, vapor pressure alone is not sufficient for such significant chronic exposures to occur. Equally necessary, is a substantial overall usage amount. In this regard, chlorpyrifos dwarfs fluazinam and mepiquat. Average annual usage for chlorpyrifos for the years 2001–2003, is estimated to have been in the range of 8 to 9 million pounds. On the other hand over the same period, mepiquat usage is estimated to have been in the range of 250,000 to 500,000 pounds. Fluazinam had so little usage it did not even show up in standard pesticide usage survey reports. (Ref. 49).

Finally, it is worth considering that occupational exposure assessments for the three pesticides as a means of comparing the relative inhalation risk posed by these pesticides. EPA's principal tool for assessing occupational exposure and risk is Pesticide Handlers Exposure Database (PHED). (Ref. 50). PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). One of the measured values is the level of pesticide residue in ambient air at the time of application. This value contains a mixture of volatized residue as well as airborne non-volatized residue and is likely to be substantially higher than any post-application levels even for highly volatile pesticides.

What PHED assessments for the three pesticides show is that for inhalation risks both fluazinam and mepiquat have high MOEs that are well above the level of concern (i.e., there is a large margin of safety) even without any protective equipment (e.g., respirators or enclosed cabs) but that chlorpyrifos had MOEs for some scenarios that are below the level of concern even assuming that applicators used enclosed cabs. (Refs. 46 at 7–8; 47 at 37 and Ref. 51).

For all of these reasons, EPA concludes the information submitted by NRDC does not suggest that the use of fluazinam and mepiquat, which have vapor pressures slightly above the 10^{-6} mmHg level, would result in significant post-application exposures due to volatilization of residues. As the material relied upon by NRDC notes, post-application drift is unlikely for the other 11 pesticides in the objections.

c. *Conclusion.* EPA concludes that NRDC's arguments concerning exposure from application and post-application drift do not undermine EPA's conclusion that it has reliable data on exposure for these pesticides. Not only does the scientific literature not support a finding that pesticide drift is a major source of exposure but (1) EPA's application drift model demonstrates that exposure from application drift is likely to be marginal everywhere other than areas immediately adjacent to fields; (2) even combining application drift exposures with other aggregate exposures in a manner likely to significantly overstate exposure does not show a risk of concern for any of the 13 pesticides; (3) the vapor pressures for 11 of the 13 challenged pesticides are sufficiently low that even NRDC appears to concede that significant post-application drift would not be expected from any of them; and (4) for the two pesticides that have slightly higher vapor pressures, individual factors regarding them indicate that siginificant post-application drift is unlikely.

C. Failed to Retain Children's 10X Safety Factor

1. *Introduction.* NRDC's objections concerning the children's safety factor principally focus on an alleged lack of data that NRDC contends does not allow EPA to conclude that the children's safety factor may be reduced or removed. First, NRDC argues that 7 of the 13 pesticides (halosulfuron-methyl, pymetrozine, mepiquat, zeta-cypermethrin, 2,4-D, acetamiprid, and fluazinam) lack a required DNT study, and that this ''is a crucial data gap that by itself should prohibit EPA from overturning the default 10X safety factor.'' (Refs. 6 at 4; 7 at 6–7; 8 at 10; and 9 at 6). In support of this argument NRDC relies on information showing that pesticides may cause developmental neurotoxic effects and that these effects may come at lower doses than doses causing other adverse effects. Second, NRDC cites, on a pesticide-by-pesticide basis, various

toxicological studies that NRDC claims are missing, or were not considered. The absence or non-consideration of these data, NRDC contends, warrants retention of the children's safety factor. Following the same pattern with exposure data, NRDC claims that the children's safety factor is required because EPA is lacking both generic data on exposure and various specific pieces of exposure information with regard to some of the individual pesticides named in the objections. NRDC's generic exposure data objections pertain to data on the exposure of farm children to pesticides and exposure to pesticides through drinking water. Additionally, NRDC claims that data are missing because EPA has allegedly failed to undertake certain, specific risk assessments as to some of the pesticides.

Each of these objections will be addressed individually.

2. *Lack of DNT study generally.* NRDC contends that ''the absence of required developmental (DNT) tests for 2,4-D is a crucial data gap that by itself should prohibit EPA from overturning the default 10X safety factor.'' (See, e.g., Ref. 8 at 9). NRDC cites essentially three grounds in support of this contention. First, NRDC claims that there is extensive evidence showing that ''pesticide exposures may disrupt the normal development of a child's brain and nervous system.'' (Id. at 9 and fn.16 (citing studies)). Second, NRDC references a paper by EPA staff scientist Susan Makris that NRDC asserts demonstrates that ''DNT testing is more sensitive than other studies in measuring the effects of exposure on proper development of the brain and nervous system . . . .'' (Id. at 9). Third, NRDC cites the EPA's 10X Task Force Report which recommends the DNT testing be part of the minimum toxicity data set for pesticides requiring a tolerance for residues in or on food. (Id. at 10). NRDC further asserts that EPA's Children's Safety Factor Policy fails in its purported attempt to justify choosing a factor other than 10X when a required DNT study has not been submitted. According to NRDC, the Children's Safety Factor Policy ''completely reverses'' the statutory presumption in favor of an additional 10X factor by allowing EPA to choose a different factor not on the basis of reliable data but on a risk assessor's ''intuition or professional judgment.'' (Id. at 11).

EPA disagrees that the mere absence of a required DNT study should, by itself, conclusively bar EPA from applying a different additional safety factor than the 10X default value. After all, the statute expressly authorizes EPA to use a different additional factor if the Agency can determine on the basis of reliable data that a different factor ''will be safe for infants and children.'' (21 U.S.C. 346A(b)(2)(C)). In line with the statute, EPA's Children's Safety Factor Policy calls for a careful examination of the existing database on a case-by-case basis to determine if a reliable basis exists for assigning a different factor. NRDC's argument here can only be successful if it can show that reliable data to support a different safety finding could never be available. This NRDC has not done. NRDC's objections contain no factual contention demonstrating that a case-specific approach cannot work or is inappropriate for the 13 pesticides in question.

a. *Pesticides may cause neurological developmental effects.* NRDC cites the National Research Council's 1993 Report on pesticides' effects on children in support of the claim that ''pesticide exposures may disrupt the normal development of a child's brain and nervous system.'' (Ref. 8 at 9). EPA does not dispute that some pesticides have that potential; however, that some pesticides have that potential does not mean that defensible judgments about that potential cannot be made in the absence of a DNT study. Further, EPA would note that the National Research Council Report did not conclude that the evidence showed that exposure to pesticides was currently resulting in neurological developmental effects. According to the National Research Council, ''[a]lthough the vulnerability of the developing brain to neurotoxic exposure is of serious concern, it is entirely unclear from the data available whether exposures at levels consistent with usual dietary exposures would pose a substantial risk to the long-term neurologic development of children in general or to particular subgroups of children that are neurologically vulnerable.'' (Id. at 65.)

NRDC also cites a number of studies showing that a particular pesticide, chlorpyrifos, does have neurological effects on the developing brain. Again, however, EPA does not deny that pesticides can cause such effects. The question is, however, whether in the absence of a DNT study, EPA can make a reliable prediction concerning whether a particular safety factor will be protective of infants and children from potential neurological effects. Citing the general capacity of a specific pesticide to cause neurological effects does not answer this question. EPA has received and reviewed a DNT study for the pesticide in question, chlorpyrifos. Although the results of the DNT study for chlorpyrifos were confirmatory of results in other chlorpyrifos toxicology studies, the DNT results did not alter the regulatory endpoints chosen for that pesticide. (Ref. 52).

b. *1998 retrospective study on submitted DNT studies.* The conclusions presented in the Makris study are more relevant to the question at hand. (Ref. 53). After reviewing nine DNT studies that had been submitted on pesticides, Makris found that (1) for eight out of nine pesticides the fetal NOEL from the DNT study was lower than the fetal NOEL from the standard prenatal developmental toxicity study; (2) for six out of nine pesticides the offspring NOEL from the DNT study was lower than the offspring NOEL from the standard two-generation reproduction study; (3) for two out of nine pesticides, the acute endpoints and associated NOELs from the DNT study were selected for the acute dietary risk assessment; and (4) the DNT study did not provide an endpoint and associated NOEL for chronic risk assessment for any of the nine pesticides. The first two findings provide valuable scientific information with regard to understanding how pesticides may affect the developing human. More relevant to a decision regarding the children's safety factor, however, are the latter two findings because they highlight whether a DNT study may affect how the risk posed by a pesticide is characterized.

Some background information may be helpful in understanding the significance of Makris' findings. In assessing the risk posed by a pesticide, EPA examines numerous toxicological studies and identifies from each study the LOAEL resulting from exposure to the pesticide and the NOAEL. These NOAEL/LOAELs are then grouped by exposure scenario taking into account both the duration of the exposure (e.g., acute, chronic) and the route of exposure (e.g., oral, dermal). For each exposure scenario EPA selects the lowest of the appropriate NOAELs for the purpose of assessing risk. For evaluating acute and chronic oral dietary exposure, EPA uses this NOAEL to derive a safe dose - this safe dose is commonly referred to as a Reference Dose (RfD). Generally, a RfD is calculated by dividing the selected NOAEL by one or more safety or uncertainty factors. When more data becomes available, it may change a RfD but only if the NOAEL from the new data is lower than all previous NOAELs identified for the relevant exposure scenario.

What Makris found in looking at the 9 pesticides was that, out of the 18 potential exposure scenarios examined

(1 acute oral and 1 chronic oral for each pesticide), in only 2 instances did the DNT study produce a NOAEL that was below all other NOAELs for that exposure scenario for that pesticide. In other words, in 16 out of 18 cases, the DNT study made no difference in the calculation of the safe human dose (i.e., RfD) for the pesticide. Although this information shows that the DNT study can be an important study is assessing the risk of pesticides because it has the potential to show adverse effects at levels below those previously identified, the potential for a DNT study to change an existing RfD is hardly so overwhelming to suggest that there is no room for exercise of the discretion to examine the individual facts involving the safety of each pesticide that is expressly provided by the statute.

Today, EPA has considerably more experience with the DNT study than when the 1998 Retrospective Study was conducted. That experience has confirmed both that the DNT study has a role to play in assessing the hazard posed by pesticides, (Ref. 54), and that DNT studies only infrequently affect the projection of a safe endpoint for a pesticide. EPA is currently in the process of completing another retrospective study of the DNT study based on the roughly 50 DNT studies it has now received. The full retrospective study will not be completed until later this year; however, some preliminary information is now available. (Ref. 55). It shows that out of the 38 pesticides for which a DNT study has been submitted and EPA's analysis completed, the DNT study has resulted in a lowering of at least 1 endpoint for a pesticide in 8 instances. Again, these numbers do not suggest there is no room for judgment in evaluating the impact a DNT study may have on a risk assessment.

c. *10X Task Force Report.* NRDC also cites the recommendation in the report of EPA's 10X Task Force that the DNT study be included in the core toxicology database for pesticides. Although the Task Force did note the significance of the DNT study for assessing potential risks for children, the Task Force also concluded that any decision on the size of any safety factor (described by the Task Force as a database uncertainty factor) used when a DNT study had not been submitted called for the exercise of ''good scientific judgment.'' (Ref. 56). According to the Task Force, ''[t]he size of the database uncertainty factor applied will depend on other information available in the database and how much impact the missing data may have on determining the potential toxicity of the pesticide for children.'' (Id.). As described above, EPA's policy on evaluating the size of the safety factor when a required DNT study has not yet been submitted is fully consistent with this recommendation by the 10X Task Force. When a required DNT study is absent, EPA has focused on the other information available on the pesticide and the possible impact the DNT study may have on estimating the risk of the pesticide.

d. *EPA's 10X Policy.* Finally, EPA disagrees that its Children's Safety Factor Policy completely reverses the statutory presumption to include an additional 10X safety factor for the protection of infants and children. In the opening paragraph of the policy the Agency states that ''[t]he Office of Pesticide Programs (OPP) interprets this statutory provision [Section 408(b)(2)(C)] as establishing a presumption in favor of applying an additional 10X safety factor.'' (Ref. 2 at 4). The presumptive aspect of the additional 10X safety factor (also described as the ''default position'') is referenced throughout the document. (See, e.g., Id. at 10, 11, 17, 26, 46, 47–48, and A–6).

