copy of the rule, to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this action and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. A major rule cannot take effect until 60 days after it is published in the **Federal Register**. This action is not a ''major rule'' as defined by 5 U.S.C. 804(2).

Under section 307(b)(1) of the Clean Air Act, petitions for judicial review of this action must be filed in the United States Court of Appeals for the appropriate circuit by June 18, 2012. Filing a petition for reconsideration by the Administrator of this final rule does not affect the finality of this action for the purposes of judicial review nor does it extend the time within which a petition for judicial review may be filed, and shall not postpone the effectiveness of such rule or action. Parties with objections to this direct final rule are encouraged to file a comment in response to the parallel notice of proposed rulemaking for this action published in the Proposed Rules section of today's **Federal Register**, rather than file an immediate petition for judicial review of this direct final rule, so that EPA can withdraw this direct final rule and address the comment in the proposed rulemaking. This action may not be challenged later in proceedings to enforce its requirements (see section 307(b)(2)).

List of Subjects in 40 CFR Part 52

Environmental protection, Air pollution control, Incorporation by reference, Intergovernmental relations, Particulate matter, Reporting and recordkeeping requirements.

Dated: March 8, 2012.

Jared Blumenfeld,

Regional Administrator, Region IX.

Part 52, Chapter I, Title 40 of the Code of Federal Regulations is amended as follows:

PART 52—[AMENDED]

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

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

Subpart F—California

■ 2. Section 52.220, is amended by adding paragraphs (b)(11)(ii), (c)(21)(xiv)(D) and (c)(381)(i)(I) to read as follows:

§ 52.220 Identification of plan.

* * * * *

(b) * * *

(11) * * *

(ii) Previously approved on May 31, 1972 in paragraph (b) of this section and now deleted without replacement, Rule 2.7.

* * * * *

(c) * * *

(21) * * *

(xiv) * * *

(D) Previously approved on June 14, 1978 in paragraph (c)(21)(xiv)(A) of this section and now deleted without replacement, Rule 2.4.

* * * * *

(381) * * *

(i) * * *

(I) Yolo-Solano Air Quality Management District.

(*1*) Rule 2.3, ''Ringelmann Chart,'' revised on January 13, 2010.

(*2*) Rule 2.11, ''Particulate Matter Concentration,'' revised on January 13, 2010.

(*3*) Rule 2.12, ''Specific Contaminants,'' revised on January 13, 2010.

* * * * *

[FR Doc. 2012–8947 Filed 4–17–12; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2008–0877; FRL–9344–1]

2,4-D; Order Denying NRDC's Petition To Revoke Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: In this Order, EPA denies a petition requesting that EPA revoke all pesticide tolerances for 2,4-dichlorophenoxyacetic acid (2,4-D) under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The petition was filed on November 6, 2008, by the Natural Resources Defense Council.

DATES: This Order is effective April 18, 2012. Objections and requests for hearings must be received on or before June 18, 2012, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Units I.B and I.C. of the **SUPPLEMENTARY INFORMATION**.)

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2008–0877. All documents in the docket are listed in the docket index available at *http://www.regulations.gov.* Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov,* or, if only available in hard copy, by appointment at One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA, between 9 a.m. to 3 p.m., Monday through Friday, excluding legal holidays. To schedule an appointment, call (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Cathryn Britton, Pesticide Re-evaluation Division, Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001; telephone number: (703) 308–0136; fax number: (703) 308–8005; email address: *britton.cathryn@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

In this document EPA denies a petition by the Natural Resources Defense Council (NRDC) to revoke pesticide tolerances. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to:

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

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. NAICS codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of

this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. Can I file an objection or hearing request?

Under section 408(g) of FFDCA, any person may file an objection to any aspect of this order and may also request a hearing on those objections. You must file your objection or request a hearing on this order in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA–HQ–OPP–2008–0877 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before June 18, 2012. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing that does not contain CBI for inclusion in the public docket that is described in **ADDRESSES**. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit this copy, identified by docket ID number EPA–HQ–OPP–2008–0877, by one of the following methods:

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

C. What should be included in objections?

The objection stage is the second stage in the multi-stage petition process under FFDCA section 408. This multi-stage process is initiated by a petition requesting establishment, modification, or revocation of a tolerance. In the petition, the petitioner has the opportunity to make its best case for why its request should be granted. Notice and comment on the petition gives interested parties the chance to express views or provide information on the subject matter of the petition.

Once EPA makes a decision on a petition, and publishes its decision in the **Federal Register**, the second stage of the petition process is triggered. At this point, parties who disagree with EPA's decision, whether it is a decision to grant or deny the petition, may file objections with EPA to the decision made. The objection stage gives parties a chance to seek review of EPA's decision before the Agency. This is an opportunity for parties to contest the conclusions EPA reached and the determinations underlying those conclusions. As an administrative review stage, it is not an opportunity to raise new issues or arguments or present facts or information that was available earlier. On the other hand, parties must do more than repeat the claims in the petition. The objection stage is the opportunity to challenge EPA's decision on the petition. An objection fails on its face if it does not identify aspects of EPA's decision believed to be in error and explain why EPA's decision is incorrect.

This two-stage process ensures that issues are fully aired before the Agency and a comprehensive record is compiled prior to judicial review. The sequential nature of the petition and objection process is essential for two reasons. The availability of administrative review before EPA gives EPA, as well as other parties, an opportunity to clearly define and articulate the complex science, policy, and legal issues involved in tolerance decisions. The two-stage process also is designed to make the administrative process as efficient as possible while still providing parties an opportunity for an adjudicatory hearing if needed. In the first stage, EPA is given the opportunity to resolve the issues raised by petition through a process similar to informal notice-and-comment rulemaking. Only material, factual issues that remain disputed following this first stage may be raised in a hearing request. Under this scheme, hearings, if needed, can focus on the key areas of factual dispute. Of course, the first stage of the petition process can only serve its winnowing function if parties are restricted at the second (objection) stage from raising new issues.

II. Background

A. What action is the agency taking?

On November 6, 2008, the Natural Resources Defense Council (NRDC) filed with EPA a petition that, among other things, requested that EPA revoke all tolerances for the pesticide 2,4-dichlorophenoxyacetic acid (2,4-D) established under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a (Ref. 1). NRDC claims that EPA's conclusion outlined in the 2005 Reregistration Eligibility Decision (RED) for 2,4-D, which allowed 2,4-D to be reregistered and its tolerances retained, was based on a risk assessment that was deficient in regard to the toxicity of 2,4-D and the amount of human exposure to the chemical. Specific to 2,4-D tolerances, NRDC asserts that EPA failed to incorporate information on the endocrine disrupting effects of 2,4-D into its human health risk assessments; EPA disregarded data on neurotoxicity related to 2,4-D; EPA disregarded information showing that 2,4-D is mutagenic; EPA ignored data showing that dermal absorption of 2,4-D is enhanced by alcohol consumption, sunscreen, and DEET; and that EPA ignored the exposure of 2,4-D via breast milk to infants. Numerous studies are cited in the petition that NRDC claims supports its assertions. EPA has reviewed all of the studies cited by NRDC.

In this order, EPA is denying NRDC's petition to revoke 2,4-D's tolerances in full. Many of NRDC's claims fail to state a sufficient ground for revocation and instead merely critique the manner in which the risk assessment underlying the 2,4-D RED was conducted. Those claims that do allege relevant statutory grounds for revocation EPA finds to be without merit. The other aspects of NRDC's petition not concerning the 2,4-D tolerances are addressed in another EPA action.

B. What is the agency's authority for taking this action?

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

III. Statutory and Executive Order Reviews

A. FFDCA/FIFRA and Applicable Regulations

1. *In general.* EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food and feed commodities under section 408 of the FFDCA. (21 U.S.C. 346a). Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide

residue is ''adulterated'' under section 402 of the FFDCA and may not be legally moved in interstate commerce. (21 U.S.C. 331, 342). Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA). Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA), which added the provisions discussed below establishing a detailed safety standard for pesticides, additional protections for infants and children, and the estrogenic substances screening program. (Pub. L. 104–170, 110 Stat. 1489 (1996)).

EPA also regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), (7 U.S.C. 136 et seq). While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, FIFRA requires the approval of pesticides prior to their sale and distribution, (7 U.S.C. 136a(a)), and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law. (7 U.S.C. 136j(a)(2)(G)).

2. *Safety standard for pesticide tolerances.* A pesticide tolerance may only be promulgated or left in effect by EPA if the tolerance is ''safe.'' (21 U.S.C. 346a(b)(2)(A)(i)). This standard applies when responding both to petitions to establish and petitions to revoke tolerances. ''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 includes numerous provisions directing how EPA should quantitatively assess the risks of pesticides in determining whether a tolerance meets the safety standard. For example, section 408 either authorizes or requires EPA to consider safety factors appropriate to use of animal experimentation data, 21 U.S.C. 346a(b)(2)(D)(ix), aggregate and cumulative exposures to the pesticide in question and other related substances, 21 U.S.C. 346a(b)(2)(D)(v) and (vi), anticipated or actual pesticide residue levels as compared to the maximum levels permitted by tolerances, 21 U.S.C. 346a(b)(2)(E), and the percentage of crops that bear pesticide residues, 21 U.S.C. 346a(b)(2)(F). *See* 21 U.S.C. 346a(b)(2)(B)(iv) (limiting an exception to the safety standard to pesticides posing risks that do not exceed ''10 times the yearly risk'' allowed under the safety standard).

Risks to infants and children are given special consideration. Providing additional protection to infants and children was a particular focus of the FQPA. Section 408(b)(2)(C) requires EPA to make a specific determination regarding the safety of tolerances to infants and children and to consider, among other things, information ''concerning the special susceptibility of infants and children to the pesticide chemical residues * * *.'' (21 U.S.C. 346a(b)(2)(C)(i)(II) and (ii)(II)). This provision also creates a presumptive additional safety factor for the protection of infants and children. Specifically, it directs that ''[i]n the case of threshold effects, * * * an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.'' (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to ''use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.'' (Id.). Due to Congress' focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years. For convenience's sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) are referred to throughout this Order as the ''FQPA safety factor for the protection of infants and children'' or simply the ''FQPA safety factor.'' '

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

Once EPA takes final action on the petition by establishing, amending, or revoking the tolerance or denying the petition, any party may file objections with EPA to EPA's decision on the petition and seek an evidentiary hearing on those objections. (21 U.S.C. 346a(g)(2)). Objections and hearing requests must be filed within 60 days. (Id.). The statute provides that EPA shall ''hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections.'' (21 U.S.C. 346a(g)(2)(B). EPA regulations make clear that hearings will only be granted where it is shown that there is ''a genuine and substantial issue of fact,'' the requestor has identified evidence ''which, if established, resolve one or more of such issues in favor of the requestor,'' and the issue is ''determinative'' with regard to the relief requested. (40 CFR 178.32(b)). Further, a party may not raise issues in objections unless they were part of the petition and an objecting party must state objections to the EPA decision and not just repeat the allegations in its petition. *Corn Growers* v. *EPA,* 613 F.2d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). EPA's final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

4. *Tolerance reassessment and FIFRA reregistration.* The FQPA required that EPA reassess the safety of all pesticide tolerances existing at the time of its enactment. (21 U.S.C. 346a(q)). EPA was given 10 years to reassess the approximately 10,000 tolerances in existence in 1996. In this reassessment, EPA was required to review existing pesticide tolerances under the new ''reasonable certainty that no harm will result'' standard set forth in section 408(b)(2)(A)(ii). (21 U.S.C. 346a(b)(2)(A)(ii)). This reassessment was substantially completed by the August 3, 2006 deadline. Tolerance reassessment was generally handled in conjunction with a similar program involving reregistration of pesticides under FIFRA. (7 U.S.C. 136a–1). Reassessment and reregistration decisions were generally combined in a document labeled a Reregistration Eligibility Decision (RED).

5. *Estrogenic substances screening program.* Section 408(p) of the FFDCA creates the estrogenic substances screening program. This provision directed EPA to ''develop a screening program to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring

estrogen, or such other endocrine effect, as the Administrator may designate.'' This screening program must use ''appropriate validated test systems and scientifically relevant information.'' (21 U.S.C. 346a(p)(1)).

Pursuant to the Administrator's discretionary authority, EPA adopted a two-tiered screening and testing strategy and expanded the EDSP to include the androgen and thyroid hormonal pathways and ecological effects. (63 FR 71542, 71544, December 28, 1998). The first tier involves screening ''to identify substances that have the potential to interact with the endocrine system'' and the second tier involves testing ''to determine whether the substance causes adverse effects, identify the adverse effects caused by the substance, and establish a quantitative relationship between the dose and the adverse effect.'' (Id. at 71545). Tier 1 screening is limited to evaluating whether a substance is ''capable of interacting with'' the endocrine system, and is ''not sufficient to determine whether a chemical substance may have an effect in humans that is similar to an effect produced by naturally occurring hormones.'' (Id. at 71550). Based on the results of Tier 1 screening, EPA will decide whether Tier 2 testing is needed. Importantly, ''[t]he outcome of Tier 2 is designed to be conclusive in relation to the outcome of Tier 1 and any other prior information. Thus, a negative outcome in Tier 2 will supersede a positive outcome in Tier 1.'' (Id. at 71554–71555).

In 2008, after an extensive validation process, including peer review of individual assays, EPA notified the public of the EDSP proposed Tier 1 battery of screening assays in a **Federal Register** Notice issued January 24, 2008 (73 FR 4216). EPA submitted the proposed battery for peer review by FIFRA Scientific Advisory Panel (SAP). A final report of the peer review is available. (Ref. 2). EPA announced the issuance of orders for Tier 1 Screening on October 21, 2009 for 67 chemicals including 2,4-D. (74 FR 54422, 54425). With regard to endocrine effects on humans, EPA has designated the 1998 rat two-generation reproduction study (870–3800) as the applicable Tier 2 study for the Endocrine Disruptor Screening Program. In this reproduction study, potential hormonal effects can be detected through behavioral changes, ability to become pregnant, duration of gestation, signs of difficult or prolonged parturition, apparent sex ratio (as ascertained by anogenital distances) of the offspring, feminization or masculinization of offspring, number of pups, stillbirths, gross pathology and histopathology of the vagina, uterus, ovaries, testis, epididymis, seminal vesicles, prostate, and any other identified target organs. EPA concluded that the rat two-generation reproduction study is valid for the identification and characterization of reproductive and developmental effects, including those due to endocrine disruption, based on the long history of its use, the endorsement of the 1998 test guideline by the FIFRA SAP, and acceptance by member countries of the Organisation for Economic Cooperation and Development (OECD).

In addition to the 1998 test guideline for the mammalian two-generation reproductive toxicity study, EPA has proposed the new OECD test guideline for the extended one-generation reproductive toxicity study as an alternate EDSP Tier 2 test. The extended one-generation reproductive toxicity study was not only designed to provide the traditional spectrum of information from a reproductive study, but was also enhanced to evaluate reproductive and developmental endpoints associated with the endocrine, nervous, and immune systems in male and female adult rodents and offspring at birth, weaning, and puberty, which may not necessarily be covered in other 40 CFR part 158 test guideline studies.

