08-3771-ag
Natural Res. Def. Council v. EPA

UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

August Term, 2010

Argued: February 14, 2011 Decided: September 16, 2011

Docket No. 08-3771-ag

NATURAL RESOURCES DEFENSE COUNCIL,

Petitioner,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondent.

Before: POOLER, WESLEY, and CHIN, *Circuit Judges*.

Natural Resources Defense Council, Inc. ("NRDC") seeks review of an Environmental Protection Agency ("EPA") order overruling NRDC's objections to, inter alia, EPA's risk assessments for the pesticide dichlorvos, and denying NRDC's requests for a public evidentiary hearing. Because EPA conducted certain dichlorvos risk assessments without using a tenfold children's safety factor that Congress provided should presumptively apply, and EPA failed to explain why it did not apply this margin of safety, we grant NRDC's petition for review in part, vacate EPA's order in part, and remand for further proceedings.

AARON COLANGELO, Natural Resources Defense Council, Washington, D.C., *for Petitioner*.

KENT E. HANSON, U.S. Department of Justice, Environment & Natural Resources Division (Ignacia S. Moreno, Assistant Attorney General, Jonathan J. Fleuchaus, U.S. Environmental Protection Agency, Office of General Counsel), Washington, D.C., *for Respondent*.

POOLER, *Circuit Judge*:

The pesticide dichlorovinyl dimethyl phosphate ("DDVP" or "dichlorvos") is used to kill many types of insects. Depending on the level of one's exposure to dichlorvos, the pesticide also may disrupt proper functioning of the human nervous system. To determine safe levels of exposure to dichlorvos for certain exposure scenarios, the Environmental Protection Agency ("EPA") relied heavily on a single study in which six people were paid to ingest a dose of the pesticide every day for three weeks. After the study detected an adverse effect, EPA used the study to attempt to estimate, to a reasonable certainty, an aggregate level of exposure to dichlorvos at which no harm would result. EPA then set tolerances regarding the maximum level of dichlorvos residue on food products. EPA also registered numerous dichlorvos products for sale and distribution in the United States.

In June 2006, NRDC petitioned EPA to revoke all tolerances and cancel all registrations for dichlorvos. EPA denied the petition and in response NRDC filed objections and requests for a public evidentiary hearing. EPA denied those requests in a July 23, 2008 final order. NRDC now seeks review of that EPA order, arguing in part that EPA failed to explain why, when assessing the safety of dichlorvos for certain exposure scenarios, EPA did not apply an additional tenfold children's safety factor, to account for potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children. Because such an explanation is required under the Food Quality Protection Act of 1996 ("FQPA"), *see* 21 U.S.C. § 346a(b)(2)(C)(ii), we grant NRDC's petition for review in part, vacate EPA's June 23, 2008 order in part, and remand for further proceedings.

NRDC also appeals EPA's decision not to apply the tenfold children's safety factor for certain risk assessments in which EPA did not rely on the above-mentioned human study. In this regard, NRDC argues only that EPA cannot reduce or waive the tenfold children's safety factor unless and until it completes the FQPA-mandated endocrine disruptor screening program. We reject this argument. FQPA allows EPA to reduce or waive the tenfold margin of safety if "reliable data" indicate that a lower margin of safety will be safe for infants and children. FQPA does not require the "reliable data" to come from the endocrine disruptor screening program. Accordingly, we deny in part NRDC's petition for review.

Lastly, having vacated the portions of EPA's June 23, 2008 order assessing the risk of dichlorvos based on the above-mentioned human study, we need not decide whether NRDC is entitled to a public evidentiary hearing regarding that study's alleged statistical invalidity and failure to obtain informed consent.

I. The Statutory Authority for the EPA's Regulation of Pesticides

A.

EPA oversees a comprehensive scheme of pesticide regulation under the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301-94, and the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), 7 U.S.C. §§ 136-36y.

FDCA regulates pesticide residues in the food supply and requires EPA to establish tolerance levels (or exemptions) for the maximum permissible level of pesticide residue on food products. 21 U.S.C. § 346a(a)-(c). "Before any agricultural commodity containing pesticide residue can be sold or distributed, a tolerance (or exemption) meeting certain safety standards must be promulgated by the EPA." *Natural Res. Def. Council v. Johnson*, 461 F.3d 164, 167 (2d Cir. 2006). Under FDCA, a safe tolerance for a pesticide is determined by considering "aggregate exposure" to the

pesticide, including "all anticipated dietary exposures." 21 U.S.C. § 346a(b)(2)(A)(ii).