NRDC cites to language in the policy statement stating that in evaluating what safety factor decision should be made for pesticides for which a DNT study has been requested, risk assessors should consider ''if the available information indicates that a DNT study is likely to identify a new hazard or effects at lower dose levels of the pesticide that could significantly change the outcome of its overall risk assessment . . . .'' (Ref. 7 at 8–9). NRDC argues that this language reverses the statutory presumption because it allows the presumption to be removed not based on reliable data but upon the ''risk assessor's expectation. (Id. at 9).

NRDC, however, is mistaken in its interpretation of this language. In directing the risk assessor to consider the likely impact of a DNT study on a risk assessment, EPA was not asking the risk assessor to guess at the results of the DNT study. Rather, EPA was directing the risk assessor to consider what the reliable data available on the pesticide told the risk assessor about the likely outcome of the DNT study. To ensure that the policy was not misunderstood on this point, the policy explicitly states that ''[d]iscussions in this document of the appropriateness, adequacy, need for, or size of an additional safety factor are premised on the fact that reliable data exist for choosing a 'different' factor than the 10X default value.'' (Ref. 2 at 12). To the extent the policy statement injects any uncertainty with regard to this issue, EPA herein confirms that a decision to choose a factor different than the default 10X factor must be based on reliable data.

e. *Conclusion.* EPA rejects NRDC's contention that an EPA finding that a DNT study is needed in evaluating the risks posed by the pesticide is outcome-determinative as regards to retaining the children's safety factor until such time as the DNT study is submitted and reviewed. The statute specifically grants EPA discretion to apply a different additional safety factor where EPA can conclude based on reliable data that the different factor is safe for infants and children. NRDC has made no argument that would justify an across-the-board conclusion that in the absence of a DNT study an individual examination of the existing data pertaining to a pesticide cannot provide a reliable basis for concluding that a different safety factor would be safe for infants and children. NRDC's claim that a DNT study may lower EPA's RfD (which EPA does not disagree with) is not by itself sufficient to bar EPA from making a case-by-case inquiry into the safety of a different additional safety factor for the protection of infants and children in the absence of such a study. Further, NRDC has offered no pesticide-specific arguments as to the pesticides in this proceeding as to why the absence of a DNT study requires the retention of the default 10X additional factor.

3. *Other pesticide-specific missing toxicity data*—a. *Diflubenzuron.* NRDC claims that EPA is missing toxicology data for two diflubenzuron metabolites, deemed necessary by EPA to justify an unconditional registration.

As EPA has previously noted, the toxicology database for diflubenzuron is complete for assessment of increased susceptibility to infants and children. (67 FR 59006, 59013, September 19, 2002; 67 FR 7085, 7089, February 15, 2002). EPA has received and reviewed all required studies bearing on the assessment of the effects of diflubenzuron following *in utero* and/or postnatal exposure. These studies demonstrated that diflubenzuron presented a low risk to the developing organism. For example, in the prenatal developmental toxicity studies in rats and rabbits, no developmental toxicity was seen at the Limit Dose (1,000 mg/kg/day) and in the two-generation reproduction study in rats toxicity in the offspring was manifested as decreased body weight at approximately 4,000 mg/kg/day (4 times the Limit Dose) The Limit Dose is generally regarded as the highest dose that could be tested in animal studies to maximize detection of potential adverse effects of a chemical (e.g, systemic toxicity,

carcinogenicity) without overloading the metabolic and/or physiological process of the animals. This upper limit dose (1,000 mg/kg/day) is equivalent to dietary concentrations of approximately 20,000 parts per million (ppm) in the diet of rats, 7,000 ppm in the diet of mice, and 40,000 ppm in the diet of dogs

With regard to the alleged need for additional data on the diflubenzuron metabolites, PCA and CPU, the **Federal Register** notice establishing the challenged tolerance specifically stated that ''there are no residue chemistry or toxicology data requirements that would preclude the establishment of a conditional registration and permanent tolerance for the combined residues of diflubenzuron, . . . and its metabolites 4-chloroaniline [PCA] and 4-chlorophenylurea [PCU] in/on pears at 0.05 ppm.'' (Id. at 7090, February 15, 2002). EPA's risk assessment for diflubenzuron noted no toxicology data needs and no other data needs other than validation of the analytical enforcement method (which has now been submitted, see Unit VII.C.5.d. of this document). (Ref. 57) The diflubenzuron registration on pears was conditional because validation of the analytical method was required. (Id.) Further, EPA considered and rejected NRDC's claims regarding the need for more toxicology data on the diflubenzuron metabolites in a tolerance rulemaking in September 2002. EPA noted that ''the rate of metabolism of diflubenzuron to PCA or CPU in plants, ruminants, and the environment is low and, thus, exposure to these metabolites will be minimal.'' (67 FR 59006, 59013, September 19, 2002). EPA relied upon the fact that when PCA and CPU were evaluated using a low dose linear model for cancer risk assessment - the most sensitive and conservative method for evaluating risk, whether from cancer or any other endpoint - these metabolites were found to pose a negligible risk. (Id.) EPA concluded that ''additional hazard testing for these metabolites will not lead to a more protective regulatory decision.'' (Id.) In these circumstances, EPA is confident that it has adequate reliable data to assign a factor different than the 10x default value to diflubenzuron, taking into account its PCA and CPU metabolites.

b. *Fluazinam.* NRDC asserts that for fluazinam EPA is missing a 28–day inhalation study, and a conditionally-required subchronic neurotoxicity battery. In response, EPA notes that a subchronic neurotoxicity study conducted with fluazinam has been received and reviewed. No treatment-related effects were observed in males or females at the highest dose tested in this study. (Ref. 58). EPA reserved the right to require this study to be redone because a toxic impurity of fluazinam was at a low level in the test material used in the study. EPA plans to reevaluate this issue once the DNT study is submitted and reviewed. (Id. at 39–40). Nonetheless, a clear NOAEL and LOAEL was identified for the impurity in other studies and EPA has ''high confidence in the hazard endpoints and dose-response assessments'' for fluazinam. (Id. at 42–44). Regarding the data requirement for the 28–day inhalation study, this study is primarily required to assess worker risk and is not relevant to the exposure patterns for fluazinam examined in making the safety determination under FFDCA section 408. Accordingly, there is reliable data to assess the risks of fluazinam to infants and children despite the lack of a repeat subchronic neurotoxicity study and 28–day inhalation study.

c. *Furilazole.* NRDC claims that EPA lacks a chronic dog study for furilazole. NRDC is correct that EPA does not have a chronic dog study for furilazole. EPA determined that because furilazole is an inert ingredient (safener) with a limited use that the chronic dog study was not needed given consideration of the rest of the toxicological data on furilazole. Nonetheless, to be protective, EPA applied an additional FQPA safety factor of 3X in deriving the chronic reference dose. The chronic reference dose was calculated by dividing the NOAEL of 0.26 mg/kg/day in the 2–year rat study (based on increased absolute and relative liver and kidney weights in males at 5.05 mg/kg/day in rats) by both the standard safety/uncertainty factors (10X for inter-species variability and 10X for intra-species variability) and a 3X factor to account for the lack of the chronic dog study (i.e, 0.26 ÷ 300X = 0.0009 mg/kg/day). A factor of 3X was judged to be adequate because the results from the subchronic toxicity studies in rats and dogs show that the toxicity of furilazole is similar, both qualitatively and quantitatively, in both species. The liver was the target organ in both species. EPA found there to be no significant quantitative difference in the relative responses of dogs and rats to the hepatotoxic effects of furilazole in the subchronic studies. The NOAELs/LOAELs for both species were based on hepatotoxicity and are effectively the same value (5/15 and 7/34 mg/kg/day in dogs and rats, respectively). No target organs were identified in dogs that were not also identified in rats. (Ref. 59).

d. *2,4-D.* In an introductory section to its objections that was not linked to any specific objection, NRDC expressed concern that EPA has not adequately considered epidemiological studies linking 2,4-D with non-Hodgkin's lymphoma and canine malignant lymphoma which NRDC; (Ref. 8 at 5), animal studies showing potential endocrine effects of 2,4-D; (Id. at 5-6), epidemiological data showing endocrine effects on adverse reproductive outcomes; (Id. at 6), and animal studies evidencing 2,4-D's affect on the developing brain and nervous system. Reference to cancer studies does not appear relevant to objections concerning the children's safety factor. That safety factor is designed to provide additional protection for risks that have a safe threshold and not non-threshold risks such as cancer. (21 U.S.C. 346a(b)(2)(C)). The epidemiological data cited by NRDC is either weak (few subjects, questionable controls, not performed by epidemiologists) or not specific to 2,4-D. (See Ref. 60). As to the animal studies on brain/nervous system effects, NRDC cites a published article involving single dose studies (Ref. 8 at 7) that show nervous system effects at levels consistent with the levels at which the data before EPA evidenced effects. (Ref. 61). Accordingly, the cited data does not materially affect EPA's analysis.

As part of the reregistration of 2,4-D, EPA is comprehensively reviewing these issues. This review has considered a considerable amount of new data that have become available since 2002. EPA's draft risk assessment for 2,4-D is available in EPA's electronic docket under the docket number OPP–2004–0167.

4. *Missing exposure data - general—*

a. *Farm children exposure.* NRDC argues that EPA is lacking data on exposure to farm children and thus may not remove the additional 10X safety factor. EPA disagrees. As discussed above and in the Imidacloprid Order, the epidemiological data cited by NRDC have not shown that there are significant exposures to farm children that occur as a result of living in close proximity to agricultural operations. EPA concluded that the evidence presented by NRDC is fragmentary, at best, as to whether pesticide exposure levels in homes of children living in agricultural areas are significantly different than levels in other homes and whether children living in agricultural areas have significantly different exposures than non-agricultural children.

NRDC also submitted two articles addressing pesticide spray drift and post-application volatilization drift of pesticides. EPA's analysis of exposure due to pesticide drift in Unit VII.B.2., however, showed that, as to the

pesticides involved here, there was little basis to find that drift could result in exposure posing a risk of concern. In fact, the recent data from the CTEPP study suggest that dietary exposure is generally the dominant exposure. What the CTEPP data show, therefore, is that NRDC, by asserting that the 10X safety factor should be retained to protect farm children from additional exposures they allegedly receive, is essentially asking that the dominant dietary exposure and other quantified non-dietary exposures be multiplied by 10 in estimating risk to protect against underestimating a potential non-dietary exposure that is likely to be, at most, a fraction of the dietary exposure alone. This is so because retaining an additional 10X safety factor decreases the estimated safe dose for humans by a factor of 10 making estimated exposure 10 times greater compared to the revised safe dose.