EPA has received all required final study reports and data from the Tier 1 battery of tests for 2,4-D. (Refs. 3,4,5,6,7,8, and 9). EPA waived the *in vivo* mammalian Tier 1 tests for 2,4-D due to the availability of a newly-submitted extended one generation reproduction study with 2,4-D. (Ref. 10). The submitted EDSP Tier 1 assays will be considered with regard to potential ecological effects and the need for Tier 2 *in vivo* studies for effects in wildlife. Although the submitted Tier 1 *in vitro* studies may inform EPA on mechanistic issues in mammalian systems (e.g., whether 2,4-D can bind to the estrogen or androgen receptor in mammals), the studies will not affect EPA's conclusions on the quantitative endocrine risks posed by 2,4-D for humans given the availability of the extended one-generation reproduction study (an *in vivo* study in rats) that comprehensively examined the risks to human health from 2,4-D's interaction with endocrine system endpoints. (See discussion in Unit VII.A.1.c.).

B. EPA Risk Assessment for Tolerances—Policy and Practice

1. *The safety determination—risk assessment.* To assess risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps:

- Identification of the toxicological hazards posed by a pesticide;
- Determination of the ''Level of Concern (LOC)'' with respect to human exposure to the pesticide;
- Estimation of human exposure to the pesticide; and
- Characterization of risk posed to humans by the pesticide based on comparison of human exposure to the LOC.

a. *Hazard identification.* In evaluating toxicity or hazard, EPA reviews toxicity data, typically from studies with laboratory animals, to identify any adverse effects on the test subjects. Where available and appropriate, EPA will also take into account studies involving humans, including human epidemiological studies. For most pesticides, the animal toxicity database usually consists of studies investigating a broad range of endpoints including gross and microscopic effects on organs and tissues, functional effects on bodily organs and systems, effects on blood parameters (such as red blood cell count, hemoglobin concentration, hematocrit, and a measure of clotting potential), effects on the concentrations of normal blood chemicals (including glucose, total cholesterol, urea nitrogen, creatinine, total protein, total bilirubin, albumin, hormones, and enzymes such as alkaline phosphatase, alanine aminotransferase and cholinesterases), and behavioral or other gross effects identified through clinical observation and measurement. EPA examines whether adverse effects are caused by different durations of exposure ranging from short-term (acute) to long-term (chronic) pesticide exposure and different routes of exposure (oral, dermal, inhalation). Further, EPA evaluates potential adverse effects in different age groups (adults as well as fetuses and juveniles). (Ref. 11 at 8–10).

EPA also considers whether the adverse effect has a threshold—a level below which exposure has no appreciable chance of causing the adverse effect. For effects that have no threshold, EPA assumes that any exposure to the substance increases the risk that the adverse effect may occur.

b. *LOC/dose-response analysis.* Once a pesticide's potential hazards are identified, EPA determines a toxicological LOC for evaluating the risk posed by human exposure to the pesticide. In this step of the risk assessment process, EPA essentially evaluates the levels of exposure to the pesticide at which effects might occur in the toxicity studies. An important

aspect of this determination is assessing the relationship between exposure (dose) and response (often referred to as the dose-response analysis). EPA follows differing approaches to identifying a LOC for effects that only occur above a threshold (''threshold effects'') and those for which a threshold dose cannot be determined (''non-threshold effects''). Because EPA identified only threshold effect risks for 2,4-D, only EPA's risk assessment procedures for threshold risks are discussed in this Order.

In examining the dose-response relationship for a pesticide's threshold effects, EPA evaluates an array of toxicity studies on the pesticide. Two critical parts of this evaluation involve identification of a quantitative dose level(s) from these studies to be used in assessing the pesticide's safety to humans (referred to as the Point of Departure) and selection of appropriate safety factors for translating the results of toxicity studies in relatively small groups of animals or humans to the overall human population, including major identifiable subgroups of consumers. The Point of Departure is used in conjunction with identified safety factors to calculate a Level of Concern for a pesticide.

i. *Point of Departure.* A Point of Departure (POD) is the dose serving as the 'starting point' in extrapolating a risk to the human population. In selecting the POD, EPA first evaluates all relevant available toxicity data and conducts a weight of the evidence analysis, considering consistency, reproducibility, temporal and dose concordance, and biological plausibility of the effects reported. EPA then selects a value from a dose-response curve that is at the low end of the observable data (the no observed adverse effect level, or NOAEL, the lowest-observed adverse effect level, or LOAEL, or an extrapolated benchmark dose) as the POD. Doses in toxicology studies are generally expressed in terms of milligrams of the test substance per kilogram of body weight of the test subject per day (mg/kg/day). EPA will make separate determinations as to the Points of Departure for both short and long exposure periods as well as for the different routes of exposure (oral, dermal, and inhalation).

ii. *Safety factors.* It has long been a standard risk assessment practice, to use numerical factors—variously referred to over time as either uncertainty or safety factors [1] in conjunction with experimental toxicity data in assessing risk to humans. The two most common safety/uncertainty factors are the factors used to address the potential difference in sensitivity between humans and experimental animals (i.e., inter-species sensitivity) and within the human population (i.e., intra-species sensitivity). Generally a factor of tenfold (10X) is used as a default for both the inter-species and intra-(human) species safety factors. When EPA bases its POD on a dose level from experimental animal data, it will generally use both factors so that it accounts both for the fact that it is extrapolating a dose level in animals to humans and that there may be a wide variation in human response to the compound. This would result in a total safety factor of 100X because each factor indicates that the potential variations addressed constitute a multiple of 10X. When EPA bases its POD on a dose level from human data, only the intra-species factor would be needed because EPA is not extrapolating a dose used in an animal study.

In addition to the inter- and intra-species factors, risk assessors also apply ''additional'' or ''modifying'' safety/uncertainty factors based on specific circumstances related to the toxicity data, particularly with regard to deficiencies in that data. Additional factors are applied to address: (1) An absence of critical toxicity data; (2) the failure of a study to identify a NOAEL; (3) the necessity of using a sub-chronic data to choose a POD for estimating chronic risk; and (4) results in a study that suggest the inter- or intra-species factors may not be sufficient. Generally, a safety factor value of 10X or 3X (which is considered to be one-half of 10X on the logarithmic scale) is used to address these concerns.

EPA's safety/uncertainty factor practice with regard to pesticides was altered to a degree by the Food Quality Protection Act (FQPA). (Ref. 12). That Act established a presumptive additional ''safety'' factor of 10X to protect infants and children. The additional factor was designed to account for the completeness of the toxicity and exposure databases and the potential for pre- and post-natal toxicity. EPA has interpreted this legislation as both a ''codification and expansion'' of prior EPA practice with regard to additional safety/uncertainty factors. (Ref. 12 at A–4–A–5). It codified EPA's prior practice by requiring the additional presumptive factor to address toxicity data completeness issues (i.e., absence of a particular study, a NOAEL in a completed study, or chronic data). These traditional additional uncertainty factors became FQPA safety factors for the protection of infants and children. EPA concluded that Congress had not intended EPA to double-up on safety factors by, for example, applying an ''additional'' uncertainty factor due to missing data, and apply a FQPA safety factor as well to address the same missing data. (Ref. 12 at A–5). Congress expanded EPA's prior practice by providing that the additional FQPA safety factor for the protection of infants and children was designed to address not just toxicity data deficiencies but exposure data deficiencies as well and by its emphasis on protecting against potential pre- and post-natal toxicity. In theory, EPA could have, prior to the enactment of the FQPA, used an ''additional'' or ''modifying'' factor to address health risks to children not otherwise protected by the inter-species, intra-species, or data deficiency safety factors, but use of such a factor was not common. The FQPA also modified the status quo by making the additional safety factor for infants and children presumptive in nature.

The narrowly-focused and highly-prescriptive nature of the FQPA safety factor provision has created some practical problems for EPA in integrating the new statutory requirements with pesticide risk assessment approaches and, more generally, with Agency risk assessment practices. As noted above, the FQPA essentially codified EPA's prior risk assessment practice as to ''additional'' uncertainty factors and it expanded the use of additional uncertainty factors into new areas. The FQPA, however, did not speak to use of traditional (non-additional) uncertainty factors. Thus, the end result was that some uncertainty factors for FFDCA pesticides remained unaffected by the new statutory requirements (the inter- and intra-species factors), some uncertainty factors became FQPA safety factors (additional uncertainty factors that addressed toxicity data deficiencies), and some safety factors that either had previously never existed or were at least extremely rare were created as a

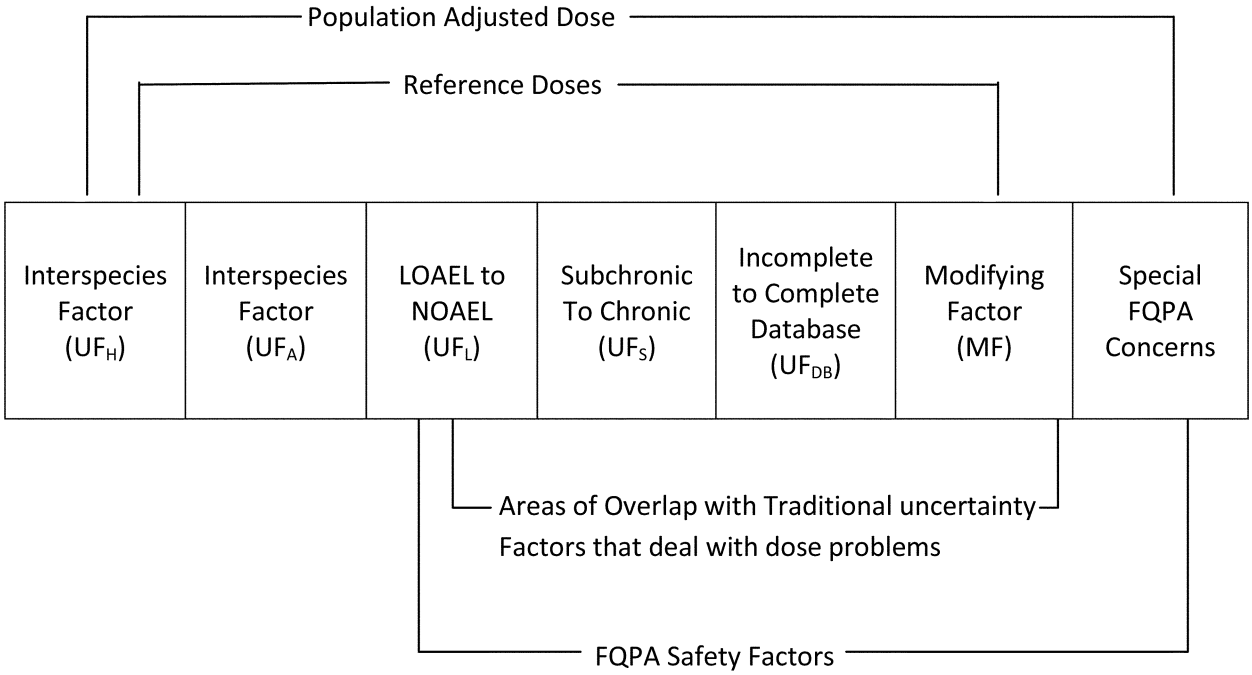
[1] Different terminology has been used to label factors used in calculating safe doses of chemical substances. At first, they were frequently referred to as ''safety'' factors. The terminology has evolved over the decades, however, such that what was once generally called a safety factor has come to be generally referred to as an uncertainty factor. (Ref. 12 at A–3). The rationale for the change was that although the use of such factors does promote safety, the factors actually address uncertainty issues (e.g., uncertainty about the differences in sensitivities of animals and humans, uncertainty concerning variation inhuman sensitivities, uncertainty created by missing data, etc.). The FQPA reintroduced the term ''safety'' factors with its reference to a ''margin of safety.'' Subsequent to the passage of FQPA, the Office of Pesticide Programs has used the terms safety factor and uncertainty factor interchangeably.

statutory phenomenon (a factor to address exposure data base deficiencies and a factor to address potential pre- and post-natal toxicity). This selective inter-weaving of statutory requirements with Agency science policy made FFDCA risk assessments for pesticides unique compared to general Agency risk assessment practice.

Pesticide risk, however, is not regulated under a single statute. Risks to workers or the environment from pesticide use are regulated by EPA under FIFRA not the FFDCA. Further, EPA may address risks posed by pesticide contamination of the environment under several other statutes, including the Safe Drinking Water Act, 42 U.S.C. 300f et seq., the Resource Conservation and Recovery Act, 42 U.S.C. 6901 et seq., and the Comprehensive Environmental Response, Compensation, and Liability Act, 42 U.S.C. 9601 et seq. Prior to enactment of the FQPA's specific provisions on pesticide risk assessment, a pesticide risk assessment performed by EPA's Office of Pesticide Programs under the aegis of FFDCA section 408 could generally be easily translated for use by the Office of Pesticide Programs under FIFRA, or by the other media offices within EPA for use under other statutes. However, once pesticide risk assessment under the FQPA became not simply a matter of good scientific practice but was channeled by explicit statutory requirements, it became incumbent upon the Office of Pesticide Programs to prepare its FFDCA pesticide risk assessments in a manner that clearly delineated what aspects of the assessment were driven solely by science and what aspects primarily by FQPA statutory requirements. Specifically, the Office of Pesticide Programs had to be transparent with regard to whether it was relying on FQPA safety factors based on unique FQPA requirements (exposure database deficiencies and potential pre- and post-natal toxicity) or FQPA safety factors that are essentially a codification of prior general EPA ''additional'' safety/uncertainty factor practice.

EPA addressed these ''transparency'' issues at length in its 2002 policy statement on the FQPA safety factor. To clarify how the FQPA safety factor provision left a portion of prior safety/uncertainty practice unchanged, codified another portion, and also expanded the use of safety factors, EPA explained the overlap between the FQPA safety factor and ''additional'' safety factors in depth and included the following figure to graphically illustrate the issue:

Figure 1. Relationship between Rfd Derivation and the PAD Calculation



Special FQPA Concerns:

- Residual Concerns with respect to exposure data
- Residual Concern for pre- and postnatal toxicity

(Ref. 12, Figure 3)

With regard to providing transparency on the FQPA safety factor decisions, EPA took two steps. First, it adopted a new term, the ''special'' FQPA safety factor, for children safety factors that were based solely on the new FQPA requirements. Second, it adopted the approach of calculating two different safe doses for a pesticide: One that excluded any ''special'' FQPA safety factors and one that included them. (See discussion of reference doses and population-adjusted doses in Unit III.B.1.b.iii, below). Introducing the new terminology on FQPA safety factors into

long-established safety factor practice has proved challenging. EPA staff frequently drafted documents that (1) claimed no FQPA safety factor was needed but applied an additional uncertainty factor to address the completeness of the data base or reliance on a LOAEL; or (2) treated the ''special'' FQPA safety factor as the only type of FQPA safety factor. Such misstatements did not substantively change risk assessment outcomes but they did raise the confusion level on an already complex topic. Eventually, EPA determined that the term ''special'' FQPA safety factor caused more problems than it solved and abandoned it. However, EPA has retained the approach of continuing to calculate both a safe dose with, and without, what was once referred to as ''special'' FQPA safety factors.