FIFRA has a slightly different focus, but is linked with FDCA in an important regard. FIFRA establishes a pesticide registration system and requires EPA to set the conditions under which pesticides may be sold or distributed in the United States. 7 U.S.C. § 136a(c)(5); *see also id.* § 136q (regulating labeling, packaging, composition, and disposal). In determining whether to register a pesticide under FIFRA, EPA must consider whether the pesticide is safe under FDCA. *Id.* § 136a(c)(5)(C). In particular, EPA may not register or reregister a pesticide if it determines that the pesticide would cause "unreasonable adverse effects on the environment," *id.*, which includes an "unreasonable risk to man" or a "human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under [21 U.S.C. § 346a]," *id.* § 136(bb). In addition, if EPA determines that a registered pesticide causes "unreasonable adverse effects on the environment," it may cancel the registration. *Id.* § 136d(b)(1).

B.

In 1988, Congress asked the National Academy of Sciences ("NAS") to appoint a committee to study the vulnerability of infants and children to pesticide residues. Five years later, the NAS's National Research Council released a report on the issue, concluding that "[t]raditional approaches to toxicological risk assessment may not always adequately protect infants and children" and recommending various reforms. National Research Council, *Pesticides in the Diets of Infants and Children* at 360 (1993), *available at* http://www.nap.edu/catalog.php?record_id=2126 (hereinafter, "Nat'l Research Council, *Pesticides Report*"). *See also id.* at 359-63.

In 1996, in response to the National Research Council report, and aiming to better coordinate the safety standards in FIFRA and FDCA, Congress passed the Food Quality Protection Act ("FQPA"). Pub. L. No. 104-170, 110 Stat. 1489 (1996). Three changes are most relevant here.

First, FQPA established a new safety standard for pesticide tolerances. Under FQPA, a pesticide tolerance is "safe" when "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). In making this determination, Congress required EPA to consider, among other things, "the validity, completeness, and reliability of the available data from studies," the anticipated and actual residue levels of the pesticide in or on foods, "the dietary consumption patterns of consumers," "the percent of food actually treated with the pesticide," and international standards. *See id.* § 346a(b)(2)(D)-(F), (b)(4). Further, Congress required EPA to consider

> safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data.

Id. at § 346a(b)(2)(D)(ix). In this regard, the House Report noted that it "expect[ed], based on discussions with [EPA]," that EPA would apply "a 100-fold safety factor . . . to the scientifically determined 'no observable effect' level when data are extrapolated from animal studies." H.R. Rep. No. 104-669, at 32 (1996) (limiting this requirement to threshold effects, in which EPA "is able to identify a level at which the pesticide chemical residue will not cause or contribute to any known or anticipated harm to human health").

Second, Congress required EPA to assess the risk of pesticide residue to infants and children when "establishing, modifying, leaving in effect, or revoking a tolerance or exemption." 21 U.S.C. § 346a(b)(2)(C). In assessing the risk, Congress required EPA to consider available information about:

> [I] consumption patterns among infants and children that are likely to result in disproportionately high consumption of foods containing

> or bearing such residue among infants and children in comparison to the general population; . . .
>
> [II] the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of in utero exposure to pesticide chemicals; and . . .
>
> [III] the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity.

21 U.S.C. § 346a(b)(2)(C)(i).

For each pesticide tolerance, Congress required EPA to "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)(I). To make this determination, Congress required EPA to use "an additional tenfold margin of safety . . . 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)(ii) (limiting this requirement to threshold effects). EPA "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." *Id.* (emphasis added).

Lastly, given FQPA's substantial changes to the method of determining pesticide safety, "FQPA required that the EPA reassess the safety of all then-existing tolerances." *Johnson*, 461 F.3d at 168. For this review, Congress required EPA to determine whether each tolerance is "safe" or exempt from the tolerance requirement. 21 U.S.C. § 346a(q)(1). If a tolerance is neither safe nor exempt, EPA must modify or revoke the tolerance. *Id.* Because this tolerance reassessment program runs concurrent to FIFRA's reevaluation of pesticide registrations, *see* 7 U.S.C. § 136a-1, and because both programs rely on the same underlying risk assessments for pesticides, *see id.* §§ 136(bb), 136a(c)(5)(C), EPA frequently has used Interim Reregistration Eligibility Decisions

("IREDs") to announce decisions on both tolerance reassessment and pesticide reregistration. *Johnson*, 461 F.3d at 169.

C.

