08-3771-ag

IN THE UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

NATURAL RESOURCES DEFENSE COUNCIL, INC.,

Petitioner,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondent.

On Petition for Review from the U.S. Environmental Protection Agency

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RESPONDENT'S BRIEF

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75 Fed. Reg. 70,558 (Nov. 17, 2010) 10

JURISDICTIONAL STATEMENT

Petitioner Natural Resources Defense Council ("NRDC") challenges Respondent United States Environmental Protection Agency's ("EPA") final order denying NRDC's objections to, and requests for hearing on, a prior order denying NRDC's petition requesting that EPA revoke all pesticide tolerances for residues of dichlorvos ("DDVP") in foods pursuant to section 408(g) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 346a. *See* Order Denying NRDC's Objections and Requests for Hearing, 73 Fed. Reg. 42,683 (July 23, 2008) (SPA 37).[1] This Court has subject matter jurisdiction over the petition for review of the Order pursuant to 21 U.S.C. § 346a(h), but does not have jurisdiction over issues never presented to EPA in the petition process, or over issues presented in NRDC's petition but not included in its objections. 21 U.S.C. § 346a(g)(2)(A); 40 C.F.R. § 178.25(a)(2). Petitioners timely filed their petition for review. *See* 21 U.S.C. § 346a(h)(1).

STATEMENT OF ISSUES

1. Whether EPA reasonably denied NRDC's request for an evidentiary hearing on NRDC's claims regarding the statistical power of the

[1] References to "SPA __" are to the Special Appendix attached to Petitioner's Brief. References to "A __" are to Petitioner's Appendix. References to "SA __" are to the Supplemental Appendix filed by Respondent EPA.

DDVP human study where NRDC neither proffered evidence relevant to the statistical question EPA decided in its petition denial order nor specifically contested the actual factual determination EPA made?

2. Whether EPA reasonably denied NRDC's request for an evidentiary hearing on the question of whether the DDVP human study's informed consent process met ethical standards where NRDC presented no evidence that the consent process failed the applicable ethical standards?

3. Whether, as alleged, EPA based its denial of NRDC's request for an evidentiary hearing based on the burdens of holding such a hearing?

4. Whether EPA's authority under 21 U.S.C. § 346a(a)(2)(C) to use a children's safety factor other than the presumptive tenfold (10X) safety factor depends on the completion of the endocrine screening program under 21 U.S.C. § 346a(p)?

5. Whether EPA supported its decision to use a threefold (3X) children's safety factor with reliable, DDVP-specific data?

STATEMENT OF THE CASE

I. Introduction

While EPA was in the process of conducting a statutory review of the safety of the pesticide DDVP, NRDC petitioned EPA to revoke all DDVP tolerances, which established safe levels for DDVP residues in food. After

finishing the statutory review and concluding that the mitigation steps taken by the pesticide registrant had reduced DDVP risks to an acceptable level, EPA considered NRDC's petition to revoke the DDVP tolerances. EPA found that NRDC had raised several significant points meriting revisions to the DDVP risk assessment, but also found that the risk assessment, as revised, did not show DDVP to be unsafe. EPA thus denied the petition to revoke the DDVP tolerances.

NRDC filed administrative objections and requested a hearing. NRDC's objections in large part ignored the reasoning EPA put forward for denying the petition and simply repeated claims from that petition. For example, NRDC's objections failed to address the final report of an independent scientific review board that was absolutely central to EPA's conclusions on several key issues in its petition denial.[2] Following review of

[2] Additionally, in multiple instances NRDC recycled criticisms of EPA's DDVP risk assessment from its petition to its objections without apparently realizing that EPA had agreed with NRDC's concern and revised its DDVP risk assessment accordingly. *See, e.g.*, 73 Fed. Reg. at 42,698 (SPA 52) (based on NRDC petition EPA drops reliance on FDA Total Diet Study in favor of more appropriate residue data; NRDC repeats criticism of FDA Total Diet Study in its objections); *Id*. at 42,701-02 (SPA 55-56) (in response to NRDC petition claim that EPA should not average residential exposure over 120 days, EPA modifies risk assessment to examine 1-day, 14-day, and 91-day exposures; NRDC repeats criticism of 120-day average in objections); *Id*. at 42,702-03 (56-57) (in response to NRDC petition claim that it was not conservative to assume that the maximum residential exposure is 16 hours per day, EPA revised risk assessment to assume 24

the objections and hearing requests, EPA issued its 2008 order denying NRDC's objections and hearing request.

NRDC seeks review in this Court of the 2008 order. As to the objection denial it challenges, NRDC relies on two arguments. The first, a legal argument, was never presented to EPA and is contradicted by the plain language of the FFDCA. The second argument has no support in the record and ignores EPA's reliance on a finding by the independent science review board. As to the hearing denials, NRDC cannot overcome the underlying lack of materiality of its objections given that it merely recycled its claims without addressing EPA's analyses and conclusions *in the petition denial order*. In particular, NRDC's hearing denial challenge collapses because of its failure to address in any way EPA's adoption of the independent scientific review board's findings that considered and rejected NRDC's various arguments.

II. Statutory and Regulatory Background

EPA regulates pesticides under the FFDCA, as amended by the Food Quality Protection Act of 1996 ("FQPA"), and the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), 7 U.S.C. § 136 - 136y. FIFRA

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hours per day exposure; NRDC repeats challenge to use of 16 hours per day assumption in its objections).

imposes a federal licensing scheme on the sale, distribution and use of pesticides; the FFDCA regulates pesticide residues in food.

A. The FFDCA's Statutory Scheme

The FFDCA authorizes EPA to establish by regulation "tolerances" setting the maximum permissible levels of pesticide residues in foods. 21 U.S.C. § 346a. A food containing pesticide residue is deemed "unsafe" unless a tolerance has been set and the residue is within the limits of the tolerance, or an exemption from the tolerance has been set for the pesticide residue. *Id*. § 346a(a)(1)-(2). An "unsafe" food may not be moved in interstate commerce legally. *Id*. §§ 331(a), 342(a)(2)(B), 346a(a).

EPA may establish or leave in effect a tolerance for a pesticide only if EPA determines that the tolerance is "safe." *Id*. § 346a(b)(2)(A)(i). The term "safe" is defined 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." *Id*. § 346a(b)(2)(A)(ii). In determining safety, EPA must consider relevant factors including "the validity, completeness, and reliability of the available data," "the nature of any toxic effect," "the aggregate exposure levels of consumers (and major identifiable subgroups of

consumers)," and "the variability of the sensitivities of major identifiable subgroups of consumers." *Id*. § 346a(b)(2)(D).

Tolerances must reflect an assessment of the risks posed by pesticide residues to infants and children (collectively, "children") based on available information concerning, among other things, "the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults." *Id*. § 346a(b)(2)(C)(i). The standard of safety for children is the same as for other groups: the tolerance must "ensure that there is a *reasonable certainty that no harm will result* to infants and children from aggregate exposure to the pesticide chemical residue." *Id*. § 346a(b)(2)(C)(ii) (emphasis added); *cf. id*. § 346a(b)(2)(A)(ii). To help achieve this protection, "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." *Id.* § 346a(b)(2)(C). This margin of safety is only presumptive. The statute provides that "[n]otwithstanding such requirement for an additional margin of safety," EPA is permitted to "use a different margin of safety for the

pesticide chemical residue [but] only if, on the basis of reliable data, such margin will be safe for infants and children." *Id.*

B. Administrative Procedures Governing Petitions to Revoke FFDCA Pesticide Tolerances

The FFDCA specifies rulemaking procedures for the establishment, modification, or revocation of tolerances. *Id*. §§ 346a(d)-(g). The discussion here focuses on the law applicable to the procedure pertaining to the petition filed by NRDC to revoke the DDVP tolerances.

"Any person may file with [EPA] a petition proposing the issuance of a regulation . . . establishing, modifying, or revoking a tolerance for a pesticide chemical residue in or on a food." *Id*. § 346a(d)(1)(A). If the filing requirements are met, EPA must publish within 30 days a notice of the petition's filing. *Id*. § 346a(d)(2) and (3). After publication of the notice, EPA must, after giving "due consideration" to the petition, either (1) issue a final regulation establishing, modifying or revoking a tolerance; (2) issue a proposed regulation and then issue a final regulation after additional public notice and comment; or (3) issue an order denying the petition. *Id*. § 346a(d)(4)(A). Here, EPA followed the third alternative and issued an order denying the petition.

The FFDCA creates a unique administrative procedure for interested parties to challenge EPA's decision denying a tolerance petition. Within 60

days after EPA issues a denial order, any person may file objections to the order and request a hearing on those objections. *Id*. § 346a(g)(2)(A). The objections must "specify with particularity the provision(s) of the order, regulation, or denial objected to, the basis for the objection(s), and the relief sought." 40 C.F.R. § 178.25(a)(2); 21 U.S.C. § 346a(g)(2)(A). As to hearings, the FFDCA 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." *Id*. § 346a(g)(2)(B) (emphasis added).

EPA's implementing regulations establish that hearings will only be granted when the requesting party shows that:

> (1) there is a genuine and substantial issue of fact for resolution at a hearing . . . ;
>
> (2) there is a reasonable possibility that available evidence identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor . . . ; *and*
>
> (3) the resolution of the factual issues in the manner sought by the requestor would be adequate to justify the action requested.

40 C.F.R. § 178.32(b).

After considering any objections, EPA must issue a final order separately stating the action taken on each objection and whether any hearing is appropriate. 21 U.S.C. § 346a(g)(2)(C).