(iii). *Level of Concern.* By Level of Concern (LOC), EPA means a numerical value that separates exposures that would generally be regarded as raising health concerns from those that do not. The POD (see Unit III.B.1.b.i. above) is used in estimating and describing the LOC; however, the LOC is expressed differently depending on whether the risk assessment addresses dietary or non-dietary exposures. The use of different approaches is due to the fact that non-dietary exposure assessments often involve combining exposures from multiple pathways.

For dietary risks, EPA uses the POD to calculate an acceptable LOC that is referred to as a reference dose (RfD). The RfD is calculated by dividing the POD by all applicable safety or uncertainty factors with one exception (see below). (Ref. 12 at 4–11). Safety/uncertainty factors are divided separately and sequentially into the POD. Thus, for example, if the POD is 1 milligram/kilogram/day (mg/kg/day) and there are two applicable 10X safety/uncertainty factors, then the reference dose would be 0.01 mg/kg/day (i.e., 1 mg/kg/day divided twice by 10). For convenience's sake, safety factors are often combined by multiplying them by each other. This product when divided into the POD would, of course, produce the same result as sequential division. For reduction of a safety factor, a similar process is followed. For example, if a safety factor is to be reduced by half, this is done by taking the square root of the factor rather than dividing by two. See 73 FR 42683, 42696 (July 23, 2008).

In implementing FFDCA section 408, EPA's Office of Pesticide Programs, also calculates a variant of the RfD referred to as a Population Adjusted Dose (PAD). A PAD is the RfD divided by any portion of the FQPA safety factor that does not correspond to one of the traditional additional safety factors used in general Agency risk assessments. (Ref. 12. at 13–16). As noted above, the reason for calculating PADs is so that other parts of the Agency, which are not governed by FFDCA section 408, can, when evaluating the same or similar substances, easily identify which aspects of a pesticide risk assessment are a function of the particular statutory commands in FFDCA section 408. Today, RfDs and PADs are generally calculated for both acute and chronic dietary risks although traditionally RfDs and PADs were only calculated for chronic risks. RfDs/PADs for acute and chronic risks will generally have different Points of Departure (because they are generally based on studies of different duration) and may be based on different safety factors as well depending on the characteristics of the studies relied on in choosing the POD. For example, if the study used to pick the POD for acute risk identified a NOAEL but the study used for chronic risk did not, any additional safety factor used to address this lack of a NOAEL in calculating the RfD/PAD for chronic risk would not be applicable to the acute RfD/PAD derivation.

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

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

i. *Exposure from food.* There are two critical variables in estimating exposure in food: (1) The types and amount of food that is consumed; and (2) the residue level in that food.

Consumption is estimated by EPA based on scientific surveys of individuals' food consumption in the United States conducted by the USDA. (Ref. 11 at 12). Information on residue values comes from a range of sources including crop field trials; data on pesticide reduction (or concentration) due to processing, cooking, and other practices; information on the extent of usage of the pesticide; and monitoring of the food supply. (*Id.* at 17).

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

commodity. These latter data are used to estimate what has been traditionally referred to by EPA as ''anticipated residues.'' More information on refining estimates of pesticide exposure can be found at Ref. 11; 70 FR 46706, 46732, August 10, 2005).

ii. *Exposure from water.* EPA may use either or both field monitoring data and mathematical water exposure models to generate pesticide exposure estimates in drinking water. Monitoring and modeling are both important tools for estimating pesticide concentrations in water and can provide different types of information. Monitoring data can provide estimates of pesticide concentrations in water that are representative of specific agricultural or residential pesticide practices and under environmental conditions associated with a sampling design. Although monitoring data can provide a direct measure of the concentration of a pesticide in water, it does not always provide a reliable estimate of exposure because sampling may not occur in areas with the highest pesticide use, and/or the sampling may not occur when the pesticides are being used.

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

iii. *Exposure from residential use of pesticides.* Residential assessments examine exposure to pesticides in non-occupational or residential settings (e.g., homes, parks, schools, athletic fields or any other areas frequented by the general public). Exposures to pesticides may occur to persons who apply pesticides or to persons who enter areas previously treated with pesticides. Such exposures may occur through oral, inhalation, or dermal routes.

Residential assessments are conducted through examination of significant exposure scenarios (e.g., children playing on treated lawns or homeowners spraying their gardens) using a combination of generic and pesticide-specific data. To regularize this process, OPP has prepared Standard Operating Procedures (SOPs) for conducting residential assessments on a wide array of scenarios that are intended to address all major possible means by which individuals could be exposed to pesticides in a non-occupational environment (e.g. homes, schools, parks, athletic fields, or other publicly accessible locations). The SOPs identify relevant generic data and construct algorithms for calculating exposure amounts using these generic data in combination with pesticide-specific information. The generic data generally involve survey data on behavior patterns (e.g., activities conducted on turf and time spent on these activities) and transfer coefficient data. Transfer coefficient data measure the amount of pesticide that transfers from the environment to humans from a defined activity (e.g., hand contact with a treated surface or plant). Specific information on pesticides can include information on residue levels as well as information on environmental fate such as degradation data.

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

For threshold risks, EPA estimates risk in one of two ways. Where EPA has calculated a RfD/PAD, risk is estimated by expressing human exposure as a percentage of the RfD/PAD. Exposures lower than 100 percent of the RfD/PAD are generally not of concern. Alternatively, EPA may express risk by comparing the MOE between estimated human exposure and the POD with the acceptable or target MOE. As described previously, the acceptable or target MOE is the product of all applicable safety factors. To calculate the actual MOE for a pesticide, estimated human exposure to the pesticide is divided into the POD. In contrast to the RfD/PAD approach, higher MOEs denote lower risk. Accordingly, if the target MOE for a pesticide is 100, MOEs equal to or exceeding 100 would generally not be of concern. As a conceptual matter, the RfD/PAD and MOE approaches are fundamentally equivalent. For a given risk and given exposure of a pesticide, if exposure to a pesticide were found to be acceptable under an RfD/PAD analysis it would also pass under the MOE approach, and vice-versa.

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

In applying the FQPA safety factor provision, EPA has interpreted it as imposing a presumption in favor of applying an additional 10X safety factor. (Ref. 12 at 4, 11). Thus, EPA generally refers to the additional 10X factor as a presumptive or default 10X factor. EPA has also made clear, however, that this presumption or default in favor of the additional 10X is only a presumption. The presumption can be overcome if reliable data demonstrate that a different factor is safe for children. (*Id.*). In determining whether a different factor is safe for children, EPA focuses on the three factors listed in FFDCA section 408(b)(2)(C)—the completeness of the toxicity database, the completeness of the exposure database, and potential pre- and post-natal toxicity. In examining these factors, EPA strives to make sure that its choice of a safety factor, based on a weight-of-the-evidence evaluation, does not understate the risk to children. (*Id.* at 24–25, 35).

IV. 2,4-D Regulatory Background

2,4-D is a phenoxy herbicide, plant growth regulator, and fungicide that has been used in the United States since the mid 1940s. It comes in multiple chemical forms and is currently found in approximately 600 end-use products registered for agricultural, residential, industrial, and aquatic uses. It is formulated primarily as an amine salt in an aqueous solution or as an ester in an emulsifiable concentrate. There are 85 tolerances for 2,4-D listed in the Code of Federal Regulations.

1. *Special review based on human carcinogenicity.* On September 22, 1986, the Agency issued a preliminary notification of Special Review of 2,4-D because of concerns for epidemiological links of 2,4-D to non-Hodgkin's lymphoma from both occupational and residential exposure. In 1987, EPA requested that the FIFRA SAP examine

the evidence bearing on 2,4-D's carcinogenicity. The Panel concluded that the present data for animals and humans were inadequate for determining carcinogenicity and that 2,4-D should be classified under *Group D* of EPA's cancer guidelines—Not Classifiable as to Human Carcinogenicity. (Refs. 13 and 14). Based upon findings that existing data did not support a link between 2,4-D and carcinogenicity, the Agency published a proposed decision Not to Initiate Special Review on March 23, 1988 (53 FR 9590) and deferred a final decision until reregistration.

To further address the potential link of non-Hodgkin's lymphoma to 2,4-D exposure, a joint Science Advisory Board (SAB)/SAP Special Joint Committee was convened to review available epidemiological and other data on 2,4-D. In 1994, the Committee concluded that ''the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma.'' (Ref. 15). In 1997, EPA re-examined the weight of the evidence on cancer taking into account two new cancer bioassays in mice and rats. (Ref. 16). These new bioassays showed no statistically significant tumor response in either species. Although EPA concurred with the Joint Committee's recommendation to classify 2,4-D under Group D, EPA requested further histopathological examinations of mouse and rat tissue from previously conducted studies to further inform its decision. These exams showed no evidence to alter the prior findings, and on March 16, 1999, the Agency notified the 2,4-D Task Force that the EPA would continue to classify 2,4-D under Group D. (Ref. 17).

Since the March 16, 1999 decision, the Agency has twice reviewed epidemiological studies linking cancer to 2,4-D exposure during the reregistration process of 2,4-D. In the first review, completed January 14, 2004, EPA concluded there was no additional evidence that would implicate 2,4-D as a cause of cancer. (Ref. 14). The second review of available epidemiological studies occurred in response to comments received during development of the 2,4-D RED. EPA's report, dated December 8, 2004, found that none of the more recent epidemiological and animal studies supported a conclusion that 2,4-D was a likely human carcinogen. (Ref. 15). Because the Agency determined that the existing data did not support a conclusion that links human cancer to 2,4-D exposure, it decided not to initiate a Special Review of 2,4-D in 2007. (72 FR 44510, August 8, 2007).

A part of this cancer assessment was the review of data bearing on 2,4-D's potential mutagenicity. EPA has consistently found that these data do not support classification of 2,4-D as a carcinogen. This view was concurred in by the Joint Committee of SAB/SAP.

2. *FFDCA tolerance reassessment and FIFRA pesticide reregistration.* As required by the Food Quality Protection Act of 1996, EPA reassessed the safety of the 2,4-D tolerances under the safety standard established in the FQPA. In the June 2005 RED for 2,4-D, EPA evaluated the human health risks associated with all registered uses of 2,4-D and determined that there is a reasonable certainty that no harm will result from aggregate non-occupational exposure to the pesticide chemical residue. (Refs.18 and 19). In making this determination, EPA considered dietary exposure from food and drinking water and all other non-occupational sources of pesticide exposure for which there is reliable information. The Agency concluded that with the adoption of the risk mitigation measures identified in the 2,4-D RED, all of the tolerances for 2,4-D meet the safety standard as set forth in section 408(b)(2)(D) of the FFDCA. Therefore, the tolerances established for residues of 2,4-D were considered reassessed as safe under section 408(q) of FFDCA.

At the time of 2,4-D reregistration, there were no available studies on 2,4-D that adequately assessed its endocrine disruption potential, and the Agency determined that a repeat 2-generation reproduction study should be conducted to evaluate comparative thyroid effects in young and adult animals as well as the gonads and reproductive/developmental endpoints more thoroughly. The 2,4-D RED indicated that a new reproduction study using the revised 2-generation reproduction study protocol and measurement of additional parameters was needed to address these data gaps. EPA also required submission of a developmental neurotoxicity study. Although these data were needed, EPA concluded that the toxicology database was adequate for identification of doses and endpoints of concern for risk assessments. The values selected for risk assessments were protective of all observed adverse effects. Additionally, EPA retained the additional FQPA 10X safety factor for the protection of infants and children to address the uncertainty raised by the missing data. Finally, 2,4-D toxicity generally occurs at doses above renal saturation, i.e., doses above which the excretory processes could readily eliminate the chemical; the Agency's risk assessment regulated at doses below this level. Consequently, the Agency had high confidence that the risk assessment did not underestimate risks from exposure to 2,4-D.

On February 28, 2006, EPA issued a data call-in for 2,4-D that, among other things, required submission of the reproduction and developmental neurotoxicity studies mentioned above. In February 2010, in response to the data call-in, the Industry Task Force II on 2,4-D Research Data submitted a state-of-the-science extended one-generation reproduction toxicity study to fulfill these requirements. The 2,4-D extended one-generation reproductive toxicity study included a detailed assessment of endocrine endpoints (thyroid, estrus cyclicity, sexual maturation (animals were observed for delays in vaginal opening and preputial separation), andrology, and ovarian staging), in addition to reproductive function, developmental neurotoxicity, and immunotoxicity endpoints.

3. *More recent actions.* EPA has conducted a number of rulemakings with respect to 2,4-D tolerances since completion of tolerance reassessment. In July, 2005, EPA established new 2,4-D tolerances on hops, soybeans, and wild rice. (70 FR 43298, July 27, 2005). This action was based on the safety determination in the 2,4-D tolerance reassessment. No comments were received. In June 2007, EPA proposed numerous changes to the 2,4-D tolerances to implement determinations made in the 2,4-D tolerance reassessment (72 FR 31221). These proposed changes included modification of the chemical terms used in the tolerance expression, the amendment of various tolerance levels, and removal of certain tolerances. No comments relevant to 2,4-D tolerances were received and EPA finalized the tolerance actions on September 12, 2007 (72 FR 52013). 2,4-D tolerances have been modified three times since 2007. In 2008, minor changes were made to correct errors in the 2007 rulemaking. (73 FR 53732, September 17, 2008). NRDC commented on the proposal for these changes but did not raise any new information that had not been addressed in response to their comments on the RED. In 2009, EPA modified the 2,4-D tolerance for cranberries. No comments were received. (74 FR 48408, September 23, 2009). In 2011, a tolerance for teff was established, for which EPA received no significant comments. (76 FR 55814, September 9, 2011).

Additionally, in response to an application to amend the 2,4-D FIFRA registration, EPA, in 2011, re-examined the risks of 2,4-D. That re-examination

took into account the newly submitted extended one-generation reproduction toxicity study evaluating 2,4-D's potential for causing endocrine, neurotoxic, or imumunotoxic effects. As part of that risk assessment, EPA re-evaluated the decision to retain the FQPA safety factor. Because the FQPA safety factor had previously been retained due to the absence of data on endocrine and neurotoxic effects and those data requirements had been met, EPA determined that the 10X FQPA safety factor should be removed. (Refs. 20 and 21).