To challenge an existing tolerance, "[a]ny person" may file with EPA a petition proposing that EPA "modify[] or revok[e] a tolerance for a pesticide chemical residue in or on a food." 21 U.S.C. § 346a(d)(1)(A). EPA requires such a petitioner to "furnish reasonable grounds for the action sought," such as "an assertion of facts (supported by data if available) showing . . . that experience with the application of the tolerance or exemption from tolerance may justify its modification or revocation." 40 C.F.R. § 180.32(b).

If EPA denies the petition, it must issue a regulation or order explaining its reasons. 21 U.S.C. § 346a(d)(4)(A). Within sixty days after such regulation or order is issued, "any person"—not just the petitioner—"may file objections thereto" with EPA. *Id.* § 346a(g)(2)(A). The objections must "specify[] with particularity the provisions of the regulation or order deemed objectionable and stat[e] reasonable grounds therefor." *Id.*

In addition, a party's objections may include "a request for a public evidentiary hearing upon the objection." *Id.* § 346a(g)(2)(B). The party is entitled to a public evidentiary hearing "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." *Id.* EPA's implementing regulations provide that a request for a hearing "will be granted" when the requesting party shows that:

> (1) There is a genuine and substantial issue of fact for resolution at a hearing. An evidentiary hearing will not be granted on issues of policy or law.
>
> (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, taking into account uncontested

> claims or facts to the contrary. . . .
>
> (3) Resolution of the factual issue(s) in the manner sought by the person requesting the hearing would be adequate to justify the action requested. . . .

40 C.F.R. § 178.32(b).

After considering the objections and requests for a hearing, EPA must issue a final order stating the action taken on each objection and request for a hearing. 21 U.S.C. § 346a(g)(2)(C). "Any person who will be adversely affected by such order" may obtain judicial review by filing an appeal in the appropriate circuit court of appeals. *Id.* § 346a(h)(1). Where such a person also "challenge[s] the registration of pesticides under FIFRA," but does so only through a challenge to the tolerances set under the FDCA, such a challenge "represent[s] an issue as to which review is . . . obtainable under Section 346a(h)" in the appropriate circuit court of appeals. *Johnson*, 461 F.3d at 176 (internal quotation marks omitted).

II. NRDC's Petition to Revoke the Dichlorvos Tolerances

A.

This appeal concerns NRDC's petition requesting that EPA revoke all tolerances and cancel all registrations for dichlorvos. Dichlorvos is a synthetic pesticide used to kill many insects, including flies, mosquitos, gnats, cockroaches, and fleas. Dichlorvos belongs to a family of pesticides known as organophosphates, developed from nerve warfare agents after World War II. Like other organophosphates, dichlorvos can disrupt proper functioning of the nervous system by inhibiting an important enzyme, cholinesterase, in red blood cells and the brain. Currently, only Amvac Chemical Corporation is registered to manufacture dichlorvos in the United States.

Since 1982, EPA has expressed varying degrees of concern about dichlorvos's safety. After studying the issue, EPA proposed in 1987 to require a cancer warning on dichlorvos products. In

1988, EPA "concluded that dichlorvos is a potential human carcinogen" and issued a Notice of Special Review, stating that "dichlorvos may pose a risk of inducing in humans an oncogenic, heritable genetic, or chronic or delayed toxic effect." Notice of Initiation of Special Review for Dichlorvos, 53 Fed. Reg. 5542, 5543 (Feb. 24, 1988) (alterations, internal quotation marks, and ellipses omitted). In 1995, EPA issued a preliminary determination of the Special Review process. EPA "concluded that the risks outweigh the benefits for most uses of dichlorvos" and proposed to cancel most uses of dichlorvos, including all residential uses. Notice of Preliminary Determination to Cancel Certain Dichlorvos Registrations, 60 Fed. Reg. 50338, 50338 (Sept. 28, 1995).

Before EPA issued a final determination of the Special Review process, Congress passed FQPA. Thereafter, EPA began to reevaluate dichlorvos under the new FQPA safety standards. In 2000, EPA released a preliminary risk assessment for dichlorvos, *see* Dichlorvos Preliminary Risk Assessment, 65 Fed. Reg. 60430, 60431 (Oct. 11, 2000), and did not implement its earlier proposed cancellations. On May 16, 2006, EPA announced that the sole dichlorvos registrant, Amvac, proposed to add new restrictions to its product labels, in an attempt to ensure the products' safe use. The labels included restrictions that larger pest strips "cannot be used in homes except in garages, attics, crawl spaces, and sheds that are occupied for less than four hours per day"; and that use of smaller pest strips in the home be "limited to closets, wardrobes, and cupboards." Further, Amvac proposed to "voluntarily delet[e] other uses of [dichlorvos] including: mushroom house, greenhouse, and warehouse handheld fogger uses; total release fogger, as well as lawn, turf/ornamental and crack/crevice uses."