After considering all of data bearing on exposure to the 13 pesticides in NRDC's objections, including both pesticide-specific data and the more general data on children's exposure to pesticides, EPA concludes it has sufficient reliable exposure data on these pesticides to find that an additional 10X factor is not needed to protect the safety of infants and children. Specifically, the data reviewed in this Order, in the Imidacloprid Order, and in the individual tolerance actions give EPA confidence that it has not underestimated exposure as to these pesticides.

In this regard, EPA would note that, for 8 of the 13 pesticides, it used its most conservative (health protective) method of estimating dietary exposure assuming that all food covered by the pesticide tolerances contained residues at the tolerance level. (66 FR at 66335, December 26, 2001 (halosulfuron); 67 FR at 3115, January, 23, 2002 (mepiquat); 67 FR at 4917, February 1, 2002 (bifenazate); (67 FR at 6424-6425, February 12, 2002 (zeta-cypermethrin); 66 FR at 33182-33183, June 21, 2001(isoxadifen-ethyl); 67 FR at 14653-54, March 27, 2002 (acetamiprid); 67 FR at 15731, April 3, 2002 (furilazole); 67 FR at 19116, April 18, 2002 (fenhexamid). (The reasons these assumptions produce such large overestimates is discussed in detail in Unit VII.D.5). Even for the other five pesticides, EPA's dietary exposure estimate was not highly refined. In none of these exposure estimates did EPA use a probabilistic risk assessment, the assessment technique that produces the most realistic picture of potential risk, or rely on food monitoring data to estimate residue levels. For all but one of the pesticides, EPA refined exposure estimates as to only some but not all food commodities. (See Unit VII.D.6; 66 FR at 66786, December 27, 2001 (for pymetrozine, exposure assessment refined only as to chronic risks); 67 FR at 7087, February 15, 2002 (for diflubenzuron, exposure assessment refined only as to chronic risks and only as to some crops); 67 FR at 10625, March 8, 2002 (for 2,4-D, exposure estimates refined for only citrus for acute risk and for only some crops for chronic risk); 64 FR at 2998, January 20, 1999 (for propiconazole, exposure estimates refined for only some crops for chronic risk; no refinement for acute risk); 67 FR at 19120, April 18, 2002, Ref. 46 at 6 (for fluazinam, exposure estimates refined for one of three crops for chronic risk; no refinement for acute risk)). Further, EPA's conservative method of modeling drinking water exposure was used, at least in part, for all of the pesticides. (See 69 FR at 30058-30065, May 26, 2004). For those pesticides that have residential uses, EPA relied upon its very conservative approach for estimating exposures that can occur around the home from such uses. (See 69 FR at 30055, May 26, 2004). The conservativeness of EPA's exposure estimates is perhaps evidenced most dramatically by a comparison between exposure estimates for 2,4-D from a study relied upon by NRDC involving actual sampling of 2,4-D residues in homes and the EPA's exposure estimates. The 2,4-D exposure estimate EPA prepared for this Order is almost two orders of magnitude greater than the estimates from the cited study and the exposure estimate for the challenged tolerance action is well over an order of magnitude greater. (See Unit VII.D.7.e).

b. *Lack of comprehensive drinking water (DW) monitoring data*. NRDC contends that, because EPA used a model for calculating drinking water exposure, EPA does not have, as a definitional matter, ''reliable data'' for choosing a factor different than the 10X default value. Similar comments were made during the development of EPA's Children's Safety Policy. This issue was addressed at length in the response to the imidacloprid objections. (69 FR at 30058–30064, May 26, 2004). That response is incorporated herein and is summarized below.

Although the availability of drinking water monitoring data has increased dramatically in the last several years, EPA still finds it necessary to rely for most pesticides upon various exposure models to estimate exposure levels in drinking water. These models are based on generic data regarding fate and transport of pesticides in the environment, and they operate by combining this generic data with pesticide-specific data on chemical properties to estimate exposure. EPA has primarily used its drinking water models to ''screen'' those pesticides that may pose unacceptable risks due to exposures in drinking water from pesticides not likely to result in such exposures. To accomplish this goal, the models are based on data from studies at sites that are highly vulnerable to runoff of pesticides to surface water or leaching of pesticides to ground water. If a pesticide fails this conservative (health-protective) screen, EPA would investigate whether the model is significantly overstating the residue levels that actually occur.

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

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.

In the Imidacloprid Order, EPA analyzed each of its water models extensively. Based on the results of design characteristics of the models, outside peer review of the models, validation of the models, and comparison between the models' predictions and extensive water monitoring data, EPA concluded that the models are based on reliable data and will produce estimates that are unlikely to underestimate exposure to pesticides in drinking water. (69 FR at 30065). Accordingly, EPA reaffirms its earlier conclusion that its drinking

water models provide a reliable basis for finding that exposure to pesticide residues in water are not underestimated.

5. *Missing exposure data - specific*—a. *Mepiquat*. NRDC asserts that there is a data gap for side-by-side residue field trials for mepiquat. (Ref. 7 at 5). The tolerance in question covers both mepiquat chloride (*N,N*-dimethylpiperidinium chloride) and mepiquat pentaborate (*N,N*-dimethylpiperidinium pentaborate) on cotton. A full toxicological and residue database was submitted on mepiquat chloride. As to mepiquat pentaborate, the petitioner relied on the mepiquat chloride data and a dissociation study demonstrating that ''pentaborate salt'' of mepiquat dissociates in water in an identical physical manner to the ''chloride salt'' of mepiquat. Based on this data, EPA concluded that the proposed foliar application of mepiquat pentaborate to cotton is not expected to result in residues of mepiquat per se greater than those resulting from the application of mepiquat chloride. (67 FR at 3114, January 23, 2002). The required residue studies are confirmatory in nature. (Ref. 62). Accordingly, EPA concludes it has reliable data on mepiquat residues in cotton.

b. *Bifenazate-assessment of drinking water exposure to bifenazate degradates*. NRDC claims that EPA has failed to complete ''an assessment of drinking water exposure to bifenazate degradates.'' (Ref. 7 at 5). As the **Federal Register** notice establishing the contested tolerances for bifenazate reveals, however, EPA scientists considered environmental persistence of bifenazate and its two major degradates, D3598 (diazinecarboxylic acid, 2-(4-methoxy-[1,1′-biphenyl]-3-yl), 1-methylethylester) and D1989 (4-methylethylester). Aqueous photolysis and soil metabolism studies demonstrated that the parent bifenazate and the D3598 degradate ''quickly metabolize under aerobic soil conditions.'' (67 FR at 4918, February 1, 2002). Noting the lack of persistence of these two compounds and the absence of any acute dietary endpoint, EPA focused its drinking water exposure assessment for bifenazate on the degradate that had a possibility of being present in drinking water. (Id.). Accordingly, NRDC is incorrect to assert that potential exposure to bifenazate degradates in drinking water was not assessed by EPA and hence, NRDC's assertion does not call into question EPA's decision concerning the children's safety factor for bifenazate.

c. *Zeta-cypermethrin—assessment of drinking water exposure zeta-cypermethrin degradates*. NRDC claims that EPA has ''failed to address drinking water exposure to zeta-cypermethrin degradates.'' (Ref. 7 at 5). To the contrary, EPA has determined that DCVA need not be included in drinking water assessments for zeta-cypermethrin or other pyrethroids.

DCVA is the hydrolysis product of several pyrethroids (permethrin, cypermethrin, zeta-cypermethrin, cyfluthrin). It is the acid portion of these insecticides (which are esters) and its full chemical name is 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid. Although it is significantly more mobile than the parent pyrethroids, EPA has not included it in drinking water assessments for the following reasons.

(1) Based on its structure (i.e., lacking the ester function in the parent insecticides), it would be devoid of the neurotoxic properties of the parent and thus, it would not be of significant concern with respect to the neurotoxicity endpoints on which the dietary risks of the pyrethroids are assessed.

(2) *Mutagenicity and acute toxicity data have been provided for DCVA*. The submitted salmonella reverse mutation assay (Ames assay) conducted with DCVA indicated that the compound was negative in the presence and absence of metabolic activation in all five tester strains. The submitted acute oral toxicity study in rats conducted with DCVA concluded that the acute oral LD_{50} is 1,609 mg/kg for males and 1,192 mg/kg for females. These values are higher than those for the parent cypermethrin compounds (cypermethrin: LD_{50} = 247 mg/kg for males, LD_{50} = 309 mg/kg for females; zeta-cypermethrin: LD_{50} = 134.4 mg/kg for males, LD_{50} = 86.0 mg/kg for females).

(3) Although DCVA does contain the electrophilic dichlorovinyl group which raises a potential concern with carcinogenicity, it is not likely this compound is a carcinogen. The latter conclusion is based on the different toxicity profiles of the parent pyrethroids which produce DCVA in significant quantities. Cyfluthrin, permethrin, and zeta-cypermethrin/cypermethrin are all extensively metabolized by cleavage of the ester linkages with formation of DCVA as shown by the amount and nature of the radioactivity appearing in urine of rats. In the case of cypermethrin, similar metabolism and pharmacokinetics are observed in mice and dogs. As a result, toxicological testing of the parent compounds results in testing of DCVA at approximately one-third of the dose of the parent on a weight basis. In spite of that fact, the parent compounds have markedly different profiles of toxicity. For example, using an earlier cancer classification system, cyfluthrin is a category E carcinogen (i.e., no evidence of carcinogenicity), zeta-cypermethrin is category C (i.e., possible human carcinogen), and permethrin is category C(q) (i.e., possible human carcinogen with sufficient evidence to quantify cancer risk). On this basis, the common metabolite DCVA is not likely to be carcinogenic.

(4) Even though DCVA is more mobile than its parent compounds, it is expected to reach groundwater in very low levels. Exposure is further mitigated by the DCVA's high polarity and the likelihood of it being readily excreted from the body due to the presence of the carboxylic acid group.(Refs. 63, 64 and 65)

d. *Diflubenzuron—Residue data on two metabolites*. NRDC states that there is a data gap for residue chemistry data on two diflubenzuron metabolites. (Ref. 7 at 6). As discussed in Unit VII.C.3.a. of this document, the only missing data at the time of the tolerance action was Agency validation of the analytical enforcement method. The **Federal Register** notice does note, however, that the analytical enforcement methods have been successfully validated independently, (67 FR at 7090; Ref. 66). The Agency validation has now been successfully completed. (Ref. 67). In any event, a second validation is conducted by EPA not for the purposes of refining its risk assessment but to insure that the procedures for conducting enforcement monitoring are adequately described so that accurate and reproducible results can be produced by enforcement personnel. Accordingly, this objection is without merit.

e. *Acetamiprid—oral exposure from residential uses*. NRDC asserts that EPA is missing data bearing on oral exposure to acetamiprid from residential uses of the pesticide. (Ref. 9 at 6). The **Federal Register** notice on the contested acetamiprid tolerance notes that ''incidental oral exposure is an insignificant pathway of exposure'' for acetamiprid. (67 FR at 14657, March 22, 2004). Little or no incidental oral exposure is expected since acetamiprid's residential uses are limited to ornamentals, flowers, vegetable gardens, and fruit trees. Incidental oral exposure to pesticides can occur when young children engage in ''mouthing'' behavior (i.e. repeatedly placing their hands or other objects in their mouth) in a location where a pesticide is present. EPA assumes that incidental oral exposure to a pesticide

may occur when a pesticide is used to treat a home lawn because young children frequently play on home lawns. EPA, however, considers it unlikely that young children would spend an extended time in flower, vegetable, or ornamental gardens, and thus treatment of such gardens with a pesticide is not likely to lead to a significant exposure to children by the incidental oral route.