V. The Petition To Revoke Tolerances

NRDC filed a petition dated November 6, 2008 (petition), requesting, among other things, that EPA revoke all 2,4-D tolerances. (Ref. 1). In response to EPA's publication of the petition pursuant to section 408(d) of the FFDCA, NRDC submitted a comment in support of its petition. (Ref. 22). The petition asserts that EPA's conclusion outlined in the 2005 2,4-D RED, allowing 2,4-D to be reregistered and its tolerances retained, was based on incorrect information and assumptions related to the toxicity of 2,4-D and the amount of human exposure to the chemical. Specific to tolerances, the petition asserts that EPA failed to incorporate information on the endocrine disrupting effects of 2,4-D into its human health risk assessments; EPA disregarded data on neurotoxicity related to 2,4-D; EPA disregarded information showing that 2,4-D is mutagenic; EPA ignored data showing that dermal absorption of 2,4-D is enhanced by alcohol consumption, sunscreen, and DEET; and that EPA ignored the exposure of infants to 2,4-D via breast milk. Numerous studies are cited in the petition that NRDC says supports their assertions. EPA has reviewed all of the studies submitted by NRDC. NRDC also relies, in part, on portions of its comments submitted on the 2,4-D RED in support of its petition. (Ref. 1 at 11; Refs. 23 and 24).

VI. Public Comment

EPA published notice of the petition for comment on December 24, 2008 (73 FR 79100). EPA received approximately 500 comments on the petition. The vast majority of the comments were against the petition, and many discussed the importance of 2,4-D to various industries, including forestry, grains, landscaping, and minor use crops. (See e.g., Ref. 25). These issues, however, are irrelevant to the safety determination under FFDCA section 408. Two of the comments opposing the petition, from the Industry Task Force on 2,4-D Research Data II (Task Force), and National Council for Air and Stream Improvement (NCASI), provided detailed comments on the petition and on the studies cited in the petition. (Refs. 26 and 27). The Task Force and NCASI cited additional studies during the comment period for EPA to consider in its response to the petition.

Twenty-three comments were in support of the petition and agreed with NRDC that 2,4-D's tolerances should be revoked. Most of the comments that were in support of the petition assert in a general way that 2,4-D is ''unsafe,'' but provide little or no reasoning for this conclusion. Two of the comments in support of the petition, one from Beyond Pesticides and a combined comment from the New York State Department of Health and New York State Department of Environmental Conservation, identified additional studies for EPA consideration. (Refs. 28 and 29). Additionally, the comment from Beyond Pesticides asserts that EPA ignored evidence that EPA endangers children by removing the FQPA 10X safety factor; and EPA has failed to perform a cumulative assessment for 2,4-D and other phenoxy herbicides. Finally, NRDC submitted as a comment additional material in support of its petition. (Ref. 22).

VII. Ruling on Petition

This Order addresses NRDC's petition to revoke 2,4-D tolerances. EPA has divided NRDC's grounds for revocation into two main categories—toxicology and exposure—and addressed separately each claim under these categories. Each specific claim of NRDC is summarized in Unit VII immediately prior to EPA's response to the claim.

This Order also constitutes a response to the comments received during the public comment period on the petition as they relate to NRDC's arguments for revoking tolerances. Below are the Agency's responses to NRDC's assertions and the related public comments. Detailed reviews of the studies cited by NRDC and commenters can be found in the docket. (Ref. 30).

A. Toxicology

NRDC has raised four toxicological issues regarding the safety of 2,4-D: Endocrine disruption, neurotoxicity, mutagenicity, and impacts on body weight. Each of these issues are addressed below.

1. *Endocrine Disruption*—a. *NRDC Claims.* In support of their petition, NRDC cites several studies that it says, ''* * * establish the dangerous endocrine disrupting effects of 2,4-D and underscore the need for EPA to consider these impacts in its assessment of the health impacts of 2,4-D.'' (Ref. 1 at 2). NRDC asks EPA to incorporate information on the endocrine disrupting effects of 2,4-D into its human health risk assessments. (Id. at 2).

Specifically, NRDC cites several studies, discussed below, that it contends show that 2,4-D is an endocrine disruptor. (Id. at 4–5). NRDC quotes a portion of the 2,4-D RED, which states: ''Based on currently available toxicity data, there is evidence of the endocrine-disrupting effects of 2,4-D on mammals. However, no specific measures of such effect have been attempted'' and a statement that when the EDSP is underway, 2,4-D may be subject to additional screening or testing. (Id. at 5–6). NRDC argues that EPA has relied on the delay in conducting the EDSP to neglect analyzing the endocrine effects of 2,4-D despite the existence of ''an entire category of existing scientific studies demonstrating adverse health effects.'' (Id. at 6). It uses atrazine as an example of a case where EPA has considered endocrine disrupting effects in the absence of the formal screening program. The atrazine example, according to NRDC, shows that EPA cannot claim that the existing studies on endocrine disrupting effects cannot be considered in human health risk assessments. NRDC states that ''EPA should have quantitatively incorporated these studies and these effects in its risk assessment of 2,4-D.'' (Id.).

b. *Public comments.* In its comments, Beyond Pesticides supports NRDC's petition to cancel all 2,4-D product registrations due to the alleged wealth of relevant scientific information available that indicates that 2,4-D is a potential endocrine disruptor. (Ref. 28 at 3). Beyond Pesticides cites additional studies to those cited by NRDC. (Id. at 3–4).

The 2,4-D Task Force, in its comments, disputes NRDC's claim that 2,4-D is an endocrine disruptor. (Ref. 26 at 11–18). Specifically, the Task Force argues that NRDC's assertions that 2,4-D has been shown to be a potent endocrine disruptor are not supported by the weight of the evidence surrounding 2,4-D's potential for endocrine disrupting effects. The Task Force disagrees with NRDC's contention that EPA ignored endocrine disrupting effects given that the Agency issued a data call-in for a study that assesses thyroid, gonadal, reproductive and other endocrine-sensitive endpoints and while awaiting the study imposed an additional 10X uncertainty factor to account for the data gap. (Id. at 11–12). The Task Force provided detailed

comments on each of the studies cited by NRDC disputing NRDC's conclusions.

Additionally, National Council for Air and Stream Improvement (NCASI), in its comments, takes issue with NRDC's characterization of various studies indicating that 2,4-D was an endocrine disruptor. (Ref. 27 at 2–3). NCASI indicates that studies cited by NRDC to support their claim for endocrine disruption concerns are not consistent with other studies of 2,4-D estrogenicity. (Id. at 3).

c. *EPA response.* With regard to endocrine effects, NRDC argues that EPA should revoke the 2,4-D tolerances because EPA failed to properly assess 2,4-D's endocrine effects in the RED risk assessment. For example, NRDC contends that ''[r]ecent studies [ ] establish the dangerous endocrine disrupting effects of 2,4-D and underscore the need for EPA to consider these impacts in its assessment of the health impacts of 2,4-D.'' (Ref. 1 at 4). NRDC concludes this portion of its petition by asserting that ''given the studies suggesting that 2,4-D has the potential to cause endocrine disrupting effects, EPA should have quantitatively incorporated these studies and these effects in its risk assessment of 2,4-D.'' (Id. at 6).

These claims by NRDC do not allege sufficient grounds for revocation of the 2,4-D tolerances. The statutory standard for revocation of a pesticide tolerance is that the tolerance is not ''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). As explained in Unit II.B., EPA has implemented this safety standard, consistent with the statute, by a quantitative risk assessment process that (1) identifies the harms or toxic effects caused by the pesticide, (2) ascertains the safe level of exposure as to those harms; and (3) determines whether aggregate exposure to the pesticide exceeds that safe level. Thus, safety is not simply a question of a pesticide's potential to cause harm but an issue involving a combination of factors including the pesticide's potential harms, the pesticide's potency (i.e., at what exposure levels will it cause harm), and the level of human exposure to the pesticide.

The flaw in NRDC's petition with regard to its endocrine claim is that it addresses only 2,4-D's potential harm and not 2,4-D's safety. NRDC claims that 2,4-D has the ''potential to cause endocrine disrupting effects * * * [and] EPA should have quantitatively incorporated [this information on 2,4-D's harmful effects] in its risk assessment of 2,4-D.'' While the reference to endocrine effects clearly addresses the first element of the risk assessment process—identification of a harm or toxic effect—NRDC's assertion that EPA should quantitatively incorporate the endocrine studies cited by NRDC in its risk assessment falls far short of addressing the other elements of the risk assessment process. NRDC does not allege that quantitative incorporation of the studies it cites would alter EPA's prior conclusion regarding the safe exposure level for 2,4-D. Yet, unless NRDC claims that the safe level of exposure should be lowered, it has no basis to argue that the toxicity data on endocrine effects it cites indicate a lack of safety. At best, NRDC is asking EPA to take a revised look at the toxicity of 2,4-D. Yet, the ground for tolerance revocation is a lack of safety. Accordingly, NRDC's claim that the 2,4-D tolerance should be revoked due to 2,4-D's endocrine effects is denied due to a failure to make a proper claim for revocation by, at the very least, alleging facts that, if proven, would meet the statutory standard for revocation.

Despite the inadequacy of petitioners' endocrine claims, EPA has examined the evidence cited by petitioners in light of the most current toxicity data on 2,4-D for the purpose of evaluating whether the evidence raises sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

To the extent data were available, EPA examined 2,4-D's potential for endocrine disruption in the 2005 RED. However, as noted there, EPA was handicapped in this evaluation due to the fact that the otherwise acceptable two-generation rat reproduction study conducted with 2,4-D did not adequately address endocrine concerns. Although several toxicity studies required under 40 CFR part 158 involve an examination of organs or endpoints related to endocrine disruption, the rat reproduction study is the most critical of these required studies. In fact, the two-generation rat reproduction study, as described in the 1998 EPA guideline, has been designated as the study that will be used in Tier 2 of the EDSP for evaluating mammalian endocrine effects. As mentioned above, EPA issued a data call-in for a two-generation reproduction study in rats to address this data gap. In response to the data call-in, the Task Force submitted an extended one-generation reproductive toxicity study to fulfill this requirement. The 2,4-D extended one-generation study examined endocrine disruption as well as developmental neurotoxicity and developmental immunotoxicity. This extended one-generation reproductive toxicity study was conducted in accordance with OECD guidelines and is considered a state-of-the-science study with regard to examining these toxicological and endocrine effects.

As to endocrine effects, the extended one-generation reproduction study examined: Potential effects on parental male and female reproductive function, offspring survival and growth including endocrine and systemic toxicity parameters such as estrous cyclicity (female adult rats and offspring); sperm parameters; anogenital distance; nipple retention; puberty onset (vaginal opening and balano-preputial separation); adrenal weight, thyroid/parathyroid gland weight, pituitary gland weight, testes and ovarian weight, thyroid hormone effects; and histopathology of a wide range of tissues including the thyroid, adrenal, pituitary, testes, and ovary. (Refs. 31 and 32). The endpoints examined in the extended one-generation reproduction study meet or exceed the specifications in the latest guideline (1998) for the two-generation reproduction study. (Ref. 33). Specifically, this extended one-generation study included evaluation of sperm parameters and thyroid assays across various age groups, which are not part of the two-generation study. The main design difference between an extended one-generation study and a two-generation study is that the latter study is run for a full two generations no matter what results are seen in the first generation. On the other hand, an extended one-generation study is not continued into the second generation if triggers on the key endpoints do not indicate there is a potential concern. This design eliminates the needless destruction of animals, but does not reduce the scientific value of the data.

The extended one-generation study for 2,4-D showed no treatment-related effects on potential estrogenic effects or androgen-sensitive endpoints (no adverse effects on anogenital distance, nipple retention, age at vaginal opening, estrous cycle length or pattern, mating, fertility, time to mating, gestation length, pre-implantation loss, number of corpora lutea, sperm parameters, ovarian follicle counts, and reproductive organ weights and histopathology; no evidence of hyposadias, ectopic tests, or treatment-related testicular prostate or seminal vesicle histopathology). Anti-androgenic

effects in terms of decreased male reproductive organ weights were observed in some animals but they were not statistically significant and were associated with decreased body weight. No treatment-related effects on reproductive organ histopathology were observed. Slight effects were seen in the thyroid (increases or decreases in thyroid weight and in T3, T4, and TSH hormones in some animals) but no dose response relationship was shown. These effects were more significant at the highest dose tested but still were considered adaptive and not adverse (i.e., the thyroid responded to insult and corrected itself) due to the fact that this dose exceeded the renal saturation level. Accordingly, the highest dose was considered a No Observed Adverse Effect Level (NOAEL) for thyroid effects.

Overall, the effects observed at the lowest doses in the extended one-generation reproductive study for both the parental rats and offspring were not based on endocrine-related endpoints but on nephrotoxicity manifested as increased kidney weights, and degenerative lesions in the proximal convoluted tubules in the main study in the first-generation adult rats (P_1 generation; 45.3 mg/kg bw/day); kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules in the adult offspring (F_1 adults; 55.6/46.7 (M/F) mg/kg/day); and decreased body weight observed in the male pup offspring (F_1, Set 1a males, PND 28–69; 76.6 mg/kg/day) (see discussion in Unit VII.A.4.c.). The NOAEL for parents and offspring for these effects is approximately 20 mg/kg/day, (Ref. 32), which is greater than the NOAEL of 5 mg/kg/day from a rat chronic toxicity study that was used as the POD in assessing chronic dietary, long-term dermal, and long-term inhalation in the human health risk assessment supporting the 2,4-D RED. (Ref. 18). In that chronic study, the effects seen at the LOAEL of 75 mg/kg/day were decreased body-weight gain and food consumption, alteration in hematology and clinical chemistry parameters, decreased T4, glucose, cholesterol, and triglycerides. The use of the NOAEL from the chronic rat study as the POD in the RED risk assessment is protective of chronic effects identified in the extended one-generation study.

The NOAEL found in the extended one-generation reproductive study is also similar to the NOAEL of 15 mg/kg/day seen in a rat subchronic oral toxicity study and used to identify a POD for subchronic effects in the RED. (Ref. 18 at 22). The effects seen at the LOAEL of 100 mg/kg/day in the rat subchronic study were decreased body weight/body-weight gain, alterations in some hematology [decreased platelets (both sexes)] and clinical chemistry [decreased T3 (females) and T4 (both sexes)] parameters, and cataract formation. This study was used for the intermediate incidental oral and intermediate dermal and inhalation assessments. Again, the NOAEL in the extended one-generation study is greater than the NOAEL chosen as a POD for subchronic effects, and therefore, the RED assessment is protective of any subchronic effects identified in the extended one-generation study.

As noted above, EPA concluded that this study showed no adverse effects on endocrine endpoints. Accordingly, the extended one-generation reproduction study's comprehensive examination of 2,4-D's potential effect on the endocrine system provides no indication that EPA should consider initiating action to revoke 2,4-D tolerances.

Nothing in the data cited by NRDC or other commenters contradicts this conclusion. For the most part, the data relied upon by NRDC address whether 2,4-D is capable of interacting with the endocrine system. The studies do not provide quantitative information appropriate for use in risk assessment or the quantitative information they provide shows that EPA's risk assessment is protective of endocrine effects. Many of the studies cited by NRDC were studies conducted to investigate 2,4-D's mechanism of action and involved testing at a single high dose designed to ensure effects were seen. In rats, although 2,4-D is readily absorbed in the blood, it is not metabolized but removed from the blood by the kidneys and rapidly excreted through the urine. Once the dose of 2,4-D in rats exceeds about 50 mg/kg/day, however, the kidney (renal) clearance mechanism is overwhelmed and 2,4-D builds up in the body resulting in toxic effects. The toxic effects seen at doses above the renal saturation level are generally not seen at lower doses. EPA has assessed the risk of 2,4-D based on the dose levels below the renal saturation level at which adverse effects occur.