Less than three weeks later, NRDC petitioned EPA to find that dichlorvos "causes unreasonable adverse effects on the environment" and to "revoke all tolerances and cancel all registrations for [dichlorvos]."

B.

In its petition, NRDC requested that EPA revoke all tolerances and cancel all registrations for dichlorvos. NRDC argued, inter alia, that EPA relied on inadequate data in its 2000 preliminary risk assessment, inadequately performed that risk assessment, and failed to apply required safety factors. Despite the numerous issues raised in its petition, we focus here on only the two issues relevant to NRDC's appeal: (1) EPA's reliance on a 1997 intentional human dosing study by A.J. Gledhill; and (2) EPA's failure to provide a legally adequate rationale for applying a children's safety factor lower than the FQPA's presumptive 10X factor.

1.

In its petition, NRDC argued that EPA "must reject" the Gledhill study, in which human subjects were paid to ingest dichlorvos, for two reasons. First, NRDC argued that the Gledhill study "included only 6 treated subjects and 3 controls" and with such a small sample size, "the results of the study are statistically meaningless and could never be used to establish safety." NRDC highlighted other alleged defects with the study, including the delay in sampling the subjects' cholinesterase levels, the failure to test for plasma cholinesterase, and the lack of controlled environmental conditions.

Second, NRDC argued that the Gledhill study did not comply with EPA's ethical research rule. That rule forbids EPA from relying on data from research initiated before April 7, 2006 if there is "clear and convincing evidence" that the research was either:

> [1] fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent), or
>
> [2] significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

40 C.F.R. § 26.1704. NRDC asserted that the Gledhill study was both "fundamentally unethical and

significantly deficient relative to prevailing ethical standards at the time." NRDC argued that the Gledhill study (a) "failed to obtain fully informed and voluntary consent" from the subjects, in part because the consent form characterized dichlorvos as a "drug" instead of a pesticide; (b) failed to provide the subjects "free power of choice"; (c) was designed "only to enrich the registrant by weakening safety standards," not "to yield fruitful results for the good of society"; (d) "caused avoidable harm"; and (e) incurred a degree of risk that "exceeded any humanitarian importance."

2.

NRDC also argued that EPA must apply FQPA's presumptive 10X children's safety factor when assessing the risk posed by dichlorvos. NRDC noted that EPA had applied a FQPA children's safety factor of 3X in its preliminary risk assessment, and NRDC suspected that EPA intended in its forthcoming IRED "to remove the FQPA safety factor entirely, as a result of a deal negotiated privately with Amvac." Either way, NRDC argued that "[i]n the absence of [1] reliable data and [2] a legally adequate rationale" for a lower safety factor, EPA was required to apply FQPA's presumptive 10X children's safety factor to determine tolerances for dichlorvos products.

First, NRDC argued that "reliable data" did not show that a children's safety factor less than 10X would be safe for infants and children. This safety factor, as NRDC noted, is designed "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." *See* 21 U.S.C. § 346a(b)(2)(C)(ii). Specifically, NRDC argued that the "potential for pre- and post-natal toxicity from exposure to [dichlorvos]," as "cited by EPA in its preliminary human health risk assessment," "combined with incomplete data regarding toxicity and exposure to infants and children, compel EPA to retain the default FQPA tenfold safety factor for [dichlorvos]." NRDC alleged various examples of "critical missing data,"

including that (a) "the results of adult testing are not a useful measure of children's toxicity"; (b) EPA did not implement an endocrine disruptor screening program with respect to dichlorvos, as required by FQPA; and (c) evidence of pre- and post-natal toxicity in animals "constitute evidence of possible increased sensitivity" in children and infants, requiring EPA to demonstrate that "a safety factor less than 10X will be safe for children and infants."

Second, NRDC argued that EPA "provided no explanation why an FQPA safety factor [less than 10X] is adequate to protect against the uncertainties in the database including the risk of increased sensitivity of children and infants." NRDC further asserted that EPA lacked a scientific explanation because of "political interference in the safety factor decision," citing EPA's alleged decision to withdraw the determination from staff scientists.

C.