EPA would note that NRDC was mistaken in its objections when it claimed that EPA estimated the MOE for short- and intermediate-term residential exposure to be 189 for adults and 239 for children aged 10–12. (Ref. 9 at 9-10). As the **Federal Register** notice made clear the MOEs for these two groups are 1,858 and approximately 3,000, respectively, for pesticide exposures in food and 18,000 and 23,000, respectively for non-dietary pesticide exposures. (67 FR at 14657).

6. *Missing risk assessments.* As to several of the pesticides, NRDC has claimed that there is a data gap for a specific type of risk assessment (e.g., short-term residential risk assessment) and that therefore the full 10X children's safety factor must be retained. There are two problems with this argument. First, a risk assessment is not data or information that is required to be submitted to EPA but rather an analysis of the data and information that is submitted. Thus, NRDC has mislabeled these allegedly missing risk assessments by calling them ''data gaps.''

Second, and more important, NRDC appears to have misread the relevant **Federal Register** notices in reaching the conclusion that various risk assessments are missing. In some cases, risk assessments that are claimed to be missing were performed and were described in the pertinent **Federal Register** notice. In other cases, NRDC may have been confused by language in **Federal Register** notices that states a certain risk assessment was not conducted or performed. In conducting the safety evaluation required by section 408, EPA performs various risk assessments depending on the types of risks posed by a pesticide and the varieties of exposure routes related to its use. The number and scope of risk assessments may vary considerably from pesticide to pesticide. Language that a risk assessment was not required or performed has been frequently used by EPA to indicate circumstances where a quantitative risk assessment was not needed either because the pesticide did not present a particular hazard (e.g., a quantitative acute risk assessment is not performed for a pesticide not judged to pose a risk due to a one-day or single exposure) or there was no exposure (e.g., a residential risk assessment is not performed when the pesticide does not have residential uses). As explained below, in each instance where NRDC objected to a ''missing'' risk assessment, EPA had either performed the risk assessment or determined that such risk assessment was not needed.

a. *Halosulfuron-methyl.* NRDC claims that EPA, in evaluating halosulfuron, failed to conduct a cancer risk assessment, and short-term and intermediate-term residential risk assessments for children and for adults. (Ref. 6 at 5). As an initial matter, EPA questions the relevance of this argument to the children's safety factor given the fact that EPA treats cancer as a non-threshold effect unless data show otherwise, and the children's safety factor only applies to threshold effects. (See 21 U.S.C. 346a(b)(2)(C)). NRDC has not contended that halosulfuron-methyl is a non-threshold carcinogen. In any event, based on its qualitative assessment of the data bearing on cancer, EPA concluded that halosulfuron-methyl was not likely to be a human carcinogen, and therefore did not conduct a quantitative risk assessment. (66 FR at 66338, Dec. 26, 2001). As to the missing short-term and intermediate-term risk assessments, those risk assessments were performed and summarized on pages 66337 and 66338 of the **Federal Register** notice to which NRDC filed objections. (Id. at 66337–66338).

b. *Bifenazate.* NRDC asserts there is a data gap for a developmental toxicity assessment for bifenazate. (Ref. 7 at 5). NRDC appears to be referring to language in the **Federal Register** notice establishing the contested bifenazate tolerances that states that ''a clear assessment of developmental toxicity was not possible'' in the range-finding study used to choose dose levels for the main developmental toxicity study in rabbits. (67 FR at 4915). The statement ''a clear assessment of developmental toxicity was not possible'' in the range finding study is an error in the Data Evaluation Record (Ref. 68) since a detailed assessment of developmental toxicity is not performed in the range finding study. The objective of this study is to demonstrate definite maternal toxicity and to guide selection of dose levels for the main study regarding development toxicity in rabbits. This main study was submitted and considered in conducting the risk assessment for bifenazate. (67 FR at 4914). The study showed no developmental toxicity at 200 mg/kg/day (highest dose tested). The doses tested in this study was judged to be adequate since abortions were seen at ≥250 mg/kg/day and decreases in body weight seen at doses ≥500 mg/kg/day in the range-finding study. This study provided a clear assessment of developmental toxicity in rabbits for bifenazate.

c. *Isoxadifen-ethyl.* NRDC claims that short-term and intermediate-term residential risk assessments are missing for isoxadifen-ethyl. (Ref. 9 at 6). As the relevant **Federal Register** notice notes, however, EPA determined these residential risk assessments were not necessary because isoxadifen-ethyl is not approved for any residential uses. (67 FR at 33185).

d. *Propiconazole.* NRDC argues that there is a data gap for all residential risk assessments for propiconazole. (Ref. 9 at 6). For propiconazole, EPA did quantitatively assess the short-term and intermediate-term residential risks resulting from the treatment of wood with propiconazole. (64 FR at 2999, January 20, 1999). EPA determined it was unnecessary to assess quantitatively short-term and intermediate-term residential risks connected with the turf use of propiconazole because of the unlikelihood of exposure. (Id.). EPA considered exposure to be minimal due to a combination of a number of factors: (1) Propiconazole is infrequently used on lawns; and (2) even when used, it is generally applied by lawn care operators rather than homeowners.

e. *Fenhexamid.* NRDC claims that short-term and intermediate-term residential risk assessments are missing for fenhexamid. (Ref. 9 at 6). As the relevant **Federal Register** notice notes, however, EPA determined these residential risk assessments were not necessary because fenhexamid is not approved for any residential uses. (67 FR at 19118, April 18, 2002).

f. *Fluazinam.* NRDC argues there is a data gap for a cancer risk assessment for fluazinam. (Ref. 9 at 6). As with its objection concerning the halosulfuron-methyl cancer risk assessment, EPA questions the relevance of this argument to the children's safety factor decision. NRDC has not contended that fluazinam is a non-threshold carcinogen. In any event, EPA did qualitatively assess the cancer potential of fluazinam and found that the data showed, at most, suggestive evidence of carcinogenicity but that the evidence was not strong enough to warrant quantifying this risk. (67 at 19128, April 18, 2002). This decision was based on the fact that there was equivocal/some evidence of carcinogenicity in one species and one sex. Thyroid tumors were seen in male rats, but not in female rats, while liver tumors were seen in male mice but not

in female mice. In addition, fluazinam was negative in mutagenicity assays. (Ref. 69).

g. *2,4-D.* NRDC claims that short-term and intermediate-term residential assessments have not been completed for 2,4-D. (Ref. 8 at 8). This claim is not supported by the record. The **Federal Register** notice associated with the challenged tolerances summarizes EPA's short-term residential risk quantitative assessment, (67 FR at 10629, March 8, 2002), and explains why no intermediate-term exposure, and hence no intermediate-term risk, is expected, (Id. at 10627).

7. *Conclusion on children's safety factor objections.* After examining each of NRDC's objections, EPA has found no basis in the objections to revise its conclusions regarding the children's safety factor as to the 13 pesticides.

C. LOAEL/NOAEL

NRDC argues that EPA cannot legally make the reasonable certainty of no harm finding for pymetrozine, mepiquat, zeta-cypermethrin, and fluazinam because EPA has relied on a LOAEL in assessing the safe level of exposure to the pesticide. NRDC claims EPA ''cannot lawfully establish tolerances in the absence of a no-observed-effect-level (NOEL).'' (Ref. 7 at 18). Implicit in this argument is that EPA cannot use a no-observed-adverse-effect-level (NOAEL) in making a safety finding. In later objections, NRDC confirmed that in fact it was contending that section 408's safety standard does not permit EPA to rely on a NOAEL in concluding a tolerance is safe. Rather, according to NRDC, EPA may only make a safety finding for a pesticide where EPA has determined the dose in animals at which no effects, adverse or otherwise, are elicited from exposure to the pesticide. (Ref. 7 at 17-18). Below EPA identifies the flaws in NRDC's generic argument concerning LOAELs and NOAELs and addresses the pesticide-specific concerns NRDC raises with regard to use of a LOAEL as to pymetrozine, zeta-cypermethrin, and fluazinam.

1. *Generic legal argument.* EPA believes that it can make a reasonable certainty of no harm finding based on a LOAEL from an animal study (where no NOAEL or NOEL was found) in appropriate circumstances. Whether or not a reasonable certainty of no harm finding can be made when only a LOAEL is identified in a study depends on whether EPA has sufficient toxicological evidence to estimate with confidence a projected NOAEL that is unlikely to be higher than the actual NOAEL. Typically, when a LOAEL but not a NOAEL has been identified by a study, EPA will, when the data support it, project a NOAEL for that study by dividing the LOAEL by a safety factor.

There is nothing in the statutory safety standard explicitly addressing the use of NOELs, NOAELs, or LOAELs. Moreover, nothing in the phrase ''reasonable certainty of no harm'' legally precludes use of NOAELs or LOAELs to make a finding regarding the likelihood that harm will occur at a given dose. Whether a NOAEL or LOAEL provides a sufficient basis for a reasonable certainty of no harm finding is a question of scientific fact. EPA fully responded to the arguments raised by NRDC in the Imidacloprid Order, (69 FR at 30066–30067, May 26, 2004), and incorporates that response herein.

2. *Objections pertaining to specific pesticides*—a. *Pymetrozine.* NRDC asserts that EPA unlawfully relied upon a LOAEL in assessing both short-term risk and acute risks to pymetrozine. (Ref. 6 at 9). NRDC is correct that EPA used the LOAEL from an acute neurotoxicity study with pymetrozine to assess both the acute dietary risk and short-term residential risk for the general population. (Acute risk to the developing fetus, however, was based on the developmental study in the rabbit which had a NOAEL.) (Ref. 70). To ensure that there would be a reasonable certainty of no harm, EPA retained two additional 3X safety factors in assessing acute risk to the infants and children. (Id. at 18). This decision was based both on the lack of a LOAEL from the acute neurotoxicity study and the absence of a required DNT study. The protectiveness of this approach is demonstrated by the fact that the LOAEL from the acute neurotoxicity study used for conducting the safety assessment for acute risk faced by the general population is only higher by a factor of 2 than the NOAEL from the subchronic neurotoxicity study. Retaining what is essentially a 10X safety factor results in a projected acute NOAEL five times lower than the NOAEL found in a subchronic study measuring the same endpoint. Thus, this projected NOAEL is more conservative for a single exposure than the measured result in the repeated exposure study (i.e., 13 weeks).