NRDC first cites a study in fish (Xie (2005)) that it contends shows that 2,4-D has ''relatively potent estrogenic effects in fish.'' (Ref. 1 at 4 and Ref. 34). As an initial matter, a study in fish would carry little weight regarding a safe tolerance level when compared to a study in mammals such as the extended one-generation reproduction study in rats. Additionally, EPA does not regard the Xie study as reliable due to a failure to identify the sex of the fish used. The study reported that 7-day exposure of rainbow trout juveniles to 1.64 mg/L 2,4-D (active or formulated product undetermined) produced a 93-fold increase in plasma vitellogenin compared to untreated fish. This was a significant difference from the untreated control. Six fish were used per test concentration, and they were described as ''juvenile rainbow trout (standard length: 11.5 ± 2.2 cm) provided by the California Department of Fish and Game Mojave River Hatchery (Victorville, California)'' with no reference to their sex or specific age information. However, the sex of the fish is significant with regard to vitellogenin levels. Male fish generally maintain null or very low levels of vitellogenin in their natural state. In the presence of endocrine disruptors, male fish will have significant levels of vitellogenin in their blood. Female fish will have naturally increasing levels of vitellogenin as they approach maturity and maintain those levels upon maturation. Given the sample size and a failure to identify the sex of the fish, the results seen may be a result of unbalanced numbers of male and female fish in the control and treated groups. Several other difficulties with the Xie study, including the failure to identify a biologically significant effect on vitellogenin, are noted in the comments of the Task Force and NCASI.

NRDC next relies on two studies (Rawlings (1998) and Charles (1996)), which it alleges show that 2,4-D causes hormone suppression in animals. (Refs. 35 and 36). In the Rawlings study, 2,4-D treatment resulted in a significant ($p < 0.05$) decrease in serum T4 concentrations compared to control. No other significant effects were noted for serum cortisol, insulin, estradiol, LH pulse frequency (mean and amplitude), mean serum FSH, progesterone, or gross signs of toxicity or body weight change. In the absence of a quantifiable relationship between serum T4 concentration and effects upon survival, growth, or reproduction, the results of this study do not evidence an adverse effect that could be incorporated directly into the Agency risk assessment process. The Charles study reports on a subchronic study in rats and was submitted to EPA and relied upon in the RED risk assessment. The study identified a NOAEL of 15 mg/kg/day and a LOAEL of 100 mg/kg/day. The effects seen at 100 mg/kg/day did include thyroid effects such as decreased thyroxine, increased thyroid weight, and hypertrophy of follicular cells. These effects were seen at a dose (100 mg/kg/day) that was well above the

renal saturation level and the NOAEL from the study was used to set the safe dose for subchronic exposures to 2,4-D and is protective of effects occurring at higher dose levels. (Ref. 18 at 36).

NRDC also cites several studies (Liu (1996), Kim (2005), Kim (2002)) which it claims show that 2,4-D can result in effects on testicular cells and the prostate. (Refs. 37, 38, and 39). Liu is an *in vitro* study investigating possible mechanisms of action in relation to Leydig cell adenomas and peroxisome proliferation. 2,4-D was one of the peroxisome proliferators evaluated in the study. Kim (2005) also is an *in vitro* study investigating potential androgenic mechanisms. EPA could not evaluate the Kim (2002) study because it is written in Korean and not available to EPA in English. The Task Force argues that the 2002 study is irrelevant because it involved doses above the renal saturation level and thus the 2005 study, which was designed to investigate the effects in the 2002 study, is of limited value given the high dosing in the 2002 study. Liu also appears to have shown statistically significant effects for 2,4-D on production of estradiol only at very high doses. In any event, EPA has adequate data in living animals regarding 2,4-D's potential to affect testicular cells or the prostate. There is an adequate/guideline cancer study in rats that dosed at levels of 5, 75, and 150 mg/kg/day (2-year study); there were no effects observed in the prostate, including no tumors. In fact, there was no increase in any tumor type in either the rat or mouse. (Ref. 19 at 29). There are numerous studies in the rat of varying duration, and no effects on the prostate have been observed. In the studies available for the 2005 RED, effects on the testes and ovary were identified, hence the request for the two-generation rat reproduction study. The extended one-generation reproductive study is now available and it assessed the prostate. There were no effects on prostate weight and no histopathology findings in the prostate or other male accessory sex organs.

Finally, NRDC argues that studies have shown that 2,4-D causes abnormalities in the estrus cycle (Duffard (1995)), lowers sperm counts and causes other sperm abnormalities (Lerda (1991)), and results in birth defects (Garry (1996)). (Refs. 40, 41, and 42). NRDC has only cited an abstract of the Duffard study, which provides little information. It is clear, however, that the Duffard study used a single dose (70 mg/kg/day) that was at or above the renal clearance level. Garry (1996) investigated the hypothesis that offspring of pesticide applicators might have increased risks of birth anomalies. Although the initial study found an apparent linkage between an area of high phenoxy use and birth anomalies, a more detailed cross-sectional analysis of this area showed no statistically significant correlations between phenoxy use and excess adverse birth or neurodevelopmental effects. (Ref. 43). Lerda (1991) reported an apparent link between exposures to 2,4-D in 32 male applicators and reproductive effects (spermatogenesis). However, these results have little weight for assessing 2,4-D risk because Lerda (1991) did not describe the nature of applicators' exposures in sufficient detail to show that 2,4-D was the causal agent and, if so, the level of that exposure. For example, Lerda (1991) lacked information on the timing/duration of exposure relative to sampling, the use of protective clothing/equipment, the possible presence of manufacturing contaminants given timeframe of study, and exposures to other pesticides. On the other hand, as noted above, the extended one-generation reproduction study assessed 2,4-D's potential impact on the estrous cycle and sperm counts/abnormalities, and no adverse effects were found in these parameters.

Beyond Pesticides, in commenting on the petition, cited Garry (2001) and Malysheva (1997), in addition to studies referenced by NRDC, as supporting NRDC's claim that 2,4-D is an endocrine disruptor. (Refs. 44 and 45). Garry (2001) indicated serum luteinizing hormone (LH) values were correlated with urinary 2,4-D levels in humans, but follicle-stimulating hormone and free and total testosterone were not. Garry (2001) also found 2,4-D levels were not correlated with chromosome aberration frequency in humans but that chromosome aberration frequencies were correlated with the total volume of herbicides applied, including products other than 2,4-D and the use of adjuvants. This study is of limited value because of the small sample size, as noted by the authors, and because it is not clear what other pesticides the individuals were exposed to and how specific components of adjuvant products in the pesticide may have impacted the findings.

According to Beyond Pesticides, the Malysheva (1997) study found that the thyroid glands of laboratory rats were sensitive to 2,4-D as decreases in the thyroid gland transport and hormone production functions, and impairment of hormone iodination in the thyroid were observed after acute exposure. However, no information on the study was presented and the cited article is in Russian and no translation was available. Thyroid function was fully evaluated in the extended one-generation reproduction study. As noted above, the extended one-generation reproduction study examined 2,4-D's potential thyroid effects and established a NOAEL for such effects demonstrating that EPA's prior risk assessment was protective.

In sum, the data cited by NRDC, Beyond Pesticides, and NYDOH do not support changing the quantitative endpoints for assessing the risk posed by 2,4-D for potential endocrine effects given the equivocal results in the studies cited and/or the high doses involved in the studies. Further, the recently-completed extended one-generation reproduction study that was specifically designed to evaluate such effects for the purpose of assessing human risks does not indicate that existing Points of Departure for assessing 2,4-D risks are under protective. Accordingly, EPA concludes that NRDC's petition does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

2. *Neurotoxicity*—a. *NRDC Claims.* NRDC asserts that ''the neurotoxic and anti-thyroid effects of 2,4-D make it highly likely that fetuses, infants, and children will be more susceptible to long-term adverse health effects from exposure to this chemical.'' (Ref. 1 at 7). It cites several studies that it claims provide evidence that postnatal exposures to 2,4-D during the critical period for development of the infant brain raise serious scientific concerns. The cited studies by the same group of authors report alterations on the neurotransmitters systems (catecholamine, indoleamine), marked depression in locomotor activity, and moderate circling towards the right side following exposure to 2,4-D via the diet, during gestation, and/or postnatally. NRDC also cites a study reporting decreased serotonin levels were found in various areas of the brain following direct injection of 2,4-D into the brain. Impairment of normal deposition of myelin in the developing brain was reported following exposure via the milk or direct subcutaneous exposure. Several studies were cited to show potential effects of 2,4-D on the brain of neonatal rats exposed lactationally. (Id.).

b. *Public comments.* The New York State Department of Health (NYS DOH) submitted comments in support of the NRDC petition, stating that various toxicological findings associated with 2,4-D in EPA's RED document are weak. (Ref. 29 at 1). The RED, for example, identified specific adverse health effects

of concern, including developmental neurotoxicity and endocrine disruption, and required further studies from the registrants to evaluate these effects. NYS DOH identifies additional studies for the Agency to consider. (Id.).

Beyond Pesticides, in its comments, argues that EPA has underestimated 2,4-D's potential neurotoxic effects, and cites studies which it says show changes to maternal behavior in rats, along with increased catecholamine levels and a drastic decrease in indolamine levels. (Ref. 28 at 3).

The 2,4-D Task Force submitted comments arguing that the studies cited by NRDC do not provide credible or substantive evidence that 2,4-D causes developmental neurotoxicity at exposure levels or routes of administration relevant to humans. (Ref. 26 at 18–21). It notes that in response the reregistration data call-in issued for 2,4-D, the 2,4-D Task Force agreed to conduct an extended one-generation reproduction study in rats of 2,4-D in the diet. The Task Force points out that this study would include assessment of developmental neurotoxicity endpoints, and states that at the time it was preparing comments, there were no dose-related statistically significant indications of developmental neurotoxicity related to 2,4-D exposures, even at dose levels demonstrated to be well above the renal clearance threshold in rat dams and pups. (Id. at 4).

c. *Agency response.* NRDC requests revocation of 2,4-D tolerances because (1) ''[t]he neurotoxic and anti-thyroid effects of 2,4-D make it highly likely that fetuses, infants, and children will be more susceptible to long-term adverse health effects from exposure to this chemical;'' and (2) data cited in the petition ''provide evidence that postnatal exposures to 2,4-D during the critical period for development of the infant brain raise serious scientific concerns.'' (Ref. 1 at 7). However, such claims, as discussed in Unit VII.A.1.c., have the same flaw as NRDC's endocrine arguments: The fact that the young are more susceptible to adverse effects of a pesticide or that data on a pesticide raise ''serious scientific concerns'' do not amount to a showing that aggregate exposure to the pesticide is unsafe, the standard for revoking tolerances. That the young may be more sensitive to a pesticide than adults may be irrelevant to the safety determination if both the young and adults have aggregate exposures below the safe dose. Similarly, that exposure to a pesticide in high dose testing may result in serious effects does not show that aggregate actual exposure to the pesticide, as opposed to exposure levels in laboratory testing, is unsafe. Again, NRDC has failed to address all the steps in the risk assessment process necessary to a safety determination. As with its endocrine claim, NRDC has done no more than allege 2,4-D has the potential to cause harm. Accordingly, NRDC's claim that the 2,4-D tolerance should be revoked due to 2,4-D's neurotoxic effects is denied due to a failure to allege facts sufficient to meet the statutory standard for revocation.

Despite the inadequacy of petitioners' neurotoxicity claims, EPA has examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding 2,4-D that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

In the 2005 RED, EPA identified neurotoxic effects in the acute and subchronic neurotoxicity studies as well as other studies. These effects included clinical signs (e.g., ataxia, tremors, decreased motor activity) as well as neuropathology (e.g., retinal degeneration); however, these effects were only seen at doses above the level of saturation of renal clearance. Given these neurotoxic effects, EPA issued a data call-in for a developmental neurotoxicity study and retained the FQPA safety factor for the protection of infants and children in the absence of that data. To address this data gap, the Task Force submitted an extended one-generation reproduction study with a developmental neurotoxicity component.

The extended one-generation reproductive toxicity study on 2,4-D assessed developmental neurotoxicity at three dose levels up to the saturation level for renal clearance. (Ref. 31). The potential for neurotoxic effects was assessed using numerous parameters. First, the study used a Functional Observation Battery (FOB) to evaluate whether there were clinical signs of neuorotoxicity. This FOB included cage-side, hand-held, and open-field observations of behavior, and measurements of body weight, rectal temperature, grip performance, and landing foot splay. Second, the study used an automated system for measuring motor activity. Third, the study assessed the startle response to auditory stimuli. Finally, a neuropathological exam was conducted on the brain (including the cerebrum, thalamus/hypothalamus, cerebellum and medulla), spinal cord, dorsal root ganglia, dorsal and ventral roots, peripheral nerves, and skeletal muscle. The examination of the brain included assessment of brain weight and gross measurements, microscopic measurements (morphometrics), and brain myelin. There were no treatment-related adverse effects on any of the numerous parameters assessed across life stages, which included multiple neurotoxicity-related endpoints similar to those in the studies cited by NRDC (*e.g.,* an assessment of motor activity, myelination, and maternal behavior). Thus, the extended one-generation reproduction study, in conjunction with all of the other data bearing on neurotoxicity, supports EPA's risk assessment of 2,4-D and provides no indication that EPA should consider initiating action to revoke 2,4-D tolerances.

The studies relied upon by NRDC in the portion of its petition addressing neurotoxicity do not suggest that EPA has not protected against potential neurotoxic effects of 2,4-D. Similar to its approach to endocrine effects, NRDC appears to take the position that the mere fact that 2,4-D could have a neurotoxic effect shows that it is unsafe. Consistent with this approach, NRDC, for the most part, relies on mechanism of action studies that involve a single, high dose as opposed to risk assessment studies designed to investigate a chemical's dose response relationship across a wide range of doses. NRDC relies on the following 2,4-D studies: A study in fish showing adverse brain effects (Ton (2006)); a study in rats showing delays in brain development and abnormal behavior patterns (Evangelista (1995)); a study in rats showing neurotoxic effects on the basal ganglia in the brain (Bortolozzi (2001)); and three studies that appear to show impairment of normal deposition of myelin in the developing brain (Rosso (2000); Duffard (1996); Konjuh (2008)). (Refs. 46, 47, 48, 49, 50, and 51). Each of these studies, however, either involve testing at levels above the renal saturation dose or use routes of exposure or methodology inappropriate to human risk assessment or both.

Ton (2006) was a research study investigating the use of zebrafish as a screening assay for identifying whether a chemical has the potential for neurotoxic effects and requires further testing in mammalian systems. For 2,4-D, appropriate testing in mammals is available, including a developmental neurotoxicity study in rats. Further, Ton only found potential neurotoxic effects at dose levels exceeding the dose concentration that is lethal to 50 percent for zebrafish (referred to as the LC_{50} (lethal concentration)). Other limitations in this study are outlined in the Task Force's comments. (Ref. 26 at 18–19).