A year and a half after NRDC filed its petition to revoke all dichlorvos tolerances and registrations, EPA published an order denying the petition. Order Denying NRDC's Petition to Revoke All Tolerances, 72 Fed. Reg. 68662 (Dec. 5, 2007). As an initial matter, after NRDC filed its petition, EPA released the Interim Reregistration Eligibility Decision ('IRED') for DDVP. *See* EPA, Office of Pesticide Programs, *Interim Reregistration Eligibility Decision for Dichlorvos (DDVP)* (2006), *available at* http://www.epa.gov/oppsrrd1/reregistration/ REDs/ddvp_red.pdf (hereinafter, "EPA, *Dichlorvos IRED*"). As EPA later explained, the IRED "addressed DDVP's eligibility for reregistration under FIFRA and assessed whether DDVP's tolerances met the new safety standard enacted by the FQPA." 72 Fed. Reg. at 68670. In the IRED, EPA approved the use of dichlorvos products in many residential areas, such as homes, closets, garages, and cupboards; commercial areas, such as picnic areas, ice cream stands, restaurants, and theaters; and agricultural areas, such as diary barns, poultry houses, and feed lots. EPA, *Dichlorvos IRED* at 11, 32-33, 36-39,

44-45. EPA noted that "NRDC submitted comments on the IRED" and stated that it would consider those comments as well, to the extent they "bore on issues in [NRDC's] petition." 72 Fed. Reg. at 68670.

In its response, as relevant here, EPA first provided an overview of its general method of risk assessment. EPA then addressed and rejected NRDC's arguments regarding the Gledhill study and the FQPA children's safety factor.

1.

In describing its general approach to determining the safety of pesticide residue to humans under FQPA, EPA stated that it applies a risk assessment process that "combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide." 72 Fed. Reg. at 68664. EPA evaluates "both short-term (e.g., 'acute') and longer-term (e.g., 'chronic') adverse effects from pesticide exposure." *Id.* For pesticides like dichlorvos in which EPA determines that the pesticide's adverse effect or effects have a threshold—that is, "a level below which exposure has no appreciable chance of causing the adverse effect"—EPA attempts to calculate a safe level of exposure. *Id.*

For the approach most relevant here, EPA "evaluates an array of toxicological studies on the pesticide" and "[i]n each of these studies, EPA attempts to identify the lowest observed adverse effect level ('LOAEL') and the next lower dose at which there are no observed adverse affect levels ('NOAEL')." *Id.* "Generally, EPA will use the lowest NOAEL from the available studies as a starting point in estimating the level of concern for humans." *Id.*

Once EPA identifies the NOAEL for an exposure scenario, EPA then determines "the margin of exposure (MOE) that is necessary to be sure that exposure to [the] pesticide is safe." *Id.* at 68665. "A safe MOE is generally considered to be a margin at least as high as the product of all applicable

safety factors for [the] pesticide." *Id.* This approach is similar to an engineer who estimates that a bridge must hold X weight, and then designs the bridge in a way that she believes will hold 3X weight, to create a margin of safety based on prior engineering practice.

As EPA acknowledges, "the use of safety factors plays a critical role in the process" it uses to assess risk. *Id.* at 68668. Generally, EPA applies at least two separate 10X safety factors, resulting in a safe margin of exposure of at least 100X. *Id.* The "traditional 10X safety factors [] account for differences between animals and humans when relying on studies in animals (inter-species safety factor) and differences among humans (intra-species safety factor)." *Id.* This approach is consistent with the House Report accompanying FQPA, which stated that it "expect[ed], based on discussions with [EPA]," that EPA would apply "a 100-fold safety factor . . . to the scientifically determined 'no observable effect' level when data are extrapolated from animal studies." H.R. Rep. No. 104-669 at 32(1996) (noting that EPA could change its approach if such approach was "adopted by regulation," "scientifically based," and "at least equally protective of public health").

In addition to the traditional safety factors, FQPA established a presumptive—and "additional"—tenfold children's safety factor. *See* 21 U.S.C. § 346a(b)(2)(C)(ii). As Congress described, this safety factor was designed "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to infants and children." 21 U.S.C. § 346a(b)(2)(C)(ii).