Syngenta, the registrant for pymetrozine, defends EPA's reliance on a LOAEL here noting that the effects observed at the LOAEL ''were reversible and not of severe magnitude (for example, body temperature was decreased at the LOEL, but only by about 2 percent compared to controls).'' (Ref. 18 at 5). EPA agrees that the severity of the effect at the LOAEL should be considered in the weight of the evidence regarding a safety determination and relied on the lack of severity and reversibility in its determination on pymetrozine. (Ref. 71).

b. *Mepiquat.* NRDC claims that for mepiquat EPA ''measured reproductive toxicity only on the basis of a LOAEL.'' (Ref. 7 at 18). NRDC was mislead, however, by the **Federal Register** notice's description of the rat reproduction study which states: ''The study did not establish a reproductive NOAEL; however, the systemic NOAEL of 1,500 ppm would also be regarded as the reproductive NOAEL.'' (65 FR at 1792, January 12, 2000). This was an error by EPA in preparing the **Federal Register** notice. In fact, in the two-generation reproduction study, the NOAEL for reproductive toxicity was 5,000 ppm (highest dose tested); a LOAEL was not established. (Ref. 72).

c. *Zeta-cypermethrin.* NRDC argues that EPA relied upon a LOAEL from a zeta-cypermethrin developmental toxicity study. (Ref. 7 at 18). NRDC, however, is mistaken. In the four developmental studies conducted with cypermethrin and zeta-cypermethrin in rats and rabbits, no developmental effects were observed at the highest dose tested. (Ref. 73). Maternal toxicity was seen in all four studies. NRDC may have been mislead by an error in one of the data tables in the **Federal Register** that lists the NOAEL for one of the four developmental studies as <35 mg/kg/day.'' (66 FR at 47981, September 17, 2001 (Table 2)). The table should have read ≥ 35 mg/kg/day. (Id.)

d. *Fluazinam.* NRDC claims that for fluazinam EPA relied upon a LOAEL in assessing dermal toxicity and that only a LOAEL was achieved in dietary studies in mice and rats. (Ref. 9 at 18). NRDC is correct that a dermal NOAEL (as distinguished from a systemic NOAEL) was not found in the 21–day dermal toxicity study. (67 FR at 19121, April 18, 2002). Nonetheless, EPA did not rely on the LOAEL from this study in setting the fluazinam tolerances because there are no residential uses for fluazinam and dermal toxicity is only relevant to exposure occurring in the residential setting. Moreover, the data were sufficient to set a systemic NOAEL from dermal exposure, as opposed to a NOAEL for dermal effects. (Ref. 58 at 14). A systemic NOAEL is the information needed to conduct an aggregate risk assessment. EPA had adequate data on oral toxicity for evaluating dietary exposure.

As to not achieving a NOAEL in dietary studies with mice and rats, NRDC appears to be referring to a 4–week dietary range-finding study in

mice and a special 90–day liver study in rats. The lack of a NOAEL in these studies is irrelevant to the fluazinam risk assessment. The lack of a NOAEL in the mouse study is not a concern because it is a range finding study (*i.e.* a preliminary study used to gauge dosing for another study) and the LOAEL (555 mg/kg/day) is approximately 50–fold higher than the LOAEL (10.7 mg/kg/day) and the NOAEL (1.1 mg/kg/day) in the chronic mouse study which was used establishing the chronic RfD. (67 at 19121, April 18, 2002 (Table 1)). The 90–day study in rats was a special non-guideline study (not requested by EPA) that tested one relatively high dose level (500 ppm) to evaluate the hepatotoxic effects of fluazinam and determine their reversibility. It was not considered for the purpose of determining a NOAEL and a RfD. Because the study only resulted in the modest liver changes of questionable toxicologic significance it was of marginal value. (Refs. 74 and 75) Neither of these studies were used for overall risk assessments (Ref. 46).

e. *Isoxadifen-ethyl, acetamiprid, propiconazole, furilazole, and fenhexamid.* NRDC has lodged a blanket legal objection to the use of NOAELs in assessing the risk to isoxadifen-ethyl, acetamiprid, propiconazole, furilazole, and fenhexamid. (Ref. 9 at 18). NRDC has offered no factual evidence or argument as to why reliance on these specific NOAELs invalidates EPA's safety determination. Accordingly, EPA denies this objection for the reasons given above and in the Imidacloprid Order, (69 FR at 30066–30067, May 26, 2004), for rejecting the argument that EPA is barred, as a matter of law, from using NOAELs in assessing the safety of pesticide residues.

D. Aggregate Exposure

1. *Worker exposure.* EPA has interpreted ''aggregate exposure'' to pesticide residues not to extend to pesticide exposure occurring at the workplace based on the language in section 408(b)(2)(D) explaining what exposures are included in the term ''aggregate exposure:''

> [T]he Administrator shall 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 the dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources . . . .

This language quite plainly directs EPA to limit consideration of aggregate exposure of pesticide residues and other related substances to those exposures arising from non-occupational sources. NRDC's claim that EPA erred by not considering worker risks in making tolerance decisions under section 408 runs afoul of Congress' explicit mandate that such exposures not be included. Although there is some ambiguity as to precisely how the factors listed in section 408(b)(2)(D) relate to the safety finding described in section 408(b)(2)(A)(ii), for the reasons set forth in the Imidacloprid Order, (69 FR at 30067–30068, May 26, 2004), NRDC's interpretation of the statutory language is unreasonable.

2. *Classification of farm children as a major identifiable population subgroup.* NRDC points out that FFDCA section 408 directs EPA to consider not just the general population in assessing aggregate exposure but also ''major identifiable subgroups of consumers.'' (21 U.S.C. 346a(b)(2)(D)(vi)). In this regard, NRDC argues that children living in agricultural communities should be treated as such a major identifiable subgroup. These children are an identifiable subgroup, according to NRDC, because of the allegedly heightened exposure to pesticides that they receive due to their proximity to farm operations and farm land and, for some, due to their contact with parents involved in agriculture. (Ref. 9 at 11–12). NRDC claims these children comprise a ''major'' subgroup citing statistics showing that ''320,000 children under the age of six live on farms in the United States[], . . . many hundreds of thousands of children play or attend schools on or near agricultural land, . . . [and] [t]he nation's 2.5 million farm workers have approximately one million children living in the United States.'' (Id.)

Whether or not EPA attaches the label ''major identifiable subgroup'' to farm children, EPA's risk assessment approach to children, including the major identifiable subgroups of children used in its risk assessments, adequately takes into account any pesticide exposures to children - whether as a result of living close to agricultural areas or otherwise. For some time, EPA has treated infants and children grouped by ages (*e.g.*, infants younger than 1 year, children 1 – 2 years) as major identifiable subgroups. These age groupings have been chosen to reflect different eating patterns of the age groups. In evaluating exposure to these or any other subgroup, however, EPA considers the range of exposures across the subgroup not just as a result of pesticide residues in food but from all non-occupational exposures. If a significant number of any of the population subgroups of children have higher exposures due to a non-food source (*e.g.*, residential uses of a pesticide, proximity to agricultural areas), EPA believes that that exposure is appropriate to consider in evaluating the range of exposures for the subgroup. The fact that the children in the subgroup receiving the higher exposures are not themselves labeled a major identifiable subgroup in no way lessens EPA's consideration of their exposures. Further, EPA questions whether NRDC has properly characterized farm children as a major identifiable subgroup in that it is not at all clear that the members of this group are readily identifiable nor does the evidence support that this group consistently receives higher pesticide exposures. These issues are discussed in greater depth in the Imidacloprid Order and that discussion is incorporated herein. (69 FR at 30068–30069, May 26, 2004).

3. *Adequacy of EPA's assessment of the aggregate exposure of children, including children in agricultural areas.* EPA believes that it has adequately assessed the aggregate exposure of children to the 13 pesticides (including both farm children and non-farm children), through its assessment of exposure through food, drinking water and residential use pathways. In support of its objection to this assessment, NRDC cites numerous studies for the proposition that other pathways (e.g., track-in) increase farm children's exposures, and it also cites information purportedly suggesting that volatilization and spray drift lead to higher exposures among farm children. For reasons discussed above (see Unit VII.B. and C.), and in the Imidacloprid Order, however, EPA does not believe that the epidemiological data relied upon demonstrate that the pathways asserted, to the extent they exist, lead to farm children experiencing pesticide exposure levels significantly higher than those experienced by other children. Rather, these studies are largely inconclusive, and to the extent they show anything, tend to suggest that farm children and non-farm children generally receive similar levels of exposure.

Further, EPA's evaluation of the potential additional exposure to the 13 pesticides challenged in these objections from spray or volatilization drift showed little likelihood of significant exposure. In any event, an overly conservative (health-protective) estimate of overall drift, food, water, and residential exposures shows no safety concerns for any of these pesticides.

4. *Residential exposure as a result of use requiring a tolerance.* NRDC also argues that EPA has erred in not assuming that additional residential exposure occurs each time an additional agricultural use is added. The reasons explained above as to why any additional exposure to children as a result of their proximity to farming operations is expected to be insignificant as regards the 13 pesticides apply with equal or more force as to this contention.

5. *Anticipated residues/exposures due to purchase of food at farm stands.* NRDC claims that EPA has underestimated aggregate exposure for several of the pesticides because EPA used ''anticipated residues'' for estimating exposure rather than assuming residues would be at the tolerance level. NRDC argues that ''EPA must ensure that the legal level of pesticide chemical residue - the established tolerance levels - are themselves safe.'' (Ref. 9 at 20). Additionally, NRDC asserts that using ''anticipated residues'' does not take into account the ''significant number of consumers who purchase produce at farmers markets, farm stands, and 'pick-your-own' farming operations.'' (Ref. 9 at 19). NRDC cites information from the National Association of Farmers' Market Nutrition Programs indicating that 1.9 million people purchase food from farm stands.

NRDC is wrong in its assertion that EPA must assume all residues in food are at tolerance levels in assessing the safety of tolerances. The statute is quite clear that EPA may consider data on anticipated or actual pesticide residue levels in establishing tolerances. (21 U.S.C. 346a(b)(2)(E)). This statutory provision essentially codifies EPA practice developed and implemented over the last 20 years.

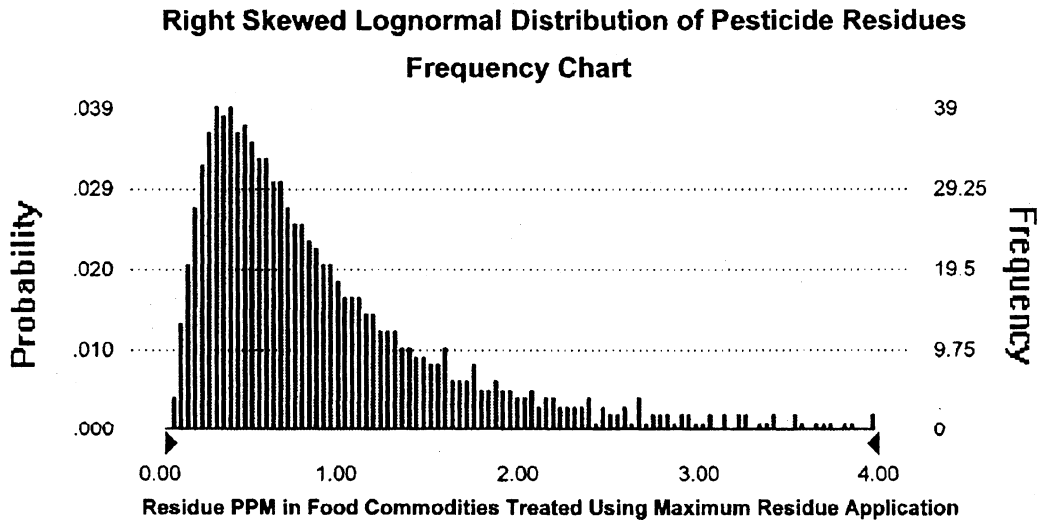
EPA's approach to estimating exposure for tolerance risk assessments, at least as far back as the late 1980's, is to first make a worst case assessment of the exposure, and then, only if this worst case exposure assessment indicates that there might be risk concerns would EPA undertake a more sophisticated assessment using more realistic data such as data on ''anticipated residues.'' (See Ref. 76). Worst case exposure was designated by EPA as the Theoretical Maximum Residue Level (TMRC) and was calculated by assuming all foods covered by tolerances had residues at the tolerance level. (See, *e.g.*, 59 FR 54818, 54820, November 2, 1994; (metalaxyl tolerance); 50 FR 26683, June 27, 1985; (chlorpyrifos-methyl tolerance)). 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.'' (Ref. 76 at 1; see, e.g., 54 FR 33044, 33045, August 11, 1989) (iprodione tolerance)).