Evangelista (1995) used doses of 50 and 100 mg/kg/day of 2,4-D. These doses meet or exceed the renal saturation level. Further compromising interpretation of this study is the fact that the identified neurotoxic effects were only detected when exposure to 2,4-D was combined with doses of amphetamine. NRDC also inaccurately describes this study as involving young rats when, in fact, adult animals were tested.

Bortolozzi (2001) investigated potential neurotoxic effects of 2,4-D by directly injecting 2,4-D into different brain areas of rats. Such a methodological approach is not useful for risk assessment because it does not correspond to the routes of exposure for humans to 2,4-D and, as noted, appropriate route of exposure studies are available for 2,4-D. Further, the Task Force described the doses in the study as being 40- to 100-fold greater than the concentration in the brain after systemic treatment.

Rosso (2000), Duffard (1996), and Konjuh (2008) each involved testing at 70 or 100 mg/kg/day. These doses exceed the renal saturation level. Other limitations in these studies are detailed in the Task Force's comments. (Ref. 26 at 20–21).

Other studies cited by NRDC and Beyond Pesticides that address neurotoxicity have similar weaknesses. Ferri (2007), Garcia (2004), and Garcia (2008) used doses exceeding the renal saturation level. Sturtz (2008) found effects on maternal care but these effects were not duplicated in the extended one-generation reproduction study and the effects were not associated with any adverse effects in the pups.

Studies cited by the New York State Department of Health in comments are similar to the NRDC studies in that they are studies investigating mechanism of toxicity and were conducted at doses exceeding the renal saturation level.

In sum, EPA does not disagree with NRDC that 2,4-D, if administered at high enough doses, may result in neurotoxic effects in animals. However, the data regarding neurotoxicity relied upon by NRDC, or cited by commenters, does not indicate that the existing Points of Departure for evaluating 2,4-D risks are underprotective. Similarly, the extended one-generation reproduction study confirms the protectiveness of the existing Points of Departure as to neurotoxic effects. Accordingly, EPA concludes that NRDC's petition does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

3. *Mutagenicity*—a. *NRDC claims.* NRDC claims that in comments submitted to EPA on the 2004 human health risk assessment for 2,4-D risk assessment, it pointed out that EPA disregarded a number of studies that highlight the mutagenicity and genotoxicity of 2,4-D. (Ref. 1 at 7). NRDC states that at the time of the RED, EPA responded that it was under no obligation to consider these studies because ''positive findings are always confined to samples of 2,4-D formulations and not the pure substance.'' (Id. at 7). NRDC claims EPA's response in 2005 was deficient first because nothing confines EPA only to consider studies that examine the pure substance (that is, the active ingredient). Second, recent studies involving just the active ingredient do indeed confirm the mutagenicity and cytotoxicity findings of the studies ignored by EPA. In light of these points, NRDC argues that EPA should not allow the continued use of 2,4-D.

NRDC also cited four studies it claims confirm the mutagenicity and cytotoxicity of 2,4-D. (Id. at 8). Two of these were published since the EPA RED was finalized and two were published shortly beforehand but were not cited in the risk assessment. Three of these studies examined just the active ingredient 2,4-D, while the third used a commercial 2,4-D product containing a mixture of 2,4-D and various inert ingredients. NRDC states that these results must be considered in determining whether users of these products are being exposed to potential toxicity.

NRDC also argues that apart from these new data, the discussion of the carcinogenicity and mutagenicity of 2,4-D that was provided by EPA in the 2004 risk assessment was inadequate because EPA failed to acknowledge numerous additional positive genotoxicity studies in the peer-reviewed scientific literature that together indicate that 2,4-D formulations are likely to be cytotoxic and mutagenic. (Id. at 9). According to NRDC, research in the open scientific literature have reported oxidant effects of 2,4-D, indicating the potential for cytotoxicity or genotoxicity. NRDC argues that another finding that may provide a unifying explanation of some of the data on 2,4-D and lymphoma is that the herbicide may increase lymphocyte replication. (Id.)

b. *Public comments.* The 2,4-D Task Force submitted comments stating that 2,4-D is not mutagenic. (Ref. 26 at 4). The Task Force claims that for reregistration, 2,4-D acid, plus eight different 2,4-D derivatives have been tested in a battery of mutagenicity tests which are comprised of a total of 28 studies. All of these studies were negative (non-mutagenic). (Id. at 22). While the Task Force acknowledges that some positive mutagenicity studies occur, it argues that the weight of the evidence overwhelmingly supports a conclusion of minimal or no concern for mammalian mutagenicity for 2,4-D. The Task Force notes that several inherent characteristics of 2,4-D suggest that there is a very low potential for it to cause mutagenic effects: The half-life of 2,4-D in humans is less than 12 hours; 2,4-D does not metabolize or transform; 2,4-D is excreted unchanged; and it does not accumulate. (Id. at 23).

Beyond Pesticides submitted comments to support the petition by NRDC requesting the cancellation of all 2,4-D product registrations and the revocation of all tolerances, stating that the Agency underestimated 2,4-D's mutagenic effects. (Ref. 28 at 1). Beyond Pesticides cites a study on plants which shows the induction and frequency of certain point mutations by 2,4-D (and dicamba), suggesting that these point mutations are important as they are frequently associated with various types of cancer. Beyond Pesticides also cites a study which they claim indicates 2,4-D is cytotoxic and induces apoptosis via direct effect on mitochondrial membranes. (Id. at 2–3).

NCASI, in its comments, asserts that the overwhelming weight of evidence indicates that 2,4-D is neither mutagenic nor genotoxic. NCASI states that tests of mutagenicity and genotoxicity are important in this context as indicators of the potential for carcinogenicity. They point out that the International Commission for Protection Against Environmental Mutagens and Carcinogens, categorization of a chemical as genotoxic is not an *a priori* indication of a health hazard. They note that there is a large body of evidence and broad scientific consensus that 2,4-D is not a carcinogen. (Ref. 27 at 4)

c. *Agency response.* NRDC's petition argues that the 2,4-D tolerances should be revoked on several grounds related to mutagenicity. First, NRDC claims that EPA did not adequately address NRDC's comments on the RED risk assessment regarding 2,4-D's mutagenicity and that subsequent data confirm the accuracy of NRDC's comments. NRDC argues that ''[i]n light of these points, EPA should not allow the continued use of 2,4-D.'' (Ref. 1 at 7). Second, NRDC asserts that ''the discussion of the carcinogenicity and mutagenicity of 2,4-D that EPA does provide in the [RED] risk assessment is wholly inadequate.'' (Id. at 8). NRDC argues that this inadequate discussion led to EPA ''failing to assess fully the

risk of cancer in humans from [2,4-D] exposure and failing to protect humans from this risk adequately.'' (Id. at 10)

These assertions do not, however, provide a sufficient basis for revoking the 2,4-D tolerances. The ground for seeking revocation of a tolerance is a showing that the pesticide is not ''safe.'' Claiming that EPA improperly conducted its reassessment of the 2,4-D tolerances by failing to consider certain data bearing on its decision on mutagenicity or carcinogenicity does not amount to a showing that the tolerance is unsafe. Neither is the allegation that 2,4-D is a mutagen or the derivative claim that EPA's failure to adequately consider mutagenicity data results in its ''failing to assess fully the risk of cancer'' sufficient to show that the 2,4-D tolerances are unsafe. As explained in Unit VII.A.1.c., with regard to its endocrine and neurotoxic claims, to properly assert grounds for revocation of a tolerance, NRDC must allege facts showing that aggregate exposure to 2,4-D poses an unsafe mutagenic risk. That, it has not done. As to mutagenicity, NRDC merely alleges that 2,4-D can cause mutagenic harm. As to carcinogenicity, NRDC's claims are even more amorphous. It argues that because EPA failed to consider 2,4-D's alleged mutagenic effects, it thereby failed to ''assess fully,'' and adequately protect against, 2,4-D's cancer risks. As to neither mutagenicity nor cancer has NRDC addressed what the safe level of exposure to 2,4-D is for humans or alleged that the exposure levels of humans to 2,4-D exceed this safe level. Accordingly, NRDC's claim that the 2,4-D tolerance should be revoked due to 2,4-D's mutagenic effects or its failure to assess 2,4-D's cancer risk in light of these mutagenic effects are denied due to a failure to make a proper claim for revocation by, at the very least, alleging facts that, if proven, would meet the statutory standard for revocation.

Despite the inadequacy of petitioners' mutagenicity claims, EPA has examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding 2,4-D that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

EPA requires the submission of mutagenicity data on pesticides to assess a pesticide's potential to cause heritable mutations that may contribute to cancer or other genetic diseases. (Refs. 52 and 53). Mutagenicity analysis has been directed primarily at investigating the mechanism of action with regard to toxic endpoints, particularly cancer. (Refs. 54 and 55). It should be noted that EPA's data requirements on mutagenicity have evolved over the years. Whereas earlier data requirements identified a wide range of genotoxicity tests, EPA's current testing requirements focus on tests for mutagenic effects, i.e., heritable changes in DNA that could potentially lead to disease. It is important to point out that genotoxicity assays include any kind of study that evaluates cellular functions involving gene damage, or interference with gene replication and repair. Mutagenic effects are a subset of genotoxic ones. The difference between the terms ''genotoxicity'' and ''mutagenicity'' is that ''genotoxicity pertains to all types of DNA damage (including mutagenicity), whereas mutagenicity pertains specifically to mutation induction at the gene and chromosome levels.'' (Ref. 56). Importantly, ''[w]hile genotoxic effects may be transient, mutagenic effects are persistent.'' (Id.). So unlike mutagenic effects which are generally non-repairable, and permanent, other genotoxic effects generally do not exhibit these same traits. Consequently, non-heritable genotoxic effects do not necessarily lead to adverse effects in a whole organism, and, for the same reason, are also not a reliable predictor of such effects. While genotoxicity data can help to inform an understanding of the adverse outcome pathway for a chemical, by themselves, EPA does not accord much weight in risk assessment to genotoxicity data that fail to show heritable effects.

EPA's current data regulations require, as to mutagenicity testing, a bacterial reverse mutation assay, an *in vitro* mammalian cell assay, and an *in vivo* cytogenetics test. 40 CFR 158.500(d). The recommended study guidelines indicate a preference for tests directed at identifying not merely genotoxicity but mutagenic effects in terms of gene mutation or chromosomal aberrations. (40 CFR 158.500(d) (test notes 31 and 32); (Refs. 57, 58, 59, 60, and 61). Omitted from the data regulations is the former requirement pertaining to ''other genotoxic effects * * * [such as] numerical chromosome aberrations, direct DNA damage and repair, mammalian cells transformation, target organ/cell analysis.'' 40 CFR 158.340(a) and (b)(22) (2007). The bacterial reverse mutation assay (commonly known as the Ames test) is designed to detect point mutations in genetic material. As the guideline indicates: ''Point mutations are the cause of many human genetic diseases and there is substantial evidence that point mutations in oncogenes and tumour suppressor genes of somatic cells are involved in tumour formation in humans and experimental animals.'' (Ref. 57). For the *in vitro* mammalian cell assay, the guidelines recommend either individual assays directed at detecting gene mutations, (Ref. 58), or structural chromosome aberrations, or both endpoints in a single assay. (Ref. 59). For an *in vivo* cytogenetics test, the regulations recommend either an assay for the detection of structural chromosome aberrations in bone marrow cells of animals, usually rodents, (Ref. 60), or an assay for the detection of cytogenetic damage which results in the formation of micronuclei containing lagging chromosome fragments or whole chromosomes. (Ref. 61). Between the *in vitro* and *in vivo* tests, the latter carry the greater weight in assessing mutagenic potential because *in vitro* tests do not capture how a living body responds to a toxic insult, including its ability to detoxify putative mutagens and genotoxicants. (Ref. 54 at 2–34; and Ref. 62).

EPA has a large body of mutagenicity and genotoxicity data for 2,4-D. Those data show little to no concern for heritable mutagenic effects in mammals but some evidence supporting 2,4-D's potential to cause genotoxic effects. More specifically, these data show: (1) That 2,4-D is negative in bacterial mutation assays; (2) some positive results for mutagenicity in assays in yeast, plants, and insects; (3) negative results for mutagenicity in *in vivo* studies in animals; and (4) mixed results for mutagenic and genotoxic results in *in vitro* tests in mammalian cells. EPA summarized the results in the last formal cancer assessment for 2,4-D in 1997 as follows:

> The mutagenic potential of 2,4-D has been extensively evaluated in a range of *in vivo* and *in vitro* assays that have included tests with human cells. Ames tests, with and without metabolic activation, were consistently negative. Negative results were also seen in a mouse bone marrow micronucleus and UDS assays in rat hepatocytes. Conflicting results were obtained in *Drosophila;* positive effects were seen in larvae, while negative results were seen in adults after feeding or injection. Conflicting results were also seen in *in vitro* mammalian cell cytogenetics assays; 2,4-D was negative for structural chromosomal damage up to an insoluble level but positive in the presence of metabolic activation at high doses. The positive evidence, however, tends to be weak and generally not supported by the data from *in vivo* cytogenetic assays. 2,4-D also was nonactive in mammalian cell DNA repair assays. Overall, the pattern of responses observed in both *in vivo* and *in vitro* tests indicated that 2,4-D was not mutagenic (although some cytogenetic effects were seen).

(Ref. 16 at 17).

Mutagenicity was considered as part of the weight of the evidence determination on cancer. EPA concluded that 2,4-D should be classified under Category D—Unclassifiable as to Human Carcinogenicity. This determination was based primarily on the finding that in the two most recent rodent studies there were no compound-related statistically significant increases in tumors in either rats or mice and the conclusion that epidemiology data failed to show a cause-and-effect relationship between 2,4-D exposure and cancer. The weak evidence on genotoxicity was not sufficient to outweigh the absence of positive findings on tumor development in rodent carcinogenicity studies or epidemiology studies. Similar conclusions on mutagenic (and carcinogenic) potential of 2,4-D have been reached by independent science review panels. In 1994, a joint committee of EPA's SAB and SAP concluded that:

> The conflicting cytogenetic results do not provide evidence for genotoxicity of 2,4-D. Studies with positive results have significant experimental deficiencies as noted above, thus limiting the value of these studies for assessing genotoxicity. Therefore, although there are serious data deficiencies, the currently available evidence suggests that 2,4-D is non-genotoxic. The lack of genotoxicity may reduce the concern for potential carcinogenicity of 2,4-D, but it is recognized that not all carcinogens are necessarily genotoxic.

(Ref. 15 at 19) (See Refs. 13 and 14 (earlier meeting of the FIFRA SAP disagreeing with EPA's conclusion that there was limited evidence supporting a carcinogenic designation for 2,4-D and instead concluding that 2,4-D should be classified no higher than Category D because evidence was only equivocal)).