Further, EPA noted that "[a]dditional safety factors may be added to address data deficiencies or concerns raised by the existing data." 72 Fed. Reg. at 68665. For example, in some cases EPA is unable to identify a NOAEL in any of the relevant studies and must estimate a NOAEL by extrapolating from a LOAEL in a study that did not find a NOAEL. *See* Order Denying NRDC's Objections and Requests for Hearing, 73 Fed. Reg. 42683, 42686 (July 23, 2008). In some cases,

EPA also chooses to estimate a NOAEL from a LOAEL despite the existence of a NOAEL in another study. *Id.* In either case, there may be considerable uncertainty about the true value of the NOAEL. *See* Order Denying Objections to Issuance of Tolerances, 70 Fed. Reg. 46706, 46729 (Aug. 10, 2005) (requiring "sufficient toxicological evidence [regarding a LOAEL] to estimate with confidence a projected NOAEL that is unlikely to be higher than the actual NOAEL") (incorporated into EPA response to NRDC, *see* 72 Fed. Reg. at 68673). To estimate a NOAEL from a LOAEL, EPA typically "divid[es] the LOAEL by a safety factor." *Id.* The size of the LOAEL-to-NOAEL safety factor depends on "the severity and consistency of the effect at the LOAEL as well as the [effect's] severity and consistency at higher doses." 72 Fed. Reg. at 68673.

Once EPA has identified a safe margin of exposure, EPA calculates the actual MOE for a number of exposure scenarios. The actual MOE is designed to measure how much of a pesticide a person would be exposed to under a given exposure scenario. To compare this actual amount to the safe MOE, EPA divides the "no observable adverse effect level" (NOAEL) by the actual exposure, where both are expressed in common units of exposure per day. *Id.* at 68665. "[T]he higher the [actual] MOE, the safer the pesticide." *Id.* "Accordingly, if the [safe MOE] for a pesticide is 1,000, [actual] MOEs exceeding 1,000 would generally not be of concern." *Id.* In contrast, an actual MOE less than the safe MOE would be of concern.

For example, suppose EPA relies on a study by A.J. Gledhill in which an adverse effect is found when 70-kilogram white men ingest 7 grams of dichlorvos per day for three weeks. Per kilogram of body weight, the effect is present at 0.1 milligrams/kilograms/day. Because of the study's (less than ideal) design, it identifies only a LOAEL (0.1 mg/kg/day), not a NOAEL. EPA performs a LOAEL-to-NOAEL estimation, determining that a 3X uncertainty factor is appropriate for this estimation. In addition, EPA finds applicable the two traditional 10X safety factors for inter-

and intra-species uncertainty, as well as FQPA's 10X children's safety factor. Thus, the safe MOE is 3,000 (3X * 10X * 10X * 10X). EPA then calculates the actual MOE for an exposure scenario, such as intermediate-term dermal (skin) exposure in a greenhouse two hours after a smoke generator spreads dichlorvos. EPA calculates dermal exposure in such a scenario to be 0.00125 mg/kg/day and then divides that number into the NOAEL of 0.1 mg/kg/day, resulting in an actual MOE of 80. Given the safe MOE of 3,000—based on the application of numerous safety factors—the actual margin of exposure of 80 is less than the safe margin of exposure, indicating that exposure to dichlorvos in such a scenario is not safe.

This example comes directly from EPA's IRED for dichlorvos. *See* EPA, *Dichlorvos IRED* at 177-178, 185-87. Moreover, it comes unchanged—with one exception. In the IRED, EPA calculated the safe margin of exposure to be 30 and thus found that the actual MOE of 80 for occupational intermediate-term dermal exposure to dichlorvos was "not of concern." *Id.* at 176, 178, 187. Unlike above, EPA applied neither the inter-species 10X safety factor, nor the 10X children's safety factor. *Id.* at 134. At this point, we note the different choices only to highlight that safety factors are very important under EPA's margin of exposure approach to determining the safety of pesticide residue to humans. Indeed, the safety factors often are the difference between the withdrawal of a pesticide from the market and its continued use. *E.g.*, *id.* at 165 (calculating that actual MOEs for long-term residential exposure to resin pest strips, even in limited uses, are below 100; and that the actual MOE for long-term residential exposure to pet flea collars is 39).

2.

After the risk assessment overview, EPA responded to the arguments raised in NRDC's petition. First, EPA considered NRDC's argument that the Gledhill study's results "are statistically meaningless and could never be used to establish safety." EPA acknowledged that the Gledhill

study used only 9 subjects (3 of whom received a placebo) and that "as a general matter more subjects would provide greater 'statistical power.'" 72 Fed. Reg. at 68675. However, EPA argued that "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." *Id.*

EPA stated that the Gledhill study was consistent with NRDC's argument that dichlorvos inhibited cholinesterase activity. In the study, "all of the 6 dosed subjects exhibited statistically significant (with respect to their pre-dose levels) [red blood cell] cholinesterase depression on one or more days." *Id.* EPA also stated that it found a statistically significant difference between the cholinesterase group means of the dosed subjects and those of the placebo subjects on five of the eight measured dosing days. *Id.*; 73 Fed. Reg. at 42703. EPA concluded that "[t]he statistics of the study clearly show the ability to demonstrate a statistically significant response." 72 Fed. Reg. at 68675. Because the Gledhill study found an effect when the 70-kg subjects ingested 7 mg of dichlorvos per day, EPA calculated that the effect occurred at a level of 0.1 mg/kg/day.