Use of percent crop treated data and anticipated residue information is appropriate because EPA's worst case assumptions of 100 percent treatment and residues at tolerance value significantly overstate residue values. There are several reasons this is true. First, all growers of a particular crop would rarely choose to apply the same pesticide to that crop; generally, the proportion of the crop treated with a particular pesticide is significantly below 100 percent. For example, the 2001 USDA Agricultural Chemical Usage survey notes 14 insecticides used on tomatoes with percent crop treated values ranging from 2 to 26 percent, including 9 insecticides used on less than 10 percent of the crop. In another example, the survey notes 39 herbicides used on corn with percent crop treated values ranging from less than 1 to 68 percent, including 32 herbicides used on less than 10 percent of the crop. (Refs. 77 and 78). Obviously, if a portion of a crop is not treated, food from that portion of the crop will not contain residues.

Second, for that portion of the crop that is treated, residues on most treated commodities are likely to be significantly lower than the tolerance value, even when the pesticide is applied in the manner and amount permitted by the label that is likely to yield the highest possible residue [hereinafter referred to as a ''maximum residue application'']. EPA's general practice is to set tolerance values just slightly above the highest value observed in crop field trials conducted using maximum residue applications. For example, based on the hypothetical pesticide residue data set in Figure 1, EPA would set the tolerance value at 4 ppm or slightly higher. As Figure 1 illustrates, there may be some commodities from a treated crop that approach the tolerance value where the maximum residue applications are followed, but most commodities generally fall significantly below. In fact, EPA's experience is that crop field trial data generally does not sort out into a normal, bell-shaped distribution; rather, the distribution when plotted based on frequency/probability (Y axis) and level of residues (X axis) is generally ''log-normal'' or ''right-skewed'' - that is, there is a clumping of values close to, or on, the Y axis (i.e. approaching non-detectable residues) with a few higher values out farther on the X axis (i.e. approaching the tolerance value) resulting in a long ''tail'' stretching out to the right. (Ref. 4 at 12, Ref. 79 and Ref. 80 at 10). Figure 1 presents a hypothetical example of how residue data generally fall in a right-skewed curve.

FIGURE 1



Third, if less than the maximum residue application is followed (e.g., lower than the maximum amount applied, applications are not as frequent as allowed, the pre-harvest interval after the last application exceeds thelegal minimum), residues will be even lower than measured by crop field trials using maximum residue applications. Essentially, the entire distribution curve illustrated in Figure 1 shifts to the left. Finally, residue levels measured in the field do not take into account the lowering of residue values that frequently occurs as a result of degradation over time and through food processing and cooking. (Ref. 4 at 14, and Ref. 79).

EPA uses several techniques to refine residue value estimates from worst case levels to more realistic levels. (See Ref. 1 at 10-12). First, where appropriate, EPA may take into account all the residue values reported in the crop field trials, either through use of an average or individually. Second, EPA may consider data showing what portion of the crop is not treated with the pesticide. Third, data may be produced showing pesticide degradation and decline over time, and the effect of commercial and consumer food handling and processing practices. Finally, EPA may consult monitoring data gathered by FDA, the US Department of Agriculture, or pesticide registrants, on pesticide levels in food at points in the food distribution chain removed from the farm, including retail food establishments. EPA's experience has been that, even without the use of probabilistic risk assessment techniques discussed below, reliance on these refinements, and particularly use of food monitoring data, reduces exposure and risk estimates by over a order of magnitude. (See 55 FR 20416, 20422, May 16, 1990) (''Earlier registrant residue monitoring studies and FDA and State monitoring studies indicate that [EBDC] residues may be 1 to 2 orders of magnitude lower than the Agency's current residue estimates.''); 54 FR 22558, 22565, May 24, 1989) (using a residue value of 1 ppm from market basket survey to assess risk of daminozide on apples; tolerance value was 20 ppm, 40 CFR 180.246(b)(1989)); (Ref. 79).

In the FQPA, Congress essentially adopted EPA's approach, including EPA's terminology with the slight change that it labeled one category of anticipated residue data, monitoring results, as ''actual residue data.'' (See 21 U.S.C. 346a(b)(2)(E)(1) (designating that data on actual residues measured in food ''includ[es] reside data collected by the Food and Drug Administration'')).

That Congress was codifying existing practice is confirmed by the legislative history of the FQPA. EPA's use of anticipated residue data had been questioned by some and several bills were introduced that essentially prohibited EPA from using its traditional risk assessment approach. For example, H.R. 1725, a bill introduced in the 101st Congress, directed that ''in calculating dietary exposure to the pesticide chemical residue in or on the raw agricultural commodity or processed food for which the tolerance is proposed or is in effect, the Administrator shall consider the level of exposure to be the amount of exposure that would occur if all the commodities and food for which the pesticide chemical residue has a tolerance have amounts of pesticide chemical residues equal to their respective tolerances. . . .'' (H.R. 1725, 101st Cong. section 4 (establishing a new section 408(b)(2)(C)(ii)) (1989) (an exception to this bar on the use of anticipated residue data was allowed if a second tolerance was established to insure residue levels did not exceed the levels used to calculate dietary exposure); see S. 722, 101st Cong. section 4 (establishing a new section 408(b)(2)(C)(ii)) (1989) (same)). A similar approach was taken in the Clinton Administration proposal in 1994. (H.R. 4362, 103d Cong. section 3 (establishing a new section 408(b)(2)(B)(i)) (the Administrator shall assume that the food bears or contains residues of the pesticide chemical equal to the level established by the tolerance set at the point closest to the time the food is purchased); see also S. 2084, 103d Cong., section 3 (establishing a new section 408(b)(2)(B)(i)) (same)). However, this approach was not included in the bill passed in 1996 as the FQPA. Rather, Congress specifically authorized EPA to consider ''anticipated residues,'' terminology EPA had long regarded as describing evidence demonstrating the residues were below tolerance levels.

NRDC is also incorrect in its claim that failure to focus on food purchased at farm stands will vastly underestimate dietary exposure to pesticides. This underestimation occurs, according to NRDC because EPA does not take into account that a significant number of consumers buy produce at farm stands. Even assuming that food consumed as a result of purchases at farm stands

constitute more than a negligible amount of the diet, NRDC's claims here are inaccurate whether EPA is relying on anticipated residues estimated based on crop field trials or monitoring data. Crop field trials measure residue levels at harvest after use of application rates and procedures that will produce maximum residues under the currently-approved pesticide label. Thus, anticipated residue values from crop field trials, if anything, will overstate the values found at farm stands or U-pick farms. Even where EPA uses monitoring data it is likely to differ little from the values at farm stands or U-pick farms. The monitoring data EPA relies upon most frequently is from the Pesticide Data Program (PDP) run by USDA. PDP data is extensive and covers a wide spectrum of residue values. Samples are generally collected at wholesale and central distribution points prior to distribution to supermarkets and grocery stores. For fresh produce, the type of food most likely to be found at a farm stand or U-pick farm, rapid distribution is critical and thus central food distribution points are likely to very close to the farm in terms of time from harvest. This would be particularly true for those commodities which are transported quickly from farm to distribution center under controlled-environment conditions (e.g., strawberries, blueberries). For all of these reasons, EPA concludes that its exposure estimates are not likely to understate exposure without use of specific data on residue levels at farm stands and U-pick farms.

6. *Population percentile used in aggregate exposure estimates*—a. *In General.* NRDC contends that EPA in making the reasonable certainty of no harm finding must make such a finding as to ''all children'' —that is, EPA must find that ''no children will be harmed'' by exposure to the pesticide. Although EPA is somewhat uncertain as to precisely what approach to risk assessment and safety findings NRDC is advocating, EPA believes that its approach to implementing the reasonable certainty of no harm standard is consistent with the statutory framework. As specified in the statute, EPA focuses its risk assessment and safety findings on major identifiable population subgroups. (21 U.S.C. 346a(b)(2)(D)(vi)). For children EPA has identified the following subgroups: nursing infants (0–6 months); non-nursing infants (6 months – year); 1–2 year-olds; 3–5 year olds; 6–12 year olds; and 13–19 year olds. EPA evaluates each of these subgroups to determine if it can be determined that there is a reasonable certainty of no harm for individuals in these subgroups. (See Refs. 2 at 40; and 1 at 14).

b. *Choice of population percentile.* NRDC asserts that EPA erred by allegedly making its safety decision as to the acute risk posed by pymetrozine, mepiquat, isoxadifen-ethyl, acetamiprid, and furilazole based on only a portion of the population, leaving the rest of the population unprotected. According to NRDC, EPA only considered 95 percent of the affected population. This argument was rejected in the Imidacloprid Order, and EPA incorporates the reasoning used there. (69 FR at 30070–30071, May 26, 2004).

EPA relies on population percentages as one of several inputs in estimating the full range of exposures in each population subgroup and not because it has concluded that a certain percentage of the population is unworthy of protection. As EPA explained in its Imidacloprid Order:

> the use of a particular percentile of exposure is a tool to estimate exposures for the entire population and population subgroups and not a means to eliminate protection for a certain segment of a subgroup. When inputs for pesticide residue values in the exposure estimate are high end (*e.g.*, assuming all food contains tolerance level residues), a lower percentile of exposure (*e.g.*, 95 percent) is thought to be representative of exposure to the overall population as well as subgroups. As increasingly realistic residue values are used (*e.g.*, information from pesticide residue monitoring), a higher percentile of exposure (e.g., 99.9 percent) is generally necessary to be protective of the overall population and its subgroups.

(69 FR at 30070). As EPA pointed out, a risk assessment using the 95th population percentile and worst case residue values is likely to estimate much higher exposure levels than an assessment using the 99.9th population percentage and residue values from monitoring studies. (Id. at 30071).

For each of the pesticides as to which NRDC raised concerns with the use of the 95th population percentile for estimating exposure, EPA estimated exposure using the gross overestimate of all crops covered by the tolerance containing residues at tolerance levels. (66 FR at 66788, December 27, 2001 (pymetrozine); 65 FR at 1790, 1792–93, January 12, 2000 (mepiquat); 66 FR 33179, 33184, June 21, 2001 (isoxadifen-ethyl); 67 FR at 14653, March 27, 2002 (acetamiprid); 67 FR at 15731, April 3, 2002 (furilazole)). Thus, EPA concludes it reasonably estimated exposure in making its reasonable certainty of no harm finding for these pesticides.