Since the 1997 EPA cancer assessment, the 2,4-D registrant has submitted a series of mutagenicity tests with 2,4-D and its various metabolites. The tests included bacteria mutation assays, and *in vitro* mammalian assays investigating gene mutation and chromosomal aberrations. These tests were uniformly negative. Further, in its comments on the petition, the Task Force offers a plausible hypothesis for the predominantly negative findings for 2,4-D in mutagenicity testing. The Task Force notes that 2,4-D does not metabolize or transform in the body and is rapidly excreted in an unchanged form. This lack of reactivity supports a conclusion of low mutagenic potential.

NRDC in its petition has cited a number of positive mutagenicity and genotoxicity studies. Taken together, these studies do not have a significant effect on the balance of the weight of evidence on mutagenicity and genotoxicity as summarized by EPA in its last cancer assessment.

Studies cited by NRDC and Beyond Pesticides do not significantly add to the weight of evidence supporting a mutagenicity conclusion for several reasons. First, NRDC only referenced one *in vivo* study (Madrigal-Bujaidar (2001)) and that study only looked at a genotoxic, as opposed to a mutagenic, endpoint (sister chromatid exchange). (Ref. 63). Further diminishing the weight of this study is the fact that the authors described it as only showing ''weak positive results,'' and concluded that given the ''moderate genotoxic effect produced by 2,4-D, * * * the hazard for the general population appears to be small.'' (Id.). Second, many of the studies cited by NRDC looked only at DNA damage (sister chromatid exchange), (Refs. 64 and 65), not mutagenic effects, and at least two of these studies showed marginal positive results at best (Arias (2003, 2007)). (Refs. 66 and 67). Although two studies cited by NRDC did show a mutagenic (chromosomal aberration) response in an *in vitro* mammalian cell assay, (Zeljezic (2004); Venkov (2000)), two other *in vitro* studies were either negative (Figg (2000) (authors conclude findings do not support a ''genotoxic pathway'') or marginal (Holland (2002)). (Refs. 68, 69, 70, 71, and 72). As noted above, conflicting results in *in vitro* testing for 2,4-D was previously recognized by EPA. Other tests (Tuschl (2003); Bukowska (2003)) showed cytotoxicity but studies on cytotoxicity alone do not provide evidence of genotoxicity. (Refs. 73 and 74). Finally, NRDC and Beyond Pesticides cited studies confirming EPA's earlier conclusion regarding positive mutagenic effects in yeast and insects (Venkov (2000); Tripathy 1993). (Refs. 75 and 76). Such studies are entitled to less weight compared to mammalian studies, particularly *in vivo* mammalian studies. Finally, NRDC's arguments regarding the reported oxidant effects of 2,4-D do not change the weight of evidence as to 2,4-D's cancer classification because the primary evidence on cancer—rodent carcinogenicity studies and human epidemiology data—do not support a positive cancer finding.

Accordingly, EPA concludes that NRDC's claim concerning mutagenicity does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

4. *Body weight.* a. *NRDC claim.* In a section of its petition addressing exposure to 2,4-D through maternal milk, NRDC argues that EPA chose an incorrect POD for addressing short-term oral exposure and should ''redo the short-term oral risk assessment * * *.'' (Ref. 1 at 11). NRDC cites a study conducted in rats by Sturtz (2006) which identified 15 mg/kg/day as a LOAEL based on ''adverse effects on breastmilk composition and on bodyweight in offspring * * *.'' (Id.; Ref. 77) NRDC contrasts this value with the 25 mg/kg/day NOAEL that EPA used as the POD in assessing short-term oral risk.

b. *Public comments.* The Task Force responded that the results in the Sturtz (2006) study were not replicated in a recent study performed under Good Laboratory Practice conditions. (Ref. 26 at 27 and Ref. 78). In this study, according to the Task Force, 2,4-D significantly decreased pup body weights at dose levels above the renal saturation level but not at lower levels.

c. *Agency response.* NRDC's request on pup body weight is for EPA to ''redo'' the short-term oral risk assessment using a lower POD based on a LOAEL rather than a NOAEL. Although this argument, like NRDC's other claims as to 2,4-D toxicity, appears to state an insufficient basis, on its face, for revoking the 2,4-D tolerances, EPA concludes that it is qualitatively different than NRDC's claims regarding endocrine disruption, neurotoxicity, and mutagenicity. Those claims did not address the statutory standard for revocation. Although not clearly articulated by NRDC, EPA can piece together a sufficient allegation supporting revocation with regard to NRDC's body weight claim: Namely, that, if EPA recalculated 2,4-D short-term risk using a revised POD of a LOAEL of 15 mg/kg/day, it would find that short-term aggregate exposure to 2,4-D exceeds the safe level.

Nonetheless, while EPA has interpreted NRDC's allegation on body weight as a legally sufficient ground for revocation, EPA denies NRDC's claim on body weight because the cited evidence does not support NRDC's allegation. EPA disagrees with NRDC's allegation that EPA has misidentified the POD for adverse effects on pup body weight. The recent extended one-generation rat reproduction study comprehensively evaluated effects on pup body weights from pre- and post-natal exposures to 2,4-D. (Refs. 31). In this study, intended doses were: 5 mg/kg/day for the low dose; 15 mg/kg/day for a mid dose; and 40 mg/kg/day for males and 30 mg/kg/day for females for a high dose. Actual calculated doses in post-natal pups following weaning (PND

21) were considerably higher with four of the five subsets within the study (Sets 1a, 1b, 2a, and 2b) receiving almost double the intended dose for the post-lactation period. Actual doses can differ from intended doses when experimental animals consume different amounts of food than projected. Body weights were tracked for all pups in the study from PNDs 1–21. There were between 24 and 28 litters per dose group with roughly 10 pups per litter which translates to roughly 250 pups per dose group. Looking across all pups in the study, no statistically significant body weight decreases were seen for males or females at any dose level for PND 1–21. A smaller subset of pups (Set 1a—20 pups per dose), was specifically examined as to general toxicity effects including body weight effects. In that subset, statistically significant effects were seen in the high dose group for males generally between PNDs 28 and 69. No statistically significant body weight effects were seen in males at the low or mid doses or at the high dose prior to PND 28. No statistically significant body weight effects were seen in females at any dose on any day. Other subsets (Sets 1b, 2a, 2b, and 3) for which dosing continued past at least PND 55 showed no statistically significant decrease in body weight at the conclusion of the study. Similar results were found in an earlier two-generation study with 2,4-D. (Refs. 79 and 80). In that study, the intended doses were: 5 mg/kg/day for the low dose; 20 mg/kg/day for a mid dose; and 80 mg/kg/day for a high dose. Actual calculated doses in post-natal pups after weaning were 7–14 mg/kg/day, 26–48 mg/kg/day, and 76–133 mg/kg/day. Body weight effects were seen at the mid-dose at PND 28 and at the high dose. No effects on body weight were observed prior to weaning at the mid-dose. Additionally, in the range-finding study for the extend one-generation reproduction study, similar effects regarding pup body weight were seen—namely, statistically significant body weight decrements were only observed at the high dose ((1,000 ppm) 123 mg/kg/day for males (calculated on PND 35) and (800 ppm) 121 mg/kg/day for females (calculated on PND 35)). (Ref. 78).

The Sturtz (2006) study reports decreases in body weight gain or absolute body weight at doses as low as 15 mg/kg/day on PNDs 6 through 16.[2] These results are not consistent with the prior two-generation reproduction study and were not replicated by either the range-finding study for the extended one-generation reproduction study or the one-generation study itself. Moreover, there are several reasons to give the Sturtz (2006) study less weight than the results of the other three studies. First, the extended one-generation and two-generation study were conducted under EPA's Good Laboratory Practice Standards regulations, see 40 CFR part 160, and all underlying data for these studies are available for review. Further, the extended one-generation study is considered state-of-the-science because it considered the toxicokinetic profile of 2,4-D as it makes its way from the mother to the offspring, as well as a variety of other endpoints that are considered more sensitive than body weight (e.g., hormones, hematology, clinical chemistry, etc). The toxicokinetic aspect is particularly important because, based on the toxicokinetic profile, the doses in the extended one-generation reproduction study were adjusted during the lactational period to prevent excessive dosing both to the maternal rat and to the pups during early lactation and due to a ''double exposure'' when pups are both nursing and starting to consume diet (as in the case on PND 16). Adjustments to the diet were also performed in the Sturtz study, although the procedures used were different and may, to some extent, explain the results in the Sturtz study compared to the extended one-generation reproduction study. Second, the Sturtz (2006) study does not show a clear dose response effect. Although there is a greater effect on body weight comparing the lowest and highest doses, the body weight effects are essentially the same in the lowest two doses despite significant differences in the doses and that same phenomena is seen with regard to the highest two doses. Third, the extended one-generation reproduction study examined a much larger sample of pups. Roughly four times as many pups were evaluated in the extended one-generation reproduction study from PNDs 1–21 compared to the Sturtz study, and the Sturtz study evaluated no pups after PND 16. Finally, NRDC infers that the Sturtz study identified an ''adverse effect'' on the composition of maternal milk. However, changes in the composition in maternal milk may provide an explanation for effects seen in the pups but do not constitute an adverse effect independent of effects in the pups.

Thus, to the extent NRDC's petition argues that the Sturtz study showed the 2,4-D tolerances to be unsafe, that claim is denied.

B. Exposure

1. *Aggregate exposures and risk—residential use*—a. *NRDC claims.* In its petition, NRDC restates its comments submitted in 2002 and 2004 concerning the Agency's aggregate assessment (Ref. 1 at 11). In its comments submitted in 2002 and 2004, NRDC claims that EPA failed to conduct adequate aggregate risk assessment due to outstanding data gaps and missing information, and that EPA did not consider exposure through drift, migration of contaminated soil, or residential track-in exposures. (Refs. 23 and 24). In its comments, NRDC cites two studies (Nishioka (1996 and 2001)) in support of these comments that pertain to track-in exposures. (Refs. 81 and 82).

b. *Public comments.* There were no public comments received on this issue.

c. *Agency response.* In addition to the generalized claims regarding inadequate assessment of aggregate exposure in the RED risk assessment, NRDC does specifically allege that ''[t]he use of 2,4-D in and around the home could itself exceed appropriate risk levels if properly calculated.'' (Ref. 24 at 28). If the evidence adduced by NRDC substantiates this point—the Nishioka studies (1996 and 2001)—this claim would be sufficient grounds for revocation of 2,4-D tolerances.

In response to NRDC's claims regarding the level of 2,4-D exposure from residential use, the Agency reviewed both Nishioka studies (1996 and 2001) to ascertain if the risk assessment completed for 2,4-D was protective. (Ref. 83 at 13).

Residential exposure to 2,4-D results from its use on turf in residential environments. In the RED risk assessment this use pattern was evaluated using a screening level methodology that considers direct contact by toddlers with treated turf. Toddlers are considered the most highly exposed group in the population to turf uses because their behavior patterns (e.g., playing on turf, mouthing of hands and other objects) lead to both increased dermal and non-dietary ingestion exposures. The screening methodology assumes that these behaviors co-occur and also aggregates exposures from the pesticide in food and water. For 2,4-D, this screening methodology did not indicate a risk of concern even taking into account that the RED risk

[2] The study does not make clear whether it was reporting decrements in body weight gain (the amount of weight gained between designated time periods) or absolute body weight. Body weight is generally regarded as the more important measure because decrements in body weight gain, which is a calculated value and may be misleading, may occur even though the pup is otherwise within normal body weight levels.

assessment retained the full 10X FQPA safety factor due to missing data on pre- and post-natal toxicity.[3]

Dusts are thought by some to possibly contribute more than negligible levels to potential exposures in indoor environments but a methodology has not been developed which definitively establishes a link between levels in dust with a clearly defined exposure pathway. This construct was discussed extensively at a 2009 meeting of the FIFRA SAP related to the revisions of the EPA's Standard Operating Procedures for Residential Exposure Assessment. (Ref. 84). The conclusions of that panel were that insufficient information is currently available to definitively link residues in dusts to specific exposure pathways. Nonetheless, to examine whether 2,4-D contamination of indoor dust might significantly alter the RED risk assessment, EPA considered how the indoor residue values in the Nishioka studies would affect the risk assessment. EPA assumed for screening purposes that toddlers consume 100 mg/day of dust containing the highest 2,4-D concentration found in Nishioka studies (67 micrograms/gram (µg/g)). The 2,4-D levels in dust in the Nishioka studies were generally much lower than 67 µg/g (e.g., 1996 maximum is 4.85 µg/g, and 2001 median is 10 µg/g). The value of 100 mg/day for dust consumption is drawn from the EPA's Child Specific Exposure Factors Handbook (Ref. 85), and is the same value assumed for soil consumption. This value was also used in the Nishioka studies. Additional conservatisms in this screening assessment are the assumptions that (1) exposures from dust residues are assumed despite the uncertainties noted in the 2009 FIFRA SAP Report; and (2) 2,4-D residues do not decline over time even though 2,4-D is known to dissipate quickly. (Ref. 84 at 26 and Ref. 86). Based on these assumptions, margins of exposure range from approximately 32,000 to 150,000 depending upon whether the duration of exposure considered is acute-, short- or intermediate-term. (Ref. 30 at 66). As such, use of this highest dust concentration value would not impact the findings of the current risk assessment. If it is further assumed that dusts persist in impacted residences in such a way that ingestion of the highest concentration would occur in a chronic exposure pattern and that the highest noted concentration in dust would never dissipate, which is counter-intuitive given how 2,4-D is used and its known rapid dissipation characteristics, risks are still not of concern. In such situations, dust would be the predominant source for chronic exposures but margins of exposure still would exceed 11,000 based on the chronic dietary POD (5 mg/kg/day). (Ref. 30 at 66). It should also be noted that Nishioka (1996) indicated that such exposures could be chronic in nature after a single application of 2,4-D, but this is viewed by EPA as unlikely due to a lack of empirical information to support such a supposition. Nishioka (1996) projected that 2,4-D would be found in residential carpet dust up to 1 year later based on short-term track-in sampling. However, the value estimated by Nishioka (0.5 µg/g) is two orders of magnitude less than the value used in the extremely conservative assessments described above. Given that these unrealistic and high-end assumptions yield MOEs greater than 10,000, EPA concludes that the cited data do not support NRDC's allegation that ''[t]he use of 2,4-D in and around the home could itself exceed appropriate risk levels if properly calculated.'' To the contrary, even assessing exposure using unrealistic, high-end values for 2,4-D, levels in dust indicates that residential dust exposures to 2,4-D are a relatively minor exposure. NRDC's claim regarding track-in exposures is denied.

Finally, it should be noted that the Agency is currently in the process of evaluating the state of the science related to the exposure pathways from indoor dust as illustrated by the SAP review of residential methods and an additional review related to exposures from volatilization. Additionally, EPA is developing more definitive methods focused on addressing and characterizing potential exposures from chemical trespass. These efforts were recently described in a 2011 meeting of the Pesticide Program Dialogue Committee. (Ref. 87). Once final, any potential modifications to methods impacting residential risk assessment will be accounted for in the upcoming registration review process for 2,4-D.