EPA characterized this effect as a LOAEL for two reasons. First, the Gledhill study "did identify an effect above background," and second, the effect appeared to be "not large." *Id.* That is, EPA reasoned that the study showed some adverse effect, and that effect was sufficiently low to act as the LOAEL—the lowest observed adverse effect level. EPA stated that it then "adjusted" that value "with a safety factor of 3X to approximate the value of a NOAEL." *Id.* at 68673. With respect to the magnitude of the adverse effect in the Gledhill study, EPA stated that it appeared "not large" because the "cholinesterase inhibition in [dosed] individuals varied from baseline within a range from 8 to 23 percent at the end of the study." *Id.* However, EPA did not explain whether the Gledhill study, with 6 dosed subjects and 3 placebo subjects, had sufficient statistical power to determine with any level of precision the magnitude of the cholinesterase inhibition.

In addition to finding the Gledhill study statistically valid for a limited purpose, EPA rejected NRDC's argument that the study violated EPA's ethical research rule. EPA acknowledged that the study's consent forms referred to dichlorvos as a "drug," but its independent experts found that the forms "clearly advised subjects that this was a study involving consuming an insecticide." *Id.* at 68675 (internal quotation marks omitted). Further, EPA acknowledged that there were "deficiencies in the monitoring of subjects both during and after the conclusion of the study," but found that "prior studies by this researcher involving higher doses had only invoked minimal responses." *Id.* Therefore, EPA concluded that there was no "clear and convincing evidence" that the Gledhill study was "fundamentally unethical" or "significantly deficient relative to the ethical standards prevailing at the time the research was conducted." *Id.* at 68674-75 (quoting 40 C.F.R. § 26.1704).

In sum, after finding the Gledhill study statistically valid for a limited purpose and not in violation of EPA's ethical research rule, EPA concluded that it could rely on the study. In fact, EPA reported that it "did rely on the Gledhill study in assessing the risk posed by DDVP" and did so "for several exposure scenarios." *Id.* at 68674.

3.

Lastly, EPA rejected NRDC's argument that EPA "has no basis upon which to apply anything lower than a 10X FQPA [children's safety] factor in the DDVP risk assessment." *Id.* at 68694. EPA stated that it has "reliable data showing it is safe for infants and children to remove the additional [10X] safety factor for all risk assessments other than [various] residential assessment[s]." *Id.* EPA acknowledged that FQPA requires it to "take into account potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children." *Id.* With respect to risk assessments that did not rely on the Gledhill study, EPA concluded that (1) "[t]he toxicity database is complete"; (2) "[t]here are no residual concerns for pre- and/or post-

natal toxicity resulting from exposure to dichlorvos," given certain "rat and rabbit developmental studies, [in which] no developmental effects were observed"; and (3) its residential and dietary exposure estimates "will [] not underestimate exposure given [EPA's] conservative assumptions." *Id.*

In contrast, for the residential risk assessments based on the Gledhill study, EPA stated that it "retained a FQPA safety factor of 3X." *Id.* at 68695. EPA clarified that this 3X safety factor was not based on its evaluation of any risk to infants or children. Rather, "[t]his additional safety factor is due to [the various residential] assessments' reliance on a LOAEL rather than a NOAEL" because the Gledhill study did not find a NOAEL. *Id.* That is, to estimate a NOAEL from a LOAEL, "EPA determined that a 3X safety factor would be more than adequate to identify a NOAEL based upon the slight adverse effect (marginal [red blood cell] cholinesterase inhibition in [the Gledhill] human study) observed at the LOAEL" in the Gledhill study. *Id.* As with the other assessments, EPA declined to apply a safety factor based on a risk to infants in children. *Id.*

EPA's decision not to apply a 10X children's safety factor in its risk assessments affected EPA's determination of the safe margins of exposure for dichlorvos as follows. EPA relied on the Gledhill human study for the following residential and occupational exposure scenarios: (1) short-, intermediate-, and long-term dermal and (2) short- and immediate-term inhalation of vapors or during application. EPA, *Dichlorvos IRED* at 138, 176. EPA also relied on the Gledhill study for residential short-term incidental oral exposure. *Id.* at 138. For each of these scenarios, EPA used a 10X safety factor to "account for intraspecies variability" and applied a 3X factor "for lack of a NOAEL" in the Gledhill study, for a total MOE of 30. *Id.* at 133-35. Since the Gledhill study was conducted in human subjects, EPA found "there was no need to account for interspecies extrapolation" and thus declined to apply an inter-species safety factor for risk assessments based

on the Gledhill study. *Id.* at 133. In addition, for such risk assessments EPA did not apply a safety factor based on risk to children or infants. *See Id.*