C. Endocrine Screening Program

The FQPA, and contemporaneous amendments to the Safe Drinking Water Act, 42 U.S.C. 300j-17, required EPA to create an estrogenic substances screening program "to determine whether [pesticide chemicals and certain other 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." *Id*. § 346a(p)(1).

To aid in the design of this program, EPA created the Endocrine Disruptor Screening and Testing Advisory Committee, which comprised members representing the commercial chemical and pesticides industries, federal and state agencies, worker protection and labor organizations, environmental and public health groups, and research scientists. 63 Fed. Reg. 71,542, 71,544 (Dec. 28, 1998). Based on the advisory committee's recommendations, EPA adopted a two-tier testing approach, with the first tier involving screening "to identify substances that have the potential to interact with the endocrine system," and the second tier involving testing "to determine whether the substance causes adverse effects, identify the adverse effects caused by the substance, and establish a quantitative relationship between the dose and the adverse effect." *Id*.

A panel of the advisory committee, comprising distinguished scientists from academia, government, industry, and the environmental community, made specific recommendations as to appropriate studies for the two tiers. For Tier 1, the panel suggested a battery of short-term *in vitro* and *in vivo* assays. 63 Fed. Reg. at 71,550-51. As to Tier 2 testing concerned with potential endocrine effects on humans, the panel recommended a two-generation reproduction study in rats -- a study required for agricultural pesticides since 1984. *Id*. at 71,555; *see* 40 C.F.R. §158.500(d). Pursuant to the suggestion of the panel, EPA has adopted modifications to this study to enhance its ability to detect endocrine effects.

EPA has issued orders requiring that 67 pesticide chemicals undergo the full battery of testing specified under the Agency's endocrine disruptor screening program. 74 Fed. Reg. 54,422 (Oct. 21, 2009). A draft list of second group of chemicals was recently published. 75 Fed. Reg. 70,558 (Nov. 17, 2010).

D. Human Research Rule

EPA decisions regarding the ethics of human studies are governed by the Protection for Subjects in Human Research final rule ("Human Research Rule"). 71 Fed. Reg. 6,138 (Feb. 6, 2006). The framework of the Human Research Rule rests on the basic principle that EPA will not, in its actions,

rely on data derived from unethical research. The rule divides studies involving intentional dosing of human subjects into two groups: those initiated after April 7, 2006 (the effective date of the rule) and those initiated before April 7, 2006. This case involves a study initiated before April 7, 2006.

As to pre-April 7, 2006 studies, the Human Research Rule forbids EPA from relying on such data "if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent) or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted." 40 C.F.R. § 26.1704. Further, reflecting the concern that scientifically invalid data are "always unethical," 71 Fed. Reg. at 6160, the rule limits the human research that can be relied upon by EPA to "scientifically valid and relevant data." 40 C.F.R. § 26.1701.

To aid EPA in making scientific and ethical determinations under the Human Research Rule, the rule established an independent Human Studies Review Board to review both proposals for new research and reports of completed human research on which EPA proposes to rely. *Id.* § 26.1603. If EPA decides to rely on the results from pre-April 7, 2006 research

conducted to identify or measure a toxic effect, EPA must submit the results of its assessment to the Review Board for evaluation of the ethical and scientific merit of the research. *Id*. § 26.1602(b)(2).

The rule directs that the Human Studies Review Board shall be composed of non-EPA employees "who have expertise in fields appropriate for the scientific and ethical review of human research, including research ethics, biostatistics, and human toxicology." *Id*. § 26.1603(a). The members of the Human Studies Review Board at the time it reviewed the DDVP human study were 16 distinguished experts in the fields of bioethics, biostatistics, human health risk assessment and human toxicology, primarily from academia. 73 Fed. Reg. at 42,713 (SPA 67).

III. Procedural History of the NRDC Petition

Dichlorvos, or DDVP, is an insecticide registered for use in commercial structures, including agricultural and food-handling facilities, and private homes. 72 Fed. Reg. at 68,669 (A 218). DDVP is a member of the organophosphate family of pesticides, and like other organophosphates, DDVP's principal hazard to human health is its effect on the nervous system.[3] *Id*.

[3] NRDC's brief also makes various allegations concerning DDVP's carcinogenic potential. Pet. Br. at 9-10. In its petition to revoke DDVP tolerances, NRDC challenged EPA's assessment of DDVP's cancer risk.

To assess the risk of DDVP, EPA has focused on DDVP's ability to inhibit the cholinesterase enzyme in red blood cells. 73 Fed. Reg. at 42,691 (SPA 45). Inhibition of cholinesterase is a disruption of the normal process by which the nervous system chemically communicates with muscles and glands. Id. at 42,688 (SPA 42). EPA does not consider cholinesterase inhibition in red blood cells to be an adverse health effect but rather an indicator of a chemical's "potential for adverse effects on the nervous system." 73 Fed. Reg. at 42,689 (SPA 43).

EPA has established different safe doses for DDVP depending on whether exposure is short- or long-term and whether exposure is by the oral, dermal, or inhalation route. In calculating these safe doses, EPA has used differing safety factors based on whether the safe dose calculation relies on animal or human toxicity data. For safe doses based on animal data, EPA has applied a 100X safety factor – 10X for extrapolation from animals to humans, and 10X for variability in human sensitivity. For safe doses based on human data, EPA has applied a 30X safety factor – 10X for variability in human sensitivity, and 3X under the children's safety factor provision. EPA

(A59-60). EPA dismissed this claim, noting that it had relied on the advice of numerous external peer reviews that concluded that the tumors seen in DDVP animal studies had little or no relevance to humans. 72 Fed. Reg. 68,662, 68,673 (Dec. 5, 2007) (SPA 211, 222). NRDC did not file an objection challenging this finding.

has not applied a children's safety factor when relying on animal data for DDVP. *Id.* at 42,691 (SPA 45).

A. FIFRA Reregistration/FFDCA Tolerance Reassessment for DDVP

EPA was required by the FIFRA amendments of 1988 and the Food Quality Protection Amendments of 1996 to reevaluate the safety of DDVP. *See* 21 U.S.C. § 346a(q). This reevaluation of DDVP safety was completed in July 2006. 73 Fed. Reg. at 42,691 (SPA 45). The reevaluation process indicated that risks from exposure to DDVP in food and water were low but that various residential uses of DDVP posed risks of concern.[4] SA000055. Prior to completion of the reevaluation, the DDVP manufacturer proposed amendments to its FIFRA registration pertaining to the residential uses to address these risks. 73 Fed. Reg. at 42,691 (SPA 45).

An important component of the reevaluation process included review of several DDVP toxicity studies involving human subjects under EPA's newly promulgated Human Research Rule. EPA's initial conclusion was that one of the studies, a study involving repeated dosing over several days

[4] Risks from DDVP residues in food are particularly low. 72 Fed. Reg. at 68,686 (A 235). DDVP residues in drinking water pose higher risks, but EPA found that dietary exposure from food and water was 'insignificant compared to exposures from [residential] pest strips." 73 Fed. Reg. at 42,699 (SPA 53). The primary sources of DDVP are other registered pesticides that degrade to DDVP in the environment. 72 Fed. Reg. at 68,679 (A 228).

conducted in 1997 by A.J. Gledhill (hereinafter referred to as the "Gledhill study"), met the ethical and scientific standards in the Human Research Rule but that the others did not. 73 Fed. Reg. at 42,692 (SPA 46). EPA sought the advice of the Human Studies Review Board on all of the studies.

The Human Studies Review Board held a public meeting on April 4-6, 2006, to review the DDVP studies and human studies for several other pesticides. NRDC filed written comments with the Review Board concerning DDVP, A 277, and also presented oral testimony at the public meeting. SA000003. NRDC's comments and oral remarks focused on whether human studies had sufficient statistical power "to detect an effect when it may occur." SPA 289. On May 23, 2006, the Human Studies Review Board published a notice in the Federal Register seeking public comment on a draft report. 71 Fed. Reg. 29,624 (May 23, 2006). NRDC filed no comments.

On June 26, 2006, the Human Studies Review Board issued its finding that reliance on the Gledhill human study was appropriate given that the study had scientific value and there was no clear and convincing evidence that the study was fundamentally unethical. 73 Fed. Reg. at 42,692 (SPA 46). The Review Board concluded that the other DDVP human studies

should not be used in the DDVP risk assessment. SA000063. These findings were unchanged from its draft report.

EPA agreed with the findings of the Human Studies Review Board and relied on the Review Board's reasoning in using the Gledhill study in its reevaluation of DDVP safety. 72 Fed. Reg. at 68,675 (A 224).

B. NRDC's Petition to Revoke Tolerances

On June 2, 2006, prior to the completion of the DDVP reregistration/tolerance reassessment process, NRDC filed a petition requesting, among other things, that by August 3, 2006, EPA conclude the FIFRA reregistration process with a finding that DDVP is not eligible for reregistration and revoke all DDVP tolerances. The petition raised myriad claims, including allegations that: (1) EPA had unlawfully reduced the children's safety factor to 3X because EPA had provided "no explanation" of why a 3X factor is safe for children, EPA lacked a developmental neurotoxicity study, and a study from the scientific literature showed the young are more sensitive to DDVP, A 56-57; (2) EPA cannot conclude the DDVP tolerances are safe because the DDVP docket does not "indicate that the Agency has conducted [the statutorily-required endocrine] screening or [other] in-depth studies of DDVP's potential for endocrine disruption," A 70; and (3) EPA cannot rely on any of the DDVP toxicity studies using

human subjects because these studies do not meet the standards in EPA's Human Research Rule, A 68. With regard to the human studies, NRDC argued in particular that the Gledhill study was scientifically and ethically flawed because its low number of subjects made it "statistically meaningless," and the study's informed consent process was marred by the description of DDVP as a "drug." *Id.* To support these claims NRDC cited several specific statements in the draft report of the Human Studies Review Board on the Gledhill study. NRDC failed to note, however, that the Board had concluded that the Gledhill study *was* consistent with the standards in EPA's Human Research Rule. *Id*.