2. *Exposure through maternal milk*—a. *NRDC claims.* NRDC asserts that EPA failed to include any lactational exposure in its aggregate risk assessment, although it was aware of research demonstrating the potential exposure to 2,4-D from maternal milk. (Ref. 1 at 11). NRDC cites several studies involving lactational exposure to show potential effects of 2,4-D on the brain of neonatal rats exposed lactationally. (Id.). The cited studies provide an assessment of the levels of 2,4-D attained in the milk of the dams and in the plasma and brain of the pups. NRDC also cites studies that it claims ''confirm the lactational exposure and identify adverse effects in the offspring.'' (Id.)

b. *Public comments.* In its comments, the Industry Task Force disputes NRDC's allegation that EPA failed to address 2,4-D exposure from maternal milk. (Ref. 26 at 24–27). The Task Force comments that EPA was aware, when conducting the aggregate risk assessment, that 2,4-D may be present in maternal milk because of the results of animal feeding studies using exaggerated doses of 2,4-D. Further, the Task Force argues that NRDC's claim that EPA failed to include any lactational exposure in its aggregate risk assessment is not correct. According to the Task Force, the Agency used half the limit of detection (LOD) for milk value in its 2005 risk assessment because no detectable residues were found in milk samples over several years of Pesticide Data Program (PDP) monitoring. Thus, the Task Force asserts that EPA assumed that 2,4-D would be present in milk at 0.004 ppm for both acute and chronic exposure (despite it being non-detectable in PDP sampling). (Id. at 26).

The Task Force states that large doses of 2,4-D administered in the Sturtz et al (2000) study cited by NRDC render the study uninformative for human health risk assessment. (Id. at 24). The Task Force cites biomonitoring data from farm families to support its contention that EPA's exposure estimates are reasonable. (Id. at 25).

c. *EPA's response.* Initially, EPA would note that the studies NRDC cited to support its claim that 2,4-D exposure through maternal milk causes adverse effects were considered together with other studies cited by NRDC pertaining to toxicity issues. See Unit VII.A. above.

With regard to human exposure to 2,4-D through maternal milk, NRDC alleges that such exposure occurs and was ignored by EPA despite the fact that it could result in ''potentially significant exposures.'' As discussed in Unit VII.A.1.c., this ground for objection is denied because (1) the standard for revocation is that the tolerance is unsafe not that there are ''potentially significant exposures'' that should be included in an aggregate assessment; and (2) NRDC presents no evidence to support its assertion that potentially significant exposures were excluded from EPA's risk assessment. Accordingly, NRDC's claim that the 2,4-D tolerance should be revoked due to exposure to 2,4-D in human breast milk is denied due to a failure to allege facts sufficient to meet the statutory standard for revocation and a failure to support the allegations that are made.

[3] In 2011, EPA removed the FQPA safety factor because the data gaps were filled by submission of the extended one-generation rat reproduction study.

Despite the inadequacy of petitioners' claim regarding 2,4-D exposure in human breast milk, EPA has examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding 2,4-D that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

NRDC is incorrect in asserting that EPA assumed that humans are not exposed to 2,4-D through maternal milk. To the contrary, EPA assumed, in its RED risk assessment, that all milk—whether animal or human—contained 2,4-D at levels that may be present in cow's milk. This is an extremely conservative assumption as it pertains to human breast milk.

Residues in various food forms of cow's milk (e.g., milk fat, nonfat milk solids, etc.) have been accounted for in the dietary exposure assessment based on monitoring data from the USDA Pesticide Data Program (PDP). There were no detections of 2,4-D in any samples, so EPA assumed that all milk contains half the detection limit for 2,4-D. (Ref. 19 at 47). This is a very conservative assumption as it pertains to human breast milk because 2,4-D levels in human breast milk are expected to be significantly lower than residues in cow's milk. Exposure of dairy cattle to pesticides are generally significantly higher than humans as residues in cows' key feed items, such as grass forage, are generally much higher than in human foods. As to 2,4-D, this is certainly the case given that the 2,4-D tolerances for grass (hay) and grass (forage) are 300 and 360 ppm, respectively, while 2,4-D tolerances for various human foods are all much lower—in the single digits or less than 1 ppm (40 CFR 180.142). Grass hay and forage can constitute 60 percent of the diets of beef and dairy cattle. (Ref. 88).

Accordingly, EPA concludes that NRDC's claim regarding exposure to 2,4-D through human breast milk does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

3. *Dermal absorption*—a. *NRDC claims.* NRDC asserts that in the final risk assessment, the dermal absorption factor used by EPA (10 percent) was too low. Specifically, NRDC claims that the EPA failed to address the possibility of enhanced dermal absorption of 2,4-D due to the potentially interacting factors of alcohol consumption and application of sunscreen, and/or the insect repellent DEET. (Ref. 1 at 12; Ref. 22 at 1). In its exposure comments on the RED, which NRDC incorporates in its petition, NRDC argued that EPA should increase its dermal absorption factor to at least 14 percent based on a human dermal absorption study by Moody (1992). (Ref. 24 at 16 and Ref. 89). NRDC claimed that such an adjustment of the dermal absorption factor would result in post-application exposures for toddlers exceeding the LOC. (Ref. 24 at 16). In addition, NRDC claims that the Agency did not sufficiently address that using rubber gloves when applying 2,4-D does not afford adequate dermal protection and the effect of 2,4-D soaking into clothing. (Ref. 1 at 13).

b. *Public comments.* In its comments, the Task Force disagrees with NRDC's allegation regarding enhanced dermal absorption due to the interacting factors of alcohol consumption, sunscreen, and DEET. The Task Force argues that the study on which EPA relied to estimate dermal absorption, Feldmann and Maibach (1974), used ''extreme'' conditions. (Ref. 26 at 28 and Ref. 90). According to the Task Force, in this study 2,4-D was applied with acetone which denatures skin and allows for increased absorption. Additionally, the Task Force noted that the skin was not protected and not washed for 24 hours to allow maximum absorption. That study showed absorption of 5.8 percent. The Task Force also cites a recent article, Ross (2005), which summarized numerous dermal absorption studies with 2,4-D. (Ref. 91). According to the Task Force, this study concluded that the available studies showed remarkable agreement and strongly supported the conclusion in the Fledmann and Maibach study.

The Task Force also commented on other issues related to dermal exposure such as the use of rubber gloves by agricultural workers. Those comments are not relevant to the FFDCA portion of NRDC's petition and are thus addressed elsewhere.

c. *EPA's response.* For the purposes of responding to the portion of NRDC's petition that requests EPA to revoke tolerances, EPA will respond to issues related to residential exposure here. Concerns about occupational exposures will be addressed elsewhere.

Unlike most of NRDC's other claims, as to dermal absorption, NRDC alleges grounds that if substantiated would provide grounds for revoking the 2,4-D tolerances. As summarized above, NRDC alleges that EPA has understated dermal absorption and adjustment of dermal absorption factor to the degree supported by Moody (1992) would show a risk of concern (i.e., a lack of safety). (Ref. 24 at 16). In the petition, NRDC's focus shifts from the Moody study to a series of *in vitro* studies investigating the effect of the use of sunscreen and alcohol on 2,4-D dermal absorption. NRDC argues that these studies show that EPA has underestimated dermal absorption. The various combinations of *in vitro* results appear to indicate that dermal absorption was enhanced by up to a factor of about 2.5 while most tested scenarios indicate a factor of 2 or less. (Refs. 92,93,94 and 95). One study used human skin and the results suggest a factor of up to 3 depending upon sunscreen ingredient tested. (Ref. 92). NRDC also claims that use of the pesticide Deet increases dermal absorption of 2,4-D. Here, NRDC turns back to the Moody study but that study actually concluded that ''Deet had no significant effect on total cumulative palmar permeability to this herbicide [2,4-D].'' (Ref. 89 at 245).

EPA believes that its use of a 10 percent dermal absorption value for 2,4-D is protective. EPA's conclusion is supported by an extensive set of high quality human research results. Ross (2005) notes that ''the degree of uncertainty and variability associated with human dermal absorption for 2,4-D is better defined than for virtually any other pesticide * * *.'' (Ref. 91 at 84). EPA principally relied on an *in vivo* human study which showed average human dermal absorption at 5.8 percent. (Ref. 90). EPA also considered four other *in vivo* human studies. (Refs. 89, 96,97 and 98). These studies involved 8 separate trials using a total of 34 participants and had an average dermal absorption value of 5.7 percent. (Ref. 91 at 84, Table 2) To account for potential variability EPA chose a value of 10 percent.

There are several factors that support reliance on these data and demonstrate the reasonableness of EPA's choice of a 10 percent dermal absorption factor. First, the data relied upon by EPA are from *in vivo* human studies. NRDC, with one exception, has cited only to *in vitro* data. EPA generally does not rely on *in vitro* dermal absorption data without corroboration from *in vivo* testing. The critical limitations with *in vitro* dermal absorption testing, such as the lack of an intact vasculature, make it an uncertain guide for risk assessment. The Moody study (1992) did involve *in vivo* human testing but the results of this study were similar to the higher values seen in the human *in vivo* studies considered by EPA. In fact, if the Moody study results from the trial combining 2,4-D and DEET are included in the overall average of dermal absorption from the human studies, the average absorption only increases from 5.7 percent to 6.4 percent. (Ref. 30). Second, the studies considered by EPA involved exposure

conditions that varied based on application site (forearms, hands), topical dose rates (1.7 to 1,100 μg/cm²), form (acid or salt), application media (water, ethanol, acetone), and exposure time. As noted, the overall average dermal absorption value for all of these data combined (N=34), regardless of design, was 5.7 percent. Examination of these variables, particularly the use of different application vehicles and different anatomical sites, is likely to have captured much of the variability measured in the sunscreen and alcohol *in vitro* studies. On this latter point, it is worth noting that NRDC placed particular emphasis on the potential additive effect of sunscreen and alcohol. Yet, the relevant study on this point found that the effect from both sunscreen and alcohol to be no higher than a factor of 2.9 and that was only with an extremely high alcohol dose. (Ref. 92). At the lowest alcohol dose tested in the study, the researchers actually concluded that alcohol had an inhibitory effect on dermal absorption. This low dose, when converted to human consumption amounts, is the equivalent of 7 ounces of 100 proof liquor for women and just slightly less than 9 ounces for men. Third, the data considered by EPA was developed by different researchers at different laboratories. The reproducibility of results across these studies gives them enhanced reliability. As Ross (2005) notes: ''Multiple human studies conducted on the forearm and hand provide remarkably consistent results, especially considering the studies were performed years apart in time, at different laboratories by different personnel on totally different human subjects.'' (Ref. 91 at 84). On the other hand, the *in vitro* studies cited by NRDC all were conducted by the same group of researchers. Finally, the value chosen by EPA for dermal absorption was nearly twice the average value seen in human testing.

Providing further support for the reasonableness of EPA's assumption on dermal absorption are exposure monitoring studies (including epidemiological analyses, environmental measurements, and methodological analyses) cited by NRDC and commenters. (Ref. 30 at 65–69). In fact, many of these studies report exposure levels that are similar to or far below exposures estimated by EPA. For example, NRDC cited results from Lerda (1991), (Ref. 99), prior to the RED, which are similar to those predicted in the 2005 EPA risk assessment for applicators wearing normal work clothing. Current labels require the use of protective clothing and gloves. NRDC also cited median urinary values in children reported by Morgan (2008), (Ref. 100), which are lower than those used to establish risk estimates in the 2005 risk assessment. Other data cited in comments, such as Alexander (2007), (Ref. 101), cited by the 2,4-D Task Force, (Ref. 26 at 30), indicate values much lower than values that would reflect a risk concern for both applicators and their family members according to the 2005 assessment. (Ref. 19 at 57–60).

Accordingly, NRDC's claim regarding dermal absorption is denied.

EPA is currently involved in processes to refine many of its exposure assessment inputs (*http://www.epa.gov/pesticides/science/handler-exposure-data.html*) and to establish better methods for the consideration of epidemiological research into the regulatory process. (See Ref. 102). The Agency is also re-evaluating pesticide risks on a cyclical basis under its registration review process. Given these two efforts, the Agency will further evaluate research related to 2,4-D during registration review. The Agency has also been actively participating in epidemiological research efforts such as the Agricultural Health Study and, as part of this process, will pursue additional information related to 2,4-D and the potential for health effects in potentially exposed populations.

C. Additional Issues Raised in Public Comments

Some comments raised issues beyond the scope of NRDC's petition. For example, Beyond Pesticides, in its comments, claimed that EPA was not justified in removing the FQPA safety factor and had failed to address cumulative effects from 2,4-D and other chlorophenoxy pesticides. (Ref. 28 at 5–6). It is not appropriate for EPA to consider these comments in support of the petition because they have not been subject to the public comment process which is critical to the EPA's administrative review of the petition under section 408(d).

VIII. Statutory and Executive Order Reviews

This action, denies a petition to revoke tolerances, is in the form of an order and not a rule. (21 U.S.C. 346a(f)(1)(C)). Under the Administrative Procedure Act (APA), orders are expressly excluded from the definition of a rule. (5 U.S.C. 551(4)). Accordingly, the regulatory assessment requirements imposed on a rulemaking do not apply to this action, as explained further in the following discussion.

A. Executive Order 12866 and Executive Order 13563

Because this order is not a ''regulatory action'' as that term is defined in Executive Order 12866 entitled ''*Regulatory Planning and Review*'' (58 FR 51735, October 4, 1993), this action is not subject to review by the Office of Management and Budget (OMB) under Executive Orders 12866 and 13563 entitled ''*Improving Regulation and Regulatory Review*'' (76 FR 3821, January 21, 2011).

B. Paperwork Reduction Act

This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*

C. Regulatory Flexibility Act

Since this order is not a rule under the APA (5 U.S.C. 551(4)), and does not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*) do not apply.

D. Unfunded Mandates Reform Act; and Executive Orders 13132 and 13175

This order denies a petition to revoke tolerances; it does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of FFDCA. As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132 entitled ''*Federalism*'' (64 FR 43255, August 10, 1999) and Executive Order 13175 entitled ''*Consultation and Coordination with Indian Tribal Governments*'' (65 FR 67249, November 9, 2000) do not apply to this order. In addition, this order does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1531–1538).

E. Executive Orders 13045, 13211 and 12898

As indicated previously, this action is not a ''regulatory action'' as defined by Executive Order 12866. As a result, this action is not subject to Executive Order 13045, entitled ''*Protection of Children from Environmental Health Risks and*

Safety Risks'', (62 FR 19885, April 23, 1997) and Executive Order 13211 entitled ''*Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'',* (66 FR 28355, May 22, 2001). In addition, this order also does not require any special considerations under Executive Order 12898 entitled ''*Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations''* (59 FR 7629, February 16, 1994).

F. National Technology Transfer and Advancement Act

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA), (15 U.S.C. 272 note).

IX. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq.* does not apply because this action is not a rule as that term is defined in 5 U.S.C. 804(3).

X. References

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List of Subjects

Environmental protection, Agricultural commodities, Pesticides and pests.

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