7. *Alleged inadequacies pertaining to specific pesticides*—a. *Pymetrozine.* NRDC argues the EPA has underestimated aggregate exposure to pymetrozine because (1) ''EPA assumes that a toddler's hand-to-mouth exposure occurs very few times per hour;'' (2) EPA fails to consider that children put other objects in their mouths beside their hands; and (3) EPA ignores children's consumption of '''feral' food - food that has been dropped on the floor and which picks up residues from contaminated surfaces.'' (Ref. 6 at 8). NRDC is incorrect. First, several years ago EPA modified its estimate of hand-to-mouth exposures from 1.28/hour to 20/hour, a 90th percentile value. (Ref. 81). As to the other types of oral exposures cited by NRDC, EPA's experience has shown that any exposures that occurs in such a manner is inconsequential beside the non-dietary oral exposures EPA estimates through its models. In modeling toddler exposure, EPA assumes that the toddler plays in the treated area engaging in repeated mouthing behavior immediately after treatment. NRDC is referencing potential exposures that may occur occasionally in areas inside the home and thus well-separated from the treatment area (the lawn).

b. *Bifenazate.* NRDC claims that EPA relied upon ''unsupported and apparently arbitrary processing factors to reduce estimates of dietary exposure to bifenazate on apples and grapes.'' (Ref. 7 at 16). Further, NRDC alleges that despite the fact that bifenazate is registered for use on landscape ornamentals, EPA ignores this source of exposure. (Ref. 7 at 17).

EPA's default processing factors are neither unsupported nor arbitrary. EPA uses all available data and analyzes it in a manner to ensure that the application of default processing factors will not understate pesticide exposure. In fact, EPA's manner of applying default processing factors tends to exaggerate greatly exposure levels in processed food compared to the level of residues that is actually present.

Default processing factors are a numerical measure of the potential of pesticide residues to concentrate in processed foods when a raw food is partitioned into its component fractions. They are derived from the weight-to-weight ratio of raw and processed commodities and intended to reflect the highest potential concentration of pesticide residue that can occur. In calculating default processing factors EPA assumes that concentration will be inversely proportional to the reduction of weight (mass) that occurs during processing (e.g., if processing reduces

the mass of processed commodity proportional to the raw commodity by 50 percent, the default processing factor would be 2X). Importantly, EPA applies default processing factors using the worst case assumption that all pesticide residue in the raw commodity remains in any commodity processed from such raw commodity. Thus, if the raw food contains 2 ppm of a pesticide and the default processing factor for a processed commodity from such raw food is 2X, EPA will assume that the processing commodity contains 4 ppm of the pesticide. The 4 ppm estimate should be regarded as a theoretical upper bound level, however, because actual processing data generally shows residues are reduced during processing, or at least not concentrated at EPA's theoretically-derived default level (i.e., the inverse proportion of reduction in mass of the processed commodity). EPA's use of default processing factors further exaggerates residue estimates in processed food because EPA assumes that each processed commodity from a raw food contains all of the pesticide present in the raw food (with the precise level being estimated by the default processing factor). (Refs. 82 and 83)

Several examples will help to elucidate how EPA calculates and applies default processing factors. Perhaps the simplest example of how EPA calculates default processing factors involves potatoes and dried potato flakes. The default processing factor for potatoes is calculated by determining the weight-to-weight ratio of whole potatoes to dried potatoes. This ratio is assumed to be the concentration factor of the pesticide in the dried potato. USDA information indicates that it takes 6.5 pounds of fresh potatoes to produce 1 pound of dried potato flakes. Thus, the default processing factor for potato flakes is 6.5X and this factor is multiplied times the residue level found in fresh potatoes to estimate residues in potato flakes. This approach produces a worst case estimate because it assumes that the processing process does not result in any loss or degradation of the pesticide residues in or on the potato - i.e, that the washing, peeling, heating, and drying that occurs in the processing of fresh potatoes into potato flakes does not result in any reduction in total pesticide residues.

The processing of potatoes also is a good example of how EPA applies default processing factors in a manner that will exaggerate estimates of pesticide levels in processed food. With potato processing, EPA assumes that all of the pesticide residue in the raw potato not only is translocated to the dried potato flakes but also is present in the potato peel which is a byproduct of processing dried potato flakes and is used as an animal feed. The level of residue assumed for the peel is based, like the level for the flakes, on the level of residue in the raw potato multiplied by the appropriate default processing factor. Obviously, it is physically impossible for all of the pesticide in the raw potato to be translocated to both the dried flakes and the peel but in the absence of more specific data on how the pesticide is distributed in the raw potato, EPA's approach is a reasonable, health-protective measure. Similar methodology is employed with other commodities that have a peel that itself is an edible commodity for animals or humans, such as citrus.

A slightly different approach is used for deriving the default processing factor for pome fruit, such as apples. For these commodities, the default processing factor is calculated by dividing the mass of the commodity that constitutes the processed commodity in question into the mass of the entire commodity. For example, USDA data indicates that the mass of a typical apple consists of 12.5 percent solids and 87.5 percent intrinsic (biological) water. To calculate the processing factor for apple juice, thus, the mass of the water (juice) portion of the apple is divided into the mass of the entire apple yielding a processing factor of 1.14X. Performing the same operation for dried apple commodities, yields a processing factor of 8X. Like with other raw commodities, to estimate residues in the processed commodities derived from apples (apple juice, dried apple pomace), EPA assumes all residue in the raw apple is translocated to each processed commodity and estimates residue levels by multiplying the appropriate default processing factor times the level of residue found in the fresh apples.

Thus, NRDC is mistaken in its conclusion that EPA uses default processing factors to reduce exposure estimates. To the contrary, EPA's derivation and use of default processing factors will generally overstate residue levels in processed commodities. NRDC's objection here is not well taken.

EPA concluded that no significant residential exposure would occur to the homeowner and family members as a result of the landscape ornamental use because (1) application of the pesticide at this site is restricted to commercial applicators; and (2) post-application exposure is unlikely where the application is limited to ornamentals (*e.g.*, bushes, shrubs). EPA routinely assumes post-application exposure may occur with residential uses in such areas as on lawns or in vegetable gardens where there is the potential for homeowners and family members (other than young children as concerns vegetable gardens) to have significant contact with the treated plant. Although in the past EPA has occasionally conducted post-application exposure assessments for ornamental uses, EPA's current view is that any post-application exposure from such a use is likely to be minimal.

c. *Zeta-cypermethrin.* As to zeta-cypermethrin, NRDC claims that EPA ''wrongly ignores indoor and outdoor residential uses of cypermethrin (which the agency states is toxicologically identical to zeta-cypermethrin for the purposes of these tolerances).'' (Ref. 7 at 17). NRDC, however, is mistaken in this allegation. EPA made clear in the **Federal Register** notice associated with the challenged zeta-cypermethrin tolerances that EPA combines residential exposures from these two pesticides. As EPA explained:

> The analytical method does not distinguish cypermethrin from zeta-cypermethrin, and the toxicological endpoints are the same. Therefore, dietary and non-dietary residential aggregate risk assessment is conducted by adding the uses of the two chemicals.

(67 FR at 6426, 6427, February 12, 2002).

d. *Diflubenzuron.* NRDC asserts that EPA has underestimated aggregate exposure to diflubenzuron because EPA concluded that application of diflubenzuron to tree canopies would result in negligible residential exposure to diflubenzuron. After review, however, EPA reaffirms that these potential exposures are expected to be limited. The label states that ''applications should be made during periods of minimal use'' and requires users to ''Notify persons using recreational facilities or living in the area to be sprayed before application.'' Diflubenzuron is only applied by commercial applicators to the tree canopy for control of gypsy moths and mosquitoes. Generally applied by helicopter, these sprays are not aerosols or ultra low volume sprays designed as space sprays, but are rather directed to the tree canopy and designed to impinge on the tree tops where they would be effective in pest control. The sprays designed for application to tree canopies utilize much larger droplet sizes which are essentially nonrespirable; therefore, minimal inhalation exposure to bystanders is expected. Additionally, due to a low dermal absorption rate (0.5 percent), the potential for dermal exposure to bystanders is expected to be minimal.

In any event, EPA would note that the results of the chronic dietary analysis indicated that the estimated chronic dietary risk associated with the proposed use of diflubenzuron was well below the Agency's level of concern for the general U.S. population. In fact, the highest exposed population subgroup (all infants <1 year of age) using a very conservative (health-protective) estimate of exposure is 5.5 percent of the safe dose. An acute dietary exposure risk assessment was not conducted since no hazard was identified for any population, including infants and children, following a single exposure to diflubenzuron (i.e., no hazard was identified, therefore, quantification of risk is not appropriate).

e. *2,4-D.* NRDC claims that ''EPA deliberately ignores known residential uses in establishing new tolerances for 2,4-D . . . [by] fail[ing] to assess and incorporate those residential uses as a source of aggregate exposure, in violation of the FQPA.'' (Ref. 8 at 18). NRDC cites to several studies allegedly demonstrating that when 2,4-D is applied to turf, residues are tracked indoors and can lead to ''significant'' exposures. Citing a rat study, NRDC also claims that children can be exposed to 2,4-D through mother's milk.

Contrary to NRDC's assertions, however, EPA did aggregate residential exposures with food and water exposures to 2,4-D in assessing its safety. EPA's quantitative aggregate assessment of the short-term risk from residential uses appears at page 10629 of the **Federal Register** notice establishing the challenged tolerance. (67 FR at 10629, March 29, 2002). EPA did not aggregate residential exposures in conducting an intermediate-term residential risk assessment because data showed that intermediate-term exposure as a result of residential uses was very low. (ID. at 10626.)

As to the study cited by NRDC on track-in exposures, EPA concludes that, at most, these data indicated some degree of elevated seasonal exposure but such exposure was minimal. (Ref. 33). The cited study noted that its estimate of the combined exposure for all routes for a 10 kg child, whether looking at the maximum (8.871 micrograms/day (µg/day)) or median values (2.421 µg/day), was well below safe levels. By comparison, the exposure assessment for 2,4-D described in Unit VII.B.2.a. estimates a 10 kg child would be exposed to 503 µg/day (excluding drift) and 756 µg/day (including drift). EPA's estimated exposure for a 10 kg child due to residential uses alone is 473 µg/day. (Ref. 33 at 9). Thus, the cited study does not suggest EPA is underestimating exposure. To the contrary, it demonstrates that EPA's asssessment approach is very conservative (health-protective).

NRDC also expressed concern that nursing infants could be exposed to 2,4-D in breast milk. (Ref. 8 at 7) NRDC cites to a study in rats that showed 2,4-D in breast-fed neonates. (Ref. 84). EPA is aware, as a result of animal feeding studies using exaggerated doses, that 2,4-D may be present in milk. It is not surprising that the study relied upon by NRDC suggests that 2,4-D is transmitted in breast milk given the massive doses of 2,4-D in that study of 50, 70, 700 milligrams/kilogram of body weight/day (mg/kg/day). By comparison, EPA estimates that the maximum dietary exposure from food to human females ages 13-50 is 0.01018 mg/kg/day and the average exposure is 0.000642 mg/kg/day. (Ref. 61). These values range from 4,900 to 1 million times lower than the values in the cited rat study.