Following EPA's release of its reregistration/tolerance reassessment decision, NRDC filed comments on that decision on August 28, 2006. 73 Fed. Reg. at 42,692 (SPA 46); SA000132. Many of those comments expanded on arguments made in its June 2, 2006 petition.

C. EPA's Response to the Petition to Revoke Tolerances

In response to NRDC's petition (including NRDC's August 2006 comments), EPA addressed all of NRDC's contentions in great detail and made substantial changes to its DDVP risk assessment. Nonetheless, EPA denied the petition because, even under the revised risk assessment, the

DDVP tolerances met the FFDCA safety standard. 72 Fed. Reg. at 68,691(A 240).

With regard to the three claims noted above, EPA rejected each of NRDC's arguments. First, as to the children's safety factor, EPA provided an extensive explanation for the safety factors it used for the various different DDVP risk assessments (e.g., acute, short-term, chronic exposures by oral, dermal, and inhalation routes). EPA specifically addressed NRDC's concerns regarding the absence of a developmental neurotoxicity study and the literature study showing sensitivity of the young. EPA explained that two developmental neurotoxicity studies had been received and incorporated into the risk assessment and that these studies resolved the neurotoxicity issues raised by the literature study. 72 Fed. Reg. at 68,694-95 (A 243-44). Further, EPA provided a detailed explanation for its children's safety factor decisions for DDVP, including discussion of the most relevant toxicity studies, adult-young sensitivity evaluations, and the exposure data and assessments. In particular, as to the 3X children's safety factor retained in assessments relying on the Gledhill study, EPA explained that its choice of a 3X safety factor relied heavily on the Human Studies Review Board's scientific evaluation of the likelihood of whether adverse effects would

occur at doses lower than the dose level at which effects were seen in the Gledhill study. *Id*. at 68,695 (A 244).

Second, EPA disagreed with NRDC's claim that EPA had not adequately considered DDVP's potential to disrupt endocrine systems in making its safety determination. EPA described the extensive mammalian toxicity data (from dog, rat, and mouse studies) that it reviewed in evaluating possible endocrine effects. 72 Fed. Reg. at 68,676-77 (A 225-226). That data included a study similar to the one chosen under the endocrine screening program for use in Tier 2 testing with regard to mammalian effects. *Id*. at 68,676 (A 225). EPA noted that although potential endocrine effects were found, these effects occurred at substantially higher exposure levels than the adverse effect (cholinesterase inhibition) upon which the risk assessment was based. EPA concluded that it had adequate data to make a safety finding as to DDVP's potential endocrine-related effects because: "(1) data bearing on potential endocrine effects from a two-generation reproduction study as well as other chronic data in which effects on reproductive organs were examined; (2) EPA well understands DDVP's most sensitive mechanism of toxicity (cholinesterase inhibition); and (3) the potential endocrine-related effects seen for DDVP appeared in the presence of significant cholinesterase inhibition and at levels

nearly two orders of magnitude above the most sensitive cholinesterase effects." *Id.* at 68,677 (A 225).

Third, EPA disagreed with NRDC's claim that the Gledhill study was not consistent with the Human Research Rule. EPA noted that the Human Studies Review Board had specifically considered NRDC's statistical arguments and criticisms of the consent process and had rejected them. *Id.* at 68,675 (A 224). Regarding statistics, EPA noted the Review Board's careful evaluation of the strengths and weaknesses of the Gledhill study. Important to the Board was the repeated dose approach which allowed examination of the sustained nature of red blood cell cholinesterase inhibition; robust analysis of RBC cholinesterase inhibition both in terms of identifying pre-treatment levels and consistency of response within and between subjects; and the observation of a low, but statistically significant RBC cholinesterase inhibition response. *Id.* EPA adopted the reasoning of the Human Studies Review Board. *Id.* Directly responding to NRDC's claims that there were too few subjects in the study and that the study lacked "statistical power," EPA added that:

> Although as a general matter more subjects would provide greater "statistical power," in this case the use of 6 to 9 subjects with the appropriate statistical methodology is acceptable to EPA because a positive response was seen. Indeed, all of the 6 dosed subjects exhibited statistically significant (with respect to their pre-dose levels) RBC cholinesterase depression on one or

> more days . . . . The statistics of the study clearly show the ability to demonstrate a statistically significant response.

Id. Also, in addressing NRDC's concern regarding extrapolating a safe dose from the subjects in the Gledhill study, EPA noted that "an intra-species safety factor of 10X was applied to the study results to address variability in human sensitivity." 72 Fed. Reg. at 68,675 (A 224).

Regarding informed consent, the Human Studies Review Board concluded that there was no clear and convincing evidence that certain references to DDVP as a "drug" in the consent form showed "that informed consent was not obtained." *Id.* Critical to the Board was that "the consent materials clearly advised subjects that this was a study involving consuming an insecticide." *Id*. Again, EPA accepted the Review Board's analysis.

D. NRDC's Objections

Following EPA's denial of NRDC's petition, NRDC filed objections to that ruling and requested a hearing on those objections. Four of those objections are relevant to this proceeding. First, NRDC argued that EPA erred in reducing the children's safety factor from 10X to 3X because EPA had based this decision on a "generic assertion" rather than "on any data specific to DDVP." A 252. Second, NRDC objected that EPA erred in reducing the children's safety factor because "EPA has never conducted

screening or in-depth studies of DDVP's potential for endocrine disruption." *Id.*

Third, NRDC claimed that the Gledhill study did not comply with EPA's Human Research Rule because of statistical inadequacies. NRDC's objection on this point mostly consists of categorical statements unsupported by evidence. For example, NRDC asserts that "[w]e are aware of no statistical test which would support the establishment of a reliable NOAEL [no observed adverse effects level] or dose response curve derived from just 6 test subjects from any toxicity study in any test species," the Gledhill study "lack[s] . . . statistical power," and "the results [of the Gledhill study] are of limited value because the test subjects were all adult males." A 260-61. Moreover, all of this language was drawn verbatim from the comments NRDC filed in August 2006 on EPA's statutory review of the safety of DDVP. *Compare* A 260-61and SA000146.

Finally, NRDC claimed that the Gledhill study did not comply with EPA's Human Research Rule because of the "misleading characterizations to [sic] DDVP as a 'drug'." A 259.

E. EPA's Denial of Objections and Hearing Requests

EPA denied each of NRDC's objections and hearing requests. With regard to the matters raised in this petition for review, EPA took the following actions:

1. *Denial of objection – Reduction of children's safety factor based on non-specific DDVP data*. EPA denied NRDC's objection that EPA's children's safety factor determination was based on a "generic assertion" rather than "on any data specific to DDVP," because that objection is flatly contradicted by the record. 73 Fed. Reg. at 42,696 (SPA 50). As EPA explained, and the record clearly shows, EPA's determination was based on the DDVP animal and human testing data and on the Human Studies Review Board's analysis of the human testing data. EPA concluded: "EPA chose a safety factor of 3X for DDVP based on its conclusion that not only was 10X overprotective but that 3X would be protective given the results seen in the relevant DDVP study." *Id.*

2. *Denial of objection – Reduction of children's safety factor unlawful because of lack of endocrine screening data or other endocrine data*. EPA denied this objection because it was a new claim not presented in the original petition for revocation. Although NRDC made a similar claim about the lack of endocrine data in its administrative petition, NRDC

specifically tied that alleged deficiency to EPA's safety finding, not to EPA's decision on the children's safety factor. *Id*. Nonetheless, EPA analyzed the objection as if it had been properly made and denied it because, first, it was premised on the incorrect legal argument that completion of the endocrine screening program was a mandatory prerequisite to removal or reduction of the children's safety factor, *Id*. at 42,696-97 (SPA 50-51), and second, NRDC's claim that EPA did not have data on endocrine effects was flatly wrong, *Id.* at 42,697-98 (SPA 51-52); moreover, NRDC's sole response to EPA's detailing of that information was merely to speculate that some other test might have showed something different. *Id*. at 42,698 (SPA 52).

3. *Denial of hearing request – statistical deficiency rendering Gledhill study scientifically invalid*. EPA read NRDC's objection on this issue as raising three separate claims: (1) the Gledhill study lacks "statistical power to detect effects caused by the test substance above background variations," A 260; (2) the Gledhill study had insufficient subjects to "support the establishment of a reliable NOAEL or dose response curve," *Id.*; and (3) the Gledhill study is of limited value because it only used adult males, A 261.

EPA denied a hearing on the "statistical power" issue because this issue is not material. As EPA explained, "statistical power measures the probability that a toxicological study will find a treatment-related adverse health outcome when there is a treatment-related adverse effect to be found." 73 Fed. Reg. at 42,705 (SPA 59). Statistical power is a critical measurement in evaluating whether a toxicity study is showing a false negative (i.e., falsely indicating that the test substance does not cause an adverse effect). But with the Gledhill study, the issue of false negatives was not a concern. The Gledhill study investigated DDVP's impact on cholinesterase inhibition in red blood cells, and the study confirmed that cholinesterase *was* inhibited.[5] EPA thus rejected all of the scientific articles NRDC submitted on statistical power because they were directed at the false negative question, despite the fact that the question of false negatives was not presented by the Gledhill study, as NRDC's articles acknowledged. *See, e.g.*, A 264.

EPA denied a hearing on NRDC's claim that the Gledhill study had insufficient test subjects because (1) NRDC submitted no evidence in

[5] The title of the study is "Dichlorvos: A Single Blind, Placebo Controlled, Randomized Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers." EPA-HQ-OPP-2002-0302-0211; *See also* A 264("the only biological end point measured in the study was cholinesterase inhibition, and this was significantly inhibited.")

support of this claim, and thus the claim was nothing more than a "mere allegation" for which NRDC was not entitled to a hearing under EPA's regulation; and (2) NRDC's objection failed to confront the reasoning EPA gave in its petition denial as to why the Gledhill study had sufficient subjects for the purposes for which it served in EPA's risk assessment. EPA explained that this affected the materiality of the objection because "[e]ven if NRDC could demonstrate in a hearing that generally more test subjects are needed to derive a . . . [safe dose], that evidence would not address the specific factors in the Gledhill study that EPA and the [Human Studies Review Board] found convincing on this question." 73 Fed. Reg. at 42,706 (SPA 60).

Finally, EPA denied a hearing on NRDC's objection to the Gledhill study's use of only adult males for basically the same reason. First, NRDC proffered no evidence on the representativeness of adult males to the general population. Second, NRDC did not object to the basis given in EPA's petition denial for why the Gledhill study provided valuable information despite the use of adult males only, namely, the fact that animal testing with DDVP showed no differences in sensitivities in regard to cholinesterase inhibition between males and females or adults and juveniles. Thus, this

objection, like the last one, was nothing more than a "mere allegation and not a material challenge to the petition denial." *Id.* at 42,707 (SPA 61).

4. *Denial of hearing request – informed consent issue*. EPA denied a hearing on NRDC's objection concerning consent in the Gledhill study for two reasons. First, EPA concluded that there were no disputed facts at issue. NRDC raised no dispute as to what information was presented to the study participants and proffered no other evidence on consent. EPA concluded that "the only question is the legal/policy one of whether use of the Gledhill study consent form is 'clear and convincing evidence' that the Gledhill study was 'fundamentally unethical' and thus not in compliance with EPA regulations." *Id.* at 42,708 (SPA 62). EPA regulations do not permit hearings on questions of law or policy. Second, once again, NRDC's objection was not material because NRDC had not confronted EPA's reasoning in the denial order – that the Human Studies Review Board had concluded that consent was informed based on information showing that the subjects had been told the test substance was an insecticide. *Id.*

STANDARD OF REVIEW

Judicial review under the FFDCA is governed by the standards set forth in the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 551-559, 701-706, which establishes a highly deferential standard of review for

agency action. Such action is valid unless it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

This Court has held that "review under this provision is narrow, limited to examining the administrative record to determine whether the [agency] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Riverkeeper, Inc. v. EPA*, 358 F.3d 174, 184 (2d Cir. 2004) (citations and internal quotes omitted); *see also NRDC v. Muszynski*, 268 F.3d 91, 97 (2d Cir. 2001) (same). The Court "may not substitute its judgment for that of the agency[.]" *Id*. at 97 (citation and internal quotation omitted). Rather, the Court should affirm EPA's decision unless EPA has:

> relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Id. (citation and internal quotations omitted). In short, this standard of review presumes the validity of agency action, *Ethyl Corp. v. EPA*, 541 F.2d 1, 34 (D.C. Cir. 1976) (*en banc*), and if the agency's reasons and policy choices conform to "certain minimal standards of rationality," the action is

reasonable and must be upheld. *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 521 (D.C. Cir. 1983).

This highly deferential standard of review applies to review of EPA's decisions establishing tolerances under the FFDCA. *Nw. Coal. for Alternatives to Pesticides v. EPA*, 544 F.3d 1043, 1047-48 (9th Cir. 2008); *Cmty. Nutrition Inst. v. Young*, 773 F.2d 1356, 1363 (D.C. Cir. 1985). The same highly deferential standard applies to review of EPA decisions determining whether an issue is material and supports a request for an evidentiary hearing under the FFDCA and EPA regulations. *Nat'l Corn Growers Ass'n v. EPA*, 613 F.3d 266, 271-72 (D.C. Cir. 2010) (Although EPA regulations establish a "summary-judgment type" standard for determining whether to hold a hearing, "our review of the EPA's exercise of discretion in determining whether an issue is material differs from our review of a summary judgment rendered by a district court, which we review *de novo*.")

When an agency's decision rests on an evaluation of complex scientific data within the agency's technical expertise and judgment, courts are "extremely deferential." *New York v. Reilly*, 969 F.2d 1147, 1152 (D.C. Cir. 1992); *see also Browning-Ferris Indus. of S. Jersey, Inc., v. Muszynski*, 899 F.2d 151, 160 (2d Cir. 1990). The Court "must look at the decision not

as the chemist, biologist, or statistician that [it is] qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality." *Ethyl Corp.*, 541 F.2d at 36; s*ee also Riverkeeper*, 358 F.3d at 184 (this Court "lack[s] the EPA's expertise when it comes to scientific or technical matters").

SUMMARY OF ARGUMENT

NRDC filed objections to, and sought a hearing on, EPA's denial of its petition to revoke DDVP tolerances. The FFDCA requires that such objections be made "with particularity" to the challenged order. Further, EPA regulations provide that an evidentiary hearing will be conducted only if EPA determines that the requesting party has submitted material that presents a genuine and substantial issue of fact and there is a reasonable possibility that the evidence, if established, would resolve one or more issues in favor of the requesting party in a manner that would be adequate to justify the action requested. EPA reasonably exercised its technical expertise and discretion in determining that NRDC's request for a hearing failed to satisfy statutory and regulatory requirements with respect to each of NRDC's claims.

First, NRDC's claim that the Gledhill study lacked statistical power necessary to avoid a false finding that DDVP is harmless is irrelevant because the Gledhill study found the effect it was investigating. NRDC also argues that the study had too few subjects to produce scientifically reliable data for establishing a safe dose for DDVP, but NRDC failed to acknowledge, must less address and submit evidence contesting, EPA's finding in its petition denial order that the results of the Gledhill study, despite the relatively low number of subjects, were "sufficiently robust" for assessing DDVP risks. EPA's finding rejecting NRDC's challenge to the scientific validity of the Gledhill study was based on a thorough analysis of the study by the Human Studies Review Board and was exhaustively explained in its petition denial order. Because NRDC did not, "with particularity," address and submit evidence contesting this central conclusion in EPA's order, EPA reasonably – and necessarily – found that NRDC failed to demonstrate the existence of a genuine, dispositive issue of material fact requiring an evidentiary hearing.

Second, NRDC's objection to the informed consent determination for the Gledhill study also did not show a disputed factual issue meriting a hearing. Although an EPA staff member, the Human Studies Review Board and EPA each reviewed the informed consent form used in the Gledhill

study and found significant deficiencies in the consent form, each also concluded that, on whole, the study met applicable ethical standards for informed consent. NRDC disputes none of the underlying facts bearing on informed consent, but nonetheless argues it is entitled to an evidentiary hearing on this issue. However, NRDC created no fact issue on this point because it framed its challenge as a purely legal one and offered no factual evidence for development at a hearing, such as testimony from an expert who had reviewed the informed consent materials, to support its argument. Further, similar to its statistical objection, NRDC failed to object "with particularity" to EPA's conclusion on informed consent in the petition denial order and thus NRDC's objection (and hearing request) is irrelevant and immaterial.

Third, there is no support in the record to support NRDC's assertion that EPA based its denial of NRDC's hearing request on the grounds that an evidentiary hearing would be burdensome. EPA's denial was based entirely on its determination that NRDC failed to satisfy applicable statutory and regulatory requirements.

EPA also acted reasonably and in accordance with law in reaching its finding that a 3X children's safety factor was supported by the scientific

data, and that the FFDCA's presumptive 10X factor was unnecessary to protect children.

First, EPA selected a 3X safety factor based on available data that EPA determined to be reliable. NRDC claims that EPA could not depart from the presumptive 10X safety factor without first having the results of an endocrine screening program required by statute. NRDC forfeited any argument that screening program results are scientifically necessary because NRDC failed to raise this argument in its petition to revoke the tolerance, and instead asserted it for the first time in its objection. In any event, NRDC's argument that the FFDCA requires that EPA obtain screening program results before departing from the 10X safety standard is contrary to the plain language of the statute.

Second, EPA concluded that a 3X factor was safe based on its comprehensive evaluation of DDVP-specific data, and not, as NRDC alleges, some "generic assertion" about safety. NRDC's argument that EPA chose 3X simply because it is half of 10X is based on a misreading of the record. NRDC's argument that EPA must calculate a "mathematically precise" safety factor is wrong; the FFDCA requires EPA to select a safety factor that it determines is safe, just as it did here. Finally, NRDC's claim that the human study data and animal study data cannot be considered in

combination to assess risks is asserted for the first time in this Court and is not supported by any evidence in the record.

EPA's scientific judgment is entitled to deference. There is no evidence that EPA abused its discretion or acted in violation of law, and EPA's decision must therefore be upheld.