Further, EPA's manner of doing risk assessment for infants is protective of any pesticide exposure to infants from human breast milk because the exposure values EPA assumes for pesticides in cow's milk greatly exceed the values that could be present in breast milk. The diet of non-nursing infants less than 1 year old still contains milk as a primary component. Importantly, dairy cows exposure to pesticides tend to be significantly higher than humans because residues in grass forage are generally higher than in human foods. For example, the tolerance for pastureland grass for 2,4-D is 1,000 ppm while the 2,4-D tolerances for various human foods are all in the single digits. (See 40 CFR 180.142). Additionally, EPA tends to use very conservative methods for calculating tolerance values and exposure levels in meat and milk in cattle (*e.g.*, relying on exaggerated feeding studies, use of worst case diets) which overstate exposure.

For the 2,4-D risk assessment, EPA assumed that 2,4-D would be present in milk at 0.004 ppm for both acute and chronic exposure. (Ref. 85). This value represents half of the level of detection from the analytical method used in studies monitoring milk for 2,4-D residues. No 2,4-D residues were detected in these studies, and in that circumstance it is common practice to estimate exposure at half of the level of detection. (Refs. 80 and 86). The conservative (health-protective) nature of this exposure value can be seen by considering data from a 2,4-D feeding study in cattle and what those data suggest regarding the levels of 2,4-D present in rat milk in the cited study and in human breast milk. What the cattle study showed was that cattle fed a diet of 1,500 ppm 2,4-D had residues of 2,4-D in their milk at the level of 0.07 ppm. (Ref. 87). Extrapolating from these figures, 2,4-D levels in rat milk in the cited study would have ranged from 0.05 ppm to 0.65 ppm. Taking into account that the dose levels in the rat study were approximately 4,900 to 70,000-fold higher (50 mg/kg/day), and 69,000 to one million-fold higher (700 mg/kg/day) than the estimated maximum and average female 13–50 dietary exposure (0.01018 mg/kg/day and 0.000642 mg/kg/day), it is striking that the estimated milk residue used to estimate dietary exposure to infants (0.004 ppm) is only approximately 12–fold lower than the rat milk residue estimated for the 4,900 - 78,000X exaggerated dose, and 162–fold less than the rat milk residue estimated for the 69,000 - 1,000,000X exaggerated dose. As to human breast milk, what the cattle study shows is that given the maximum and average exposure levels of females ages 13–50 to 2,4-D, the expected maximum and average levels in breast milk are roughly 200 and 4,000 times lower, respectively, than the exposure value used for cow's milk. (Ref. 88). Thus, EPA concludes that its aggregate exposure assessment was protective for all children, including nursing infants.

f. *Isoxadifen-ethyl, acetamiprid, fluazinam.* Repeating the allegations made as to bifenazate, NRDC argues that EPA relied upon ''unsupported and apparently arbitrary processing factors to reduce estimates of dietary exposure'' for isoxadifen-ethyl, acetamiprid, and fluazinam. (Ref. 9 at 16). For the reasons described above in Unit VII.D.7.b., EPA denies these objections.

E. Human Testing

NRDC claims that EPA used a human study to assess exposure to turf use of 2,4-D in violation of EPA's policy on use of human studies as announced in a press release on December, 14, 2001, and in violation of ''the Nuremberg Code, the Helsinki Declaration, and EPA's common rule.'' (Ref. 8 at 21-22). NRDC states that EPA has not clarified whether the human study in question was an epidemiology study or involved third-party human testing. If the study falls in the latter category, according to NRDC, EPA's consideration of it would violate its own policy as well as the other cited authorities.

EPA disagrees with NRDC's claim that it was improper for EPA to consider the study in question in assessing the risk posed by 2,4-D. To clarify, the study is not an epidemiology study; rather it is a biomonitoring study conducted by the

Canadian Centre for Toxicology. (Ref. 89). Because it was not conducted or supported by a department or agency of the U.S. Government, EPA refers to it as a ''third-party'' study. In this biomonitoring study, adult male and female volunteers were selected from the faculty, staff, and students of the University of Guelph. The study participants ''were supplied with written information outlining the possible risks they would be taking to participate in the study. . . . Consent forms were signed before the initiation of the study.'' (Ref. 89 at 12). In addition, ''[t]he protocol was appraised and approved by the University of Guelph Ethical Review Board.'' (Id.) Volunteers were exposed to 2,4-D while performing activities specified by the researchers (walking, sitting, and lying) for one hour on turf previously treated (consistent with product's label instructions) with 0.88 lb acid equivalent/acre 2,4-D. The product did not specify any restricted entry interval or require that people entering treated areas wear any special personal protective equipment. The researchers measured the amount of 2,4-D detectable in urine collected from the human participants for a period of 96 hours following this exposure.

NRDC's objection appears to be based on their belief that the 2,4-D biomonitoring study was unethical and that the decision to rely on the data violated existing international standards (the Nuremberg Code and the Helsinki Declaration), as well as Agency regulations (the Common Rule) and policy (presumably the position announced in a December 14, 2001 press release). Each of these is discussed below.

The Nuremberg Code contains basic, broad ethical precepts to guide all types of scientific research with human subjects. The text of the Code was developed in 1949 and is available at: *http://ohsr.od.nih.gov/guidelines/nuremberg.html.* The Code indicates that for a human study to be considered ethical the subjects must participate voluntarily, they should be informed of the nature and purpose of the research, and they should be allowed to withdraw at any time. Also, the study should be designed to produce scientifically useful information and be conducted by appropriately qualified researchers. The Code also indicates researchers should take measures to protect the subjects and must terminate the research if continuation of the study would result in injury to a participant.

The Agency has reviewed the ethical conduct of the 2,4-D biomonitoring study using the principles in the Nuremberg Code. While the available information on the biomonitoring study does not address each of the paragraphs in the Code, the information does indicate that the study complied with the broad principles of the Code. EPA is aware of no information to indicate that any of the Code's principles was not followed.

The international medical research community has developed and maintains ethical standards documented in the Declaration of Helsinki, first issued by the World Medical Association in 1964 and revised several times since then. The latest version of the Declaration is available at: *http://www.wma.net/e/policy/b3.htm* . These standards are available to guide research on matters relating to the diagnosis and treatment of human disease, and to research that adds to understanding of the causes of disease and the biological mechanisms that explain the relationships between human exposures to environmental agents and disease. Because the 2,4-D biomonitoring study did not involve research on matters relating to the relationship between human exposure to environmental agents and human disease, or otherwise fall within the scope of the Declaration of Helsinki, the Declaration does not apply to this research.

The Agency's rules for ''Protection of Human Subjects,'' generally referred to as the ''Common Rule,'' apply to ''all research involving human subjects conducted [or] supported . . . by any Federal department or agency.'' (40 CFR 26.101). Because the 2,4-D biomonitoring study was not conducted or supported by an agency or department of the U.S. Government, it was not subject to the Common Rule.

At the time EPA prepared its risk assessment for the 2,4-D soybean tolerance, the Agency had a general practice of using ''third-party'' human studies, unless the studies involved intentional dosing of human subjects for the purpose of identifying or quantifying a toxic effect. (Ref. 90). This policy or practice (as described in the December, 2001 Press release) applied only to intentional dosing studies conducted to identify or quantify a toxic effect and the 2,4-D biomonitoring study was not such a study.

It should be noted that the approach described in the 2001 press release has been set aside. In early 2002 various parties from the pesticide industry filed a petition with the U. S. Court of Appeals for the District of Columbia for review of EPA's December 2001 press release. These parties argued that the Agency's interim approach constituted a ''rule'' promulgated in violation of the procedural requirements of the Administrative Procedure Act and the Federal Food, Drug, and Cosmetic Act. On June 3, 2003, the Court of Appeals concluded that:

> For the reasons enumerated above, we vacate the directive articulated in EPA's December 14, 2001 Press Release for a failure to engage in the requisite notice and comment rulemaking. The consequence is that the agency's previous practice of considering third-party human studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide, is reinstated and remains in effect unless and until it is replaced by a lawfully promulgated regulation.

Crop Life America v. EPA, 329 F.3d 876, 884 – 85 (D.C. Cir. 2003)).

In sum, the information available to EPA does not suggest that the 2,4-D human biomonitoring study was performed in an unethical manner and therefore should not have been considered by the Agency. Rather, the researchers in the 2,4-D study informed the participants of potential risks from participating in the study and obtained their written consent. In addition, the researchers obtained an assessment by an independent ethical review board of the proposed study design prior to conducting the study. While the Journal article describing the 2,4-D biomonitoring study does not reference any applicable ethical framework as governing its conduct, these measures - a prior ethics review by an independent board and informed consent - are the principal protections required by the Common Rule adopted in the United States in 1991. Accordingly, EPA has determined that the 2,4-D biomonitoring study is not significantly deficient relative to the ethical standards prevailing when the study was conducted, some time prior to 1992. EPA has also determined that the study is not fundamentally unethical. Moreover, EPA notes that this study is not subject to the Helsinki Declaration, EPA's Common Rule, or EPA's now overturned December 2001 policy on third-party human testing. Finally, NRDC provided no specific information or argument to support its objection. Therefore, EPA concludes that it properly considered the data from the 2,4-D biomonitoring study.

F. 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

EPA has responded to many of the comments that pertained specifically to

the individual pesticides and pesticide tolerances in Unit VII. The more general comments filed by the IWG, IR-4, and the public were responded to in the Imidacloprid Order. That response is adopted herein. (69 FR at 30072–30074, May 26, 2004). Other comments are addressed below.

ISK Biosciences noted that the challenged fluazinam tolerance applied to wine grapes and children do not usually consume wine. Although this is true, section 408(b) requires EPA to consider aggregate exposure to a pesticide and not just exposure under the specific tolerance at issue. Further, ISK Biosciences argues that EPA's assessment of exposure to fluazinam in wine is very conservative. EPA generally agrees with this comment.

FMC Corporation argues that because a data call-in has not been issued for a DNT study on zeta-cypermethrin there can be no data gap and the database must be complete. In response, EPA would note that the ''completeness'' inquiry in the children's safety factor provision is not a formalistic exercise turning on whether mandatory data call-ins have been issued. As EPA stated in its Children's Safety Policy:

> the ''completeness'' inquiry should be a broad one that takes into account all data deficiencies. In other words, the risk assessor should consider the need for traditional uncertainty factors not only when there are inadequacies or gaps in currently required studies on pesticides, but also when other important data needed to evaluate potential risks to children are missing or are inadequate.

(Ref. 2 at 20).

Bayer CropScience states that historical control information relating to effects seen in a rat teratology study submitted to EPA demonstrates that the young do not have increased sensitivity to isoxadifen-ethyl. After reviewing this historical control data, EPA has again concluded that the developmental effects seen at the mid- and high-doses in the rat teratology study were statistically significant and treatment-related. (Ref. 9)

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).

XI. Time and Date of Issuance of This Order

The time and date of the issuance of this Order shall, for purposes of 28 U.S.C. 2112, be at 1 p.m. eastern time (daylight savings time) on the date that is 2 weeks after the date when the document is published in the **Federal Register**.

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List of Subjects

Environmental protection, pesticides and pest.

Dated: August 3, 2005.

James Jones,

Director, Office of Pesticide Programs.

[FR Doc. 05–15840 Filed 8–9–05; 8:45 am]

BILLING CODE 6560–50–S