ARGUMENT

I. NRDC Did Not Satisfy the Standard for Obtaining an Evidentiary Hearing Under the FFDCA.

NRDC was entitled to a hearing on its objections to EPA's 2008 order only "if and to the extent [EPA] 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). EPA has implemented this statutory provision by promulgating regulations articulating specific requirements that must be satisfied before a request for hearing will be granted. 40 C.F.R. § 178.32(b).

First, the hearing request must involve "a genuine and substantial issue of fact . . . ." *Id.* § 178.32(b)(1). Evidentiary hearings "will not be granted on issues of policy or law." *Id*. Second, the hearing request and submitted supporting material must show that "[t]here is a reasonable possibility that available *evidence* identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor,

taking into account uncontested claims or facts to the contrary." *Id.* § 178.32(b)(2) (emphasis added). "An evidentiary hearing will not be granted on the basis of mere allegations, denials, or general descriptions of positions and contentions, nor *if the Administrator concludes* that the data and information submitted, even if accurate, would be insufficient to justify the factual determination urged." *Id.* (emphasis added). Finally, the hearing request must demonstrate that "[r]esolution of the factual issue(s) in the manner sought by the person requesting the hearing would be adequate to justify the action requested." *Id.* § 178.32(b)(3). Hearings will not be granted on issues that will not affect the outcome. *Id.*

While the process for deciding whether to conduct an evidentiary hearing is often described as "summary judgment-like," the threshold showing required to trigger a hearing is higher under the regulations than under rules applicable to summary judgment. A civil litigant can defeat summary judgment and obtain a hearing by demonstrating a genuine issue of material fact, Fed. R. Civ. P. 56(c)(2), while a party objecting to a tolerance must not only establish the existence of a genuine and substantial fact issue, but also each of the other requirements of 40 C.F.R. § 178.32(b). This higher threshold is permissible because Congress has "great leeway" in setting standards regarding the regulation of chemicals, whereas there are

"sharper limitations on the use of summary judgment." *See Weinberger v. Hynson, Westcott & Dunning, Inc*., 412 U.S. 609, 622 (1973) (finding Food and Drug Administration "hearing regulations unexceptionable on any statutory or constitutional ground"). "Properly viewed, the objection stage is an opportunity for internal agency review, an opportunity for an interested party to challenge -- and for the agency to correct -- a matter of fact, law, or policy that appeared for the first time in the Final Regulation, so-called." *Nat'l Corn Growers*, 613 F.3d at 273.

NRDC claims that EPA arbitrarily and capriciously determined that NRDC's hearing request failed to meet all of the requirements of 40 C.F.R. § 178.32(b) with respect to two issues: (1) whether the Gledhill study lacked adequate statistical power; and (2) whether the consent given by study participants met applicable standards for informed consent. NRDC's claims must be rejected for the reasons discussed below.

A. NRDC's claims regarding the statistical power of the DDVP human study did not raise issues of fact material to EPA's tolerance decision.

NRDC claims that, because the Gledhill study involved six test subjects, the study lacks "statistical power" to detect a health risk from DDVP or determine an exposure level that is a safe dose for humans. Pet. Br. at 21. EPA specifically examined each of these claims, determined that

the evidence submitted by NRDC was not material to EPA's denial of NRDC's petition to revoke the DDVP tolerance, and denied NRDC's hearing request. 73 Fed. Reg. at 42,704-06 (SPA 58-60). EPA's decision was not arbitrary or capricious.

Statistical power is a concept used to measure the probability that a given sample size in a study will be able to find an effect if such an effect is present. Analysis of a study's statistical power is important to avoid false negatives (i.e., concluding that a pesticide is harmless when in fact it is not). As EPA explained, however, the issue of a study's statistical power is irrelevant if the study has found the effect it is looking for. *Id.* at 42,705-06 (SPA 59-60). DDVP is a cholinesterase-inhibiting pesticide. As NRDC acknowledges, the Gledhill study was designed to test for cholinesterase inhibition, and it found such inhibition. It is undisputed that the Gledhill study did not produce a false negative, therefore any evidence about the statistical power of the Gledhill study is not material to EPA's decision to rely on the study to detect a risk of cholinesterase inhibition, and could not have changed that decision. Accordingly, NRDC's hearing request on this subject failed to satisfy the requirements of 21 U.S.C. § 346a(g)(2)(B) and 40 C.F.R. § 178.32(b)(2) and (3).

Whether the Gledhill study had an adequate number of subjects for EPA to rely on its result in establishing a safe dose for DDVP is potentially a relevant objection to EPA's use of the study. However, NRDC's request for hearing on this issue also failed to satisfy requirements for obtaining a hearing because NRDC failed to submit any evidence in support of its objection and, contrary to the requirements of EPA's regulations, NRDC's objection failed to address EPA's findings in the petition denial.

NRDC asserted in its petition to revoke the tolerances that the Gledhill study had too few subjects. EPA rejected this claim in its petition denial, relying on the Human Studies Review Board's conclusion that the Gledhill study "was sufficiently robust for developing a [safe dose] for estimating dermal, incidental oral, and inhalation risk from exposure to DDVP in a single chemical assessment." 72 Fed. Reg. at 68,675 (A 224). EPA and the Board cited many factors in support of their conclusions as to the robustness of the Gledhill study data, including: "the repeated dose approach which allowed examination of the sustained nature of RBC cholinesterase inhibition; robust analysis of RBC cholinesterase inhibition both in terms of identifying pre-treatment levels and consistency of response within and between subjects; and the observation of a low, but statistically significant RBC cholinesterase inhibition response." *Id.* EPA also noted

that "the group means of RBC cholinesterase activity in treated subjects are statistically below the group means of the placebo controls on days 7, 11, 14, 16 and 18 by [the statistical measure of]repeated measures analysis of variance. The statistics of the study clearly show the ability to demonstrate a statistically significant response." *Id*. Finally, EPA noted that in addition to the 3X children's safety factor, it was applying a 10X safety factor to address "variability in human sensitivity." 72 Fed. Reg. at 68,675 (A 224). Thus, in computing a safe dose for DDVP based on the Gledhill data, EPA used an overall safety factor of 30X.

In response to EPA's detailed statistical analysis of the results of the Gledhill study, NRDC's objection offered nothing more than the statement that: "We are aware of no statistical test which would support the establishment of a reliable NOAEL or dose response curve derived from just 6 subjects."[6] A 260. This statement is taken verbatim from NRDC

[6] NRDC did contest EPA's statement in the petition denial that the number of subjects was not meaningfully different than the subjects in a chronic toxicity study in dogs (four per dose for each sex), a required test for pesticides. NRDC claimed, without providing any support, that the dog study was also statistically meaningless and rarely relied upon by EPA. A 260. In response, EPA noted that (1) the requirement for a chronic dog study was a long-standing one; (2) EPA had only recently repromulgated by rule the requirement for a chronic dog study; (2) the U.S. Food and Drug Administration and governmental agencies in other major developed countries all recommend the same number of subjects in the chronic dog study; and (3) a review of EPA actions showed frequent reliance on the

comments filed with EPA in August 2006 – 15 months prior to EPA's denial of the petition to revoke DDVP tolerances. SA000132.

EPA properly concluded that a hearing was not appropriate on such an objection. First, the objection was nothing more than a "mere allegation" or "denial" of EPA's position; under EPA's hearing regulations, hearing requests based on mere allegations or denials *must* be denied. 40 C.F.R. § 178.32(b)(2). Second, by failing to contest EPA's specific conclusions in its petition denial order but simply recycling comments made earlier to EPA, NRDC's objection and the supporting materials failed to satisfy the materiality requirement of the statute and the rule. As the D.C. Circuit recently held: "[T]he petitioners, by simply re-submitting their Comments, without addressing the responses the EPA had made to them in the Final Regulation, 'failed to lodge a relevant objection.' . . . By statute, an Objection and Hearing Request must be directed 'with particularity [to] the provisions of the [final rule] deemed objectionable.' 21 U.S.C. § 346a(g)(2); *see also* 40 C.F.R. § 178.25(a)(2)." *Nat'l Corn Growers*, 613 F.3d at 273.

None of the "evidence" submitted by NRDC with its hearing request addresses EPA's (and the Human Studies Review Board's) detailed findings

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chronic dog study, including in the DDVP risk assessment. 73 Fed. Reg. at 42,706 (SPA 60). Hearings are not warranted on mere allegations and NRDC has not argued, in this Court, that its unsupported claims regarding the chronic dog study justified a hearing.

with regard to the statistical merit of using the Gledhill study for calculating a safe dose. NRDC's evidence contains nothing more than generalized conclusions about "statistical power," which, as explained above, is irrelevant to the Gledhill study. None of the evidence supports a conclusion that the Gledhill study had too few subjects to support EPA's decision establishing a safe dose. Moreover, none of the evidence even addresses the other factors that EPA relied on to support its decision. Each of NRDC's submissions is analyzed below:

1. Sass & Needleman, *Industry Testing of Toxic Pesticides on Human Subjects Concluded "No Effect," Despite the Evidence*. A 264. The authors of this letter to the editor dispute -- as did EPA -- the DDVP registrant's claim that the Gledhill study showed no effect on cholinesterase inhibition. The authors broadly criticize the use of just "a handful of healthy adult subjects" in studies, claiming that "[s]uch studies often lack enough subjects to provide adequate statistical power to detect an effect if it is present." *Id*. The authors make no attempt to explain how this general criticism applies to the Gledhill study, which did detect the presence of the effect being studied.

2. Sass & Needleman, *Human Testing: Sass and Needleman Respond to Industry* (A 265-66). This short follow-up to the authors' earlier letter does nothing other than repeat the generalized criticism that small

sample sizes result in low statistical power, and provide a computation of the statistical power of such studies. Implicitly acknowledging that the possibility of a false negative did not occur in the Gledhill study, this letter approvingly cites EPA's conclusion that the Gledhill study did show a statistically- and biologically-significant effect on cholinesterase. *Id*. at 265.

3. Lockwood, *Human Testing of Pesticides: Ethical and Scientific Considerations*. A 267-75. This article provides a broad critique of human studies. It contains a short discussion of statistical power in relation to the Gledhill study and five other studies. However, this discussion states nothing more than: "A power analysis to define the proper size of study group(s) is an essential part of design. [] If too few [subjects] are enrolled, the investigator *risks* erroneous acceptance of the null hypothesis [i.e. a false negative]. Underpowered studies are inconclusive . . . . All of these studies were underpowered." A 271 (emphasis added). The author did not comment about the fact that the risk of a false negative did not materialize in the Gledhill study. Moreover, the author says nothing about whether the statistically-significant results found in the Gledhill study are appropriate for use in calculating a safe dose.

4. Sass, *PowerPoint Presentation to the Human Studies Review Board*. A 277-98. This presentation contains four PowerPoint slides that

address DDVP, A 286-89, and several slides generally discussing statistical power. The latter slides state that statistical power is a critical element of study design because "[a] study with inadequate power to find an effect is by definition unethical." These slides also contain a hypothetical computation to show how many subjects would be needed for a study to have adequate power to detect an effect that occurred in one out of one thousand children. None of this speaks to the Gledhill study given that that study found the effect it was looking for. As to DDVP, there is one slide primarily addressing cancer risk, two slides supporting EPA's conclusion that a significant cholinesterase effect was seen in the Gledhill study, and one slide offering a few general science/policy criticisms of human studies. A 289. The presentation contains no analysis of whether the statistically-significant results seen in the Gledhill study are appropriate for calculating a safe dose.

5. Lockwood, *The Ethical Bar Drops to Unacceptable*. A 276. This one-page article for a legal publication briefly summarizes the author's longer article and critiques EPA's proposed Human Research Rule. Lockwood repeats his earlier conclusion that the six studies he reviewed were "statistically invalid," but presents no analysis or explanation. In a parenthetical remark, Lockwood reminds the reader that "Vioxx was tested on thousands and used by millions" before it was withdrawn because of

drug-related complications." *Id*. The author makes no effort to relate this statement to the Gledhill study, and says nothing about the validity of a statistical analysis of a study that did identify effects without being "tested on thousands."

As NRDC nears the end of its argument about the reliability of the Gledhill study it shifts ground, claiming that EPA "missed the point," and failed to recognize that "an underpowered study is unreliable for two reasons: (1) it could identify a harmful effect at the *wrong exposure level*; and (2) it could fail to detect *other* harmful effects entirely." Pet. Br. at 26 (emphasis in original). This argument is unavailing for several reasons.

First, as explained above, EPA did identify the first argument, which is just another way of restating NRDC's claim that EPA could not rely on the Gledhill study to establish a safe dose. EPA denied a hearing on this claim because (1) it was based on nothing more than a mere allegation without supporting evidence and (2) NRDC failed to object to the detailed statistical analysis EPA presented as to why the Gledhill study results were "sufficiently robust" to use in setting a safe dose. *See* Section I.A, *supra*.

Second, EPA could not have identified the "fail to identify other effects" argument, because no mention of it appears in the part of NRDC's objections cited in its brief (i.e., A 260-61), or elsewhere. NRDC's omission

violates the requirement that objections "[s]pecify with particularity . . . the basis for the objections." 40 C.F.R. § 178.25(a)(2); 21 U.S.C. § 346a(g)(2)(A). This requirement makes clear that EPA need not analyze an objector's submissions and respond to objections that, in theory, could have been made. Because this claim could have been -- but was not -- raised in NRDC's objection as required by section 346(g), NRDC may not raise the claim in this Court. *NRDC v. Johnson*, 461 F.3d 164, 173 (2d Cir. 2006) ("[I]f it is or was possible to obtain review under the administrative review procedures of Section 346a(g), then Section 346a(h) limits judicial review to the courts of appeals and forecloses such review prior to the exhaustion of administrative remedies.); c*f. Nader v. EPA*, 859 F.2d 747, 753-54 (9th Cir. 1988) (interpreting parallel pre-FQPA provision of the FFDCA as requiring exhaustion of internal procedures before challenging denial of petition for rulemaking in court of appeals).

Finally, even if the claim were properly before this Court, it is disingenuous for NRDC to claim that this is a serious objection to the Gledhill study. As NRDC's filings and cited articles admit, DDVP is a cholinesterase-inhibiting pesticide and the Gledhill study was designed to investigate cholinesterase inhibition in red blood cells. The Gledhill study did not detect harmful effects other than red blood cholinesterase inhibition

because it only examined cholinesterase inhibition, not because of some statistical deficiency in the study.

Based on its expertise, EPA determined that NRDC's hearing request and supporting evidence were too generic and conclusory to be material to, raise a genuine fact issue about, or be determinative of, the issue of whether EPA reasonably relied on the Gledhill study as one factor in establishing a tolerance for DDVP. The administrative record does not support a conclusion that EPA abused its discretion, and the Court should not substitute its judgment for the Agency's on such highly technical matters. *See Nat'l Corn Growers,* 613 F.3d at 273.

B. NRDC presented no evidence that raised material issues of fact on which NRDC could reasonably prevail on the question of whether the Gledhill study's informed consent process met ethical standards.

NRDC argues that EPA arbitrarily denied NRDC's request for a hearing to determine whether the Gledhill study complied with ethical standards applicable to the informed consent process. Pet. Br. at 27. No hearing was required because NRDC failed to present any evidence that created a disputed issue of fact that had a reasonable possibility of being resolved in NRDC's favor.

The question of whether the informed consent process complied with ethical standards could involve fact issues about what occurred during that

process. Cases relied on by NRDC articulate this principle. *E.g., Rainwater v. Alarcon*, 268 Fed. Appx. 531, 534 (9th Cir. 2008). Here, however, NRDC's objections failed to raise such issues. The evidence concerning the consent process is not in dispute. The consent form used in the Gledhill study is included in the study report, and NRDC proferred no evidence suggesting that there were other disputed facts relevant to the process of obtaining consent from participants in the study.

Instead, in its objection and hearing request, NRDC framed the adequacy of the Gledhill consent form as a *legal* issue, arguing, for example, that the form "would have violated FIFRA Section 12(a)(2)(P)." A 261. EPA properly declined NRDC's request for a hearing on such issues, 73 Fed. Reg. at 42,703 (SPA 57), because "evidentiary hearings may not be obtained to resolve legal issues." 40 C.F.R. § 178.32(b)(2).

Given that NRDC is not disputing the facts concerning the consent process, NRDC, to justify a hearing, would have to, at a minimum, present testimony of a qualified expert that the informed consent process in the Gledhill study was unethical and failed to obtain the informed consent of the subjects. *See Rodriguez v. City of New York*, 72 F.3d 1051, 1063 (2d Cir. 1995) (conflicting expert testimony regarding what is the customary and acceptable medical standard creates an issue of fact); *cf. Semler v. Oregon*

State Bd. of Dental Exam'rs, 294 U.S. 608, 612 (1935) ("What is generally called the 'ethics' of the profession is but the consensus of expert opinion as to the necessity of such standards."). NRDC, however, proffered no such testimony.

In fact, NRDC's hearing request referenced no evidence to suggest that it could, at an evidentiary hearing, present clear and convincing evidence that the consent form failed to comply with ethical standards applicable to informed consent. NRDC's claim that it did submit factual evidence is based on two documents that concluded that the consent form met ethical standards (an internal memorandum authored by EPA employee John Carley, A 3-5, and a draft report by the Human Studies Review Board on DDVP, A 26-42), and an article by author who states that he did not review the consent form (Alan Lockwood article, A 267-75).[7] NRDC, however, cannot create a fact issue by its attorney's arguments that Mr. Carley, the Human Studies Review Board, and EPA reached the wrong

[7] Only two of these three documents, however, are even mentioned in its objections, and nowhere does NRDC explain what evidence they contain, contrary to the requirements of 40 C.F.R. § 178.27(d).

conclusion. As the statute makes clear, hearings are for the purpose of "receiv[ing] factual evidence." 21 U.S.C. § 346a(g)(2)(B).[8]

Mr. Carley's memorandum does note the undisputed fact that the consent form refers to the test substance as "the drug." However, NRDC's brief fails to note that Mr. Carley's memorandum concluded that there was no clear and convincing evidence that the Gledhill study did not obtain informed consent. *See* A 5. Accordingly, the Carley memorandum is not evidence that creates a reasonable possibility that the informed consent issue would be resolved in NRDC's favor, and it does not support a hearing request. *See* 40 C.F.R. § 178.32(b)(2).

NRDC's reliance on misleadingly juxtaposed sentence fragments from the draft report of the Human Studies Review Board, Pet. Br. at 28, also fails to provide evidence that would support a finding in NRDC's favor. While the draft report contains statements critical of aspects of the disclosure form, "[t]he Board determined that there was not clear and convincing evidence that references to the test material as a drug . . . that appear in the materials to obtain informed consent should be considered significantly

[8] NRDC also implies that a hearing is needed so that a "neutral arbiter" can resolve these "facts." Pet. Br. at 30. But more is needed to justify a hearing than a desire for a neutral arbiter. To the extent NRDC seeks a neutral arbiter, it could have appealed EPA's objection denial to this Court for determination of whether EPA reasonably relied on an independent scientific body's judgment on informed consent. But NRDC has not done so.

deficient relative to the ethical standards prevailing when the study was conducted." A 41. The draft also notes that "other wording in the consent materials *clearly advised* subjects that this was a study involving consuming an insecticide." *Id*. (emphasis added). Moreover, like the Carley memorandum, the Human Studies Review Board concluded that there was no clear and convincing evidence that the Gledhill study did not obtain informed consent.

Finally, the Lockwood article, A 267-75, does not satisfy the need for an expert opinion on consent or otherwise create a genuine and substantial issue of fact, as required by 40 C.F.R. § 178.32(b)(2), because Lockwood never reviewed the consent form for the Gledhill study. Lockwood summarized his review of six studies in a table. A 269. The Gledhill study appears in row three of that table. In the column titled "Written Informed Consent Available," Lockwood entered "No, but protocol states 'volunteers completed a consent form.'" *Id*. Thus, when Lockwood gave as an example of unacceptable deficiencies in consent documents the "failure to identify the test compound as a pesticide," he could not have been referring to his review of the Gledhill consent documents. Even if he were referring to that study, testimony of an expert who has not examined the consent form cannot create a factual issue. *See, e.g., Triton Energy Corp. v. Square D Co.*, 68

F.3d 1216 (9th Cir. 1995) (testimony of expert who had not examined allegedly defective product could not establish fact issue).

C. EPA did not deny any hearing request based on consideration of the burden of holding a hearing.

NRDC claims that EPA denied NRDC's hearing requests because EPA thought it would be a burden to hold such a hearing. Pet. Br. at 32. The administrative record contradicts NRDC's claim.

In a closing section of its denial order, EPA summarized its grounds for denying NRDC's hearing requests: "EPA's close examination of each of the 19 sub-issues involved in these two hearing requests demonstrates that none of the issues satisfies the standard for granting a hearing in 40 C.F.R. § 178.32. Most fail for multiple reasons." 73 Fed. Reg. at 42,709 (SPA 63). EPA then summarized the issues that did not present an issue of genuinely disputed fact, were not material, or were unsupported by evidence which, if established, would resolve the issue in NRDC's favor. *Id*. at 42,709-10 (SPA 63-64).

EPA next commented that NRDC's failure to offer relevant evidence in support of its contentions through the several stages of the tolerance setting had defeated the goal of making the regulatory process no more resource intensive than necessary. "Presumably, Congress created a multi-stage administrative process for resolution of tolerance petitions to give EPA

the opportunity in the first stage of the proceeding to resolve factual issues, where possible, through a notice-and-comment process, prior to requiring EPA to hold a full evidentiary hearing -- which can involve a substantial investment of resources by all parties taking part." *Id*. at 42,710 (SPA 64). *Accord Nat'l Corn Growers*, 613 F.3d at 272-73 (rulemaking stage of the process would be "redundant and superfluous" if a party can withhold evidence from EPA until the objection stage).[9] EPA, however, was clear that this consideration raised questions of concern, but was not a ground for its order in this case: "In these circumstances [i.e., NRDC's failure to submit evidence at earlier stages of this proceeding], EPA *questions* whether granting a hearing would have been appropriate *even if* NRDC had, at this last stage of the administrative process, suddenly produced factual evidence in support of its claims." 73 Fed. Reg. at 42,710 (SPA 64) (emphasis added)

EPA did not rely on an improper factor to deny NRDC's hearing requests.

[9] Effective use of agency resources is an appropriate consideration in establishing procedures limiting the availability of evidentiary hearings. *Hynson*, 412 U.S. at 621 ("If FDA were required automatically to hold a hearing for each product whose efficacy was questioned . . ., even though many hearings would be an exercise in futility, we have no doubt that it could not fulfill its statutory mandate to remove from the market all those drugs which do not meet the effectiveness requirements of the Act.").

II. EPA's Decision to Apply a 3X Children's Safety Factor was Neither Contrary to Law Nor Arbitrary or Capricious.

A. EPA properly denied NRDC's objection to EPA's children's safety factor decision based on the absence of data from endocrine screening program because it was not raised in NRDC's petition.

EPA has interpreted 21 U.S.C. 346a(g)(2) as requiring that tolerance petitioners exhaust their claims through the administrative petition process and bars claims filed for the first time in objections. "The FFDCA's tolerance revocation procedures are not some sort of 'game,' whereby a party may petition to revoke a tolerance on one ground, and then, after the petition is denied, file objections to the denial based on an entirely new ground not relied upon by EPA in denying the petition." 72 Fed. Reg. 39,318, 39,324 (July 18, 2007); *see Nat'l Corn Growers*, 613 F.3d at 272-73 ("The EPA's refusal to consider at the objections stage evidence and arguments that could have been but were not submitted during the comment period is also of a piece with the general rule of forfeiture we apply when reviewing agency decisions, *viz.*, that the court will not consider an argument the agency was not given a fair opportunity to consider during the rulemaking.") (citations omitted). In its petition, NRDC claimed that EPA lacked sufficient data on endocrine effects to determine the safety of DDVP. EPA responded by explaining in detail the data it did have on endocrine

effects and why that data permitted it to make a safety finding. In its objections, NRDC raised a new argument, namely, that the absence of data from the endocrine screening program established by 21 U.S.C. § 346a(p) invalidated EPA's decision on the children's safety factor. Because this argument was not presented in NRDC's petition, EPA properly denied it as waived.

B. EPA's authority to establish an appropriate children's safety factor does not depend on the completion of the endocrine screening program.

Even assuming NRDC's challenge to EPA's children's safety factor decision based on the absence of data from the endocrine screening program is properly before this Court, it is without merit. NRDC contends that the FFDCA requires EPA to apply the presumptive tenfold (10X) children's safety factor to a pesticide unless the endocrine screening program has been completed for that pesticide. Pet. Br. at 34-37. NRDC does not contest EPA's factual finding regarding the extensive data it has on endocrine effects.[10] The plain language of the statute does not support NRDC's reading.

[10] In its objections, NRDC argues that EPA's existing data are not adequate under the endocrine screening program, but does not substantively contest EPA's scientific conclusion that these studies provide valuable information on potential endocrine effects. A 252-53.

The children's safety factor provision, 21 U.S.C. § 346a(a)(2)(C), requires that in establishing tolerances "an additional tenfold margin of safety . . . shall be applied for infant(s) and children to take into account pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children," but also provides that "[n]othwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Section 346a(a)(2)(C) leaves it to EPA's discretion to determine what constitutes "completeness of the data" and "reliable data," and requires only that EPA's assessment of risks be based on "available information." 21 U.S.C. § 346a(a)(2)(C)(i). The children's safety factor provision contains no requirement that data from the endocrine screening program mandated by 21 U.S.C. § 346a(p) be available before EPA can use its discretion to depart from the presumptive margin of safety. EPA has consistently interpreted the statute in this manner. 71 Fed. Reg. 43,906, 43,920 (Aug. 2, 2006) ("EPA's contemporaneous and consistent approach to the endocrine screening program has been to treat that information-gathering exercise as not imposing some type of statutorily-

prescribed, automatic injunction barring removal of the children's safety factor until completion of information-gathering under the program.").

Similarly, nothing in the provision creating the endocrine screening program, 21 U.S.C. § 346a(p), refers to – let alone limits – EPA's discretion to adjust the children's safety factor before the screening program has been completed. The provision mandates that EPA implement the screening program, but requires only that EPA take appropriate action after receiving results from the screening program: "In the case of any substance that is found, as a result of testing and evaluation under this section, to have an endocrine effect on humans, the Administrator shall, as appropriate, take action under such statutory authority as is available to the Administrator . . . as is necessary to ensure the protection of public health." 21 U.S.C. § 346a(p)(6).

The unambiguous requirements of the FFDCA cannot be amended by NRDC's interpretation of "congressional purpose and common sense." Pet. Br. at 35. Congress imposed requirements to ensure that EPA's regulation of pesticides accounted for the completeness and reliability of available data; waiting for the results of the endocrine screening program was not one of those requirements. In rejecting NRDC's petition to revoke the tolerances, EPA explained why, in the absence of results from the screening program,

available data on DDVP's endocrine effects allowed EPA to evaluate DDVP's safety. A 225-26. NRDC did not object to that finding, and its legal argument is contrary to the statute.

C. EPA supported its children's safety factor decision with reliable, DDVP-specific data.

EPA properly denied NRDC's objection that EPA's choice of a 3X children's safety factor "is a generic assertion not based on any data specific to DDVP." A 252. NRDC's claim is flatly contradicted by the record.

In its denials of NRDC's petition and objections, EPA provided a comprehensive explanation of its reasoning on its children's safety factor decision stressing at each point the relevant DDVP data. In that explanation, EPA addressed each of the key factors mentioned in the children's safety factor provision – the completeness of the toxicity and exposure databases and potential pre- and post-natal toxicity – as well as all of the concerns raised by NRDC. With regard to the toxicity database, EPA focused on the completeness issues raised by NRDC – relating to developmental neurotoxicity and endocrine effects – explaining in detail what data was available on those effects and why that data could be reliably used in choosing a safe dose for infants and children. 72 Fed. Reg. at 68,676-77 and 68,984 (A 225-226 and 243). EPA also discussed the results of each study involving the testing of young animals and explained why it believed all

concerns regarding potential increased sensitivity in the young from pre- and post-natal toxicity were addressed by its risk assessment. *Id*. at 68,694 (A 243). In large part, this conclusion was based on data showing similar sensitivity in adults and the young to DDVP's cholinesterase effects, the effect that occurs at the lowest dose.[11] *Id*.

Based on this comprehensive evaluation, EPA determined that, for DDVP risks where the calculation of a safe dose was based on animal data, the additional factor for the protection of infants and children could be removed in its entirety. *Id*. However, EPA concluded that, for DDVP risks where calculation of a safe dose was based on the human data from the Gledhill study, a children's safety factor of 3X should be retained. This additional safety factor for infants and children was not retained because the Gledhill study involved only adults. As EPA has noted, cholinesterase data on DDVP in animals shows no differences in the responses of adults and the young. Rather, an additional safety factor was considered necessary because of a weakness in the Gledhill study – namely, the study only identified a dose level at which cholinesterase inhibition would occur and not a dose at

[11] In addition, EPA explained, as to each of its exposure assessments (food, water, and residential), why underlying data and EPA's conservative assumptions assured that the assessment would not understate exposure. To the extent NRDC questioned the completeness of EPA's exposure information, EPA responded in detail. 72 Fed. Reg. at 68,984-85 (A 243-45).

which cholinesterase would not be inhibited. *Id*. at 68,695 (A 244). Accordingly, EPA evaluated whether the uncertainty raised by this weakness in the Gledhill study warranted retention of the 10X children's safety factor or a different factor.

In conducting this evaluation, EPA, as is its practice, examined whether a full 10X factor was needed or whether a 3X factor (a value EPA considers to be half of 10X)[12] would be sufficient, rather than attempting to derive a mathematically precise value of the lowest possible safety factor needed to assess the risks of children. EPA concluded, after a close statistical examination of the level of the effects seen in the Gledhill study, that the data in the study showed that a 10X factor would be overprotective and that a 3X factor would sufficiently cabin the uncertainty surrounding

[12] EPA has explained in detail its scientific basis for why it considers half of a 10X safety factor to be 3X. 72 Fed. Reg. at 68,695 (A 244). More simply, EPA generally applies safety factors in increments of an order of magnitude or logarithmically when data are not available to quantitatively estimate a reduced safety factor. Thus, EPA generally does not use safety factors of 1X, 2X, 3X, 4X, etc., but rather factors of 1X, 10X, 100X, 1000X, etc. Because EPA uses logarithmic (order of magnitude) steps in choosing safety factors, if EPA decides to reduce an individual safety factor by half, it does so logarithmically. Accordingly, half of the logarithmic value of 10^1 would be $10^{0.5}$ or approximately 3. Put another way, given that EPA combines safety factors by multiplying them and not adding them (e.g., combining two safety factors of 10X yields a value of 100X not 20X), in reducing individual safety factors by half it is appropriate to take the square root of the factor not divide by two (e.g., thus half of a 10X factor is approximately 3X not 5X).

what dose would produce no measurable effect on cholinesterase inhibition (i.e., 3X would be more than sufficient to protect children). EPA's scientific conclusion on this point was confirmed by the Human Studies Review Board which concluded that "because the decreased activity in RBC [red blood cell] cholinesterase activity observed in this study was at or near the limit of what could be distinguished from baseline values, it was unlikely that a lower dose would produce a measurable effect in RBC cholinesterase activity." 72 Fed. Reg. at 68,695 (A 244). EPA's resolution of this complex scientific issue is entitled to the highest deference. *See, e.g., Browning-Ferris Indus.*, 899 F.2d at 160.

NRDC argues that EPA's decision was facially deficient in three respects, none of which is supported the FFDCA or the record in this case. First, NRDC claims that "EPA applied a threefold safety factor for dichlorvos simply because it considered that level to be about half as protective as a factor of ten." Pet. Br. at 37. This is simply wrong. EPA did not choose a 3X factor for DDVP because 3X is half of 10X but because it determined that the relevant DDVP data showed that a 3X factor would be safe. NRDC has confused the rationale EPA has used to choose what safety factor below 10X it will generally consider in determining whether the value

of 10X can safely be reduced, with EPA's justification for determining that a 3X safety factor protects the safety of children with respect to DDVP.

Moreover, NRDC is also wrong to the extent it is claiming that EPA was arbitrary because, as EPA admitted, it did not attempt "to mathematically derive a precise replacement safety factor." Pet. Br. at 37. NRDC misreads the FFDCA. The statute does not require a mathematically precise replacement safety factor; it requires that if EPA chooses a different factor that different factor must be "safe." 21 U.S.C. § 346a(a)(2)(C). EPA selected a safety factor it determined to be safe and explained the data that supported that finding. That was all that was required.[13]

Second, NRDC challenges EPA's choice of a 3X safety factor claiming that "EPA's exact reasoning on this point" was found deficient by

[13] EPA's remarks about mathematical precision have been taken out of context by NRDC. EPA was simply responding to NRDC's claim that EPA had to justify why it chose 3X and rather than 4X or some other number. As EPA explained:

> EPA disagrees with NRDC, however, to the extent it is suggesting that as part of this reasoned explanation for its selection of a children's safety factor, EPA must show why it did not choose some other mathematical value. Rather, the statute imposes upon EPA, if it decides to vary from the presumptive 10X children's safety factor, the burden to show that any "different" safety factor is safe. Once EPA has made that showing, its obligation to offer a reasoned explanation is complete.

73 Fed. Reg. at 42,696 (SPA 50).

the Ninth Circuit in *Northwest Coalition for Alternatives to Pesticides*, 544 F.3d at 1052, a case involving three different pesticides. Pet. Br. at 39. As NRDC acknowledges, however, the Ninth Circuit held that "EPA must provide a pesticide-specific explanation for why the particular margin of safety applied by the agency is safe." *Id*. at 38. In other words, each case must be decided on its own facts. EPA's reasoning on DDVP is in no way similar to its children safety factor determinations that were held to be arbitrary in *Northwest Coalition*. In that case, EPA offered basically one-sentence explanations for its children's safety factor decisions and failed to "explain the connection between the toxicological data and the 3X margin of safety selected . . . ." 544 F.3d at 1052. Here, EPA has provided an exhaustive rationale for its decision, and NRDC has done nothing other than make conclusory assertions about the lack of rationality in EPA's decision. Indeed, in its objections and in its opening brief, NRDC does not even acknowledge, must less confront, EPA's analysis of results of the Gledhill study – an analysis that was both confirmed by the Human Studies Review Board and central to EPA's choice of a 3X safety factor.

Finally, contradicting its prior "generic assertion" arguments, NRDC admits that EPA relied upon DDVP data in its children's safety factor determination, but claims that the data do not support EPA's decision. Pet.

Br. at 38-39. NRDC's argument here is that it was improper to consider (1) the Gledhill study in the children's safety factor determination because the test subjects in that study were adults; and (2) the animal data showing no difference in adult-young sensitivity to DDVP's cholinesterase effects – the very data that shows why the Gledhill study is appropriate for the entire population – because the *Northwest Coalition for Alternatives to Pesticides* case held relative sensitivity data cannot be used to justify a 3X safety factor. For multiple reasons, this argument must be rejected.

First, this claim was never exhausted before Agency, and thus this Court has no jurisdiction to consider it. *See Nat'l Corn Growers,* 613 F.3d at 272-73. NRDC argued the exact opposite position to EPA in its petition and objections – that EPA's children's safety determination was unlawful because it relied on "generic assertions" and not "on any data specific to DDVP." A 252. Second, the second prong of the argument is demonstrably false. The *Northwest Coalition* court held only that it was arbitrary for EPA not to explain how sensitivity information supported its decision, not that such information is irrelevant. NRDC's reading of the case would contradict the plain statutory language requiring EPA to assess risk to children based on "information concerning the special susceptibility of infants and children to the pesticide chemical residues . . . ." 21 U.S.C. 346a(b)(2)(C)(i)(II).

Third, EPA has in this proceeding addressed the question of the appropriateness of relying on the Gledhill study in assessing the DDVP risk. EPA specifically rejected NRDC's argument that the Gledhill study's use of adult subjects only made it "invalid for use by EPA to set exposure standards for a diverse population." A 260. EPA made this determination relying on the animal cholinesterase data showing no increased sensitivity to the young with regard to cholinesterase effects. 73 Fed. Reg. at 42,707 (SPA 61); 72 Fed. Reg. at 68,694 (A 243). NRDC has not challenged that scientific determination before this Court and that unchallenged determination is conclusive on this issue. Finally, to the extent that the Court believes it is appropriate to reach the merits of NRDC's claim on this point, EPA's explanation for why animal cholinesterase data show that the Gledhill data is relevant to infants and children is challenged only by NRDC's conclusory assertion that this approach is irrational. NRDC has offered no scientific evidence or argument on this point. In these circumstances, the Court must defer to EPA's scientific judgment.

EPA's decision to apply a 3X children's safety factor comported with the FFDCA and was amply supported by evidence in the record.

CONCLUSION

For the foregoing reasons, the petition for review should be denied.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains 13,166 words excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

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s/ Kent E. Hanson

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I hereby certify that a copy of the foregoing was served by first-class mail, postage pre-paid and by e-mail, on November 18, 2010, upon:

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