For acute and long-term inhalation of dichlorvos vapors in residential and occupational settings, EPA did not rely on the Gledhill study to calculate margins of exposure. *Id.* at 138, 176. For each of these scenarios, EPA applied a 10X intra-species safety factor. *Id.* at 135, 138, 176. In addition, EPA stated that "[s]ince the NOAEL is expressed in concentration units (RfC methodology)" for the acute and long-term exposure scenarios, "the interspecies extrapolation factor is 3X." *Id.* at 139, 176. Lastly, EPA stated that "[t]he FQPA Safety Factor has been reduced to 1X, since [EPA] analysis of studies with pup and adult [cholinesterase] depression results did not demonstrate any substantial numerical differences in [lowest observable adverse effect] values (all values were approximately 1 mg/kg)." *Id.* at 132. The resulting margin of exposure was 30. *Id.* at 135.

Finally, for dietary, acute dermal, and acute incidental oral exposure scenarios, EPA applied the traditional inter- and intra-species safety factors but found the children's safety factor unnecessary. *See id.* at 130-34. Because EPA did not express the NOAEL in concentration units for these exposure scenarios, EPA did not reduce the inter-species safety factor to 3X. *Id.* at 138-39. For these exposure scenarios, the resulting MOE was 100. *Id.*

In sum, EPA applied a margin of exposure of 30 for all but the dietary, acute dermal, and acute incidental oral exposure scenarios. As a result, although numerous uses of dichlorvos had a low actual MOE, EPA found that such uses were safe. *E.g.*, *id.* at 165 (calculating actual MOEs for long-term exposure to closet-sized resin pest strip (34), small closet strip (48), cupboard strip (95)); *id.* at 182-88 (calculating actual MOEs for occupational exposure in mushroom houses, greenhouses, railcars, and trucks); *see also* 72 Fed. Reg. at 68687-91 (revising pest strip exposure data, but

concluding that "the pest strips do not pose a risk of concern").

D.

Within 60 days after EPA issued an order denying NRDC's petition, NRDC submitted its objections to EPA. In addition, NRDC exercised its right under FQPA to request "a public evidentiary hearing upon the objection[s]." *See* 21 U.S.C. § 346a(g)(2)(B).

1.

Again, NRDC argued that EPA could not legally rely on the Gledhill human study because the study "is unethical, unscientific, and statistically invalid." With respect to the study's scientific validity, NRDC first argued that the study did not measure the true magnitude of adverse effects. Because the Gledhill study tested for cholinesterase inhibition in red blood cells "24 hours after ingestion and just before the next dose is administered," NRDC argued that this testing regime "was apparently designed to detect [cholinesterase] effects at the lowest ebb each day, and not to measure true adverse effects." In addition, NRDC argued that "the 4 day delay in taking the last [red blood cell] sample appears obviously intended to allow [cholinesterase] values to return closer to normal than would have been the case if the last sample had been taken promptly." Further, NRDC argued that the Gledhill study's "failure to measure plasma levels is also a serious flaw in the study, because plasma levels could be a more sensitive indicator of [cholinesterase] effects" than red blood cell measurements.

NRDC also objected to the Gledhill study's use of "only 6 dosed subjects." NRDC argued that "six test subjects is far too small a number to provide a sound basis for extrapolating NOAELs or dose response curves to the general human population." "The lack of statistical power" of the Gledhill study, NRDC argued, "is exacerbated by the fact that the toxic endpoint"—cholinesterase inhibition in red blood cells—is "quite variable, not only between humans, but also in individuals

measured over time." Given the large range of variability, NRDC argued that "[t]he inadequate number of test subjects employed renders the study far too insensitive to establish either NOAELs or dose response curves for any [cholinesterase] effects."

With respect to whether the study violated EPA's ethical research rule, NRDC argued that EPA was "well aware" of the numerous alleged "ethical deficiencies of [the Gledhill] study"—indeed, EPA wrote a memorandum on the subject—but that EPA wrongly concluded that the study did not violate the ethical research rule. Further, NRDC argued that EPA did not explain "why the failure to take proper steps to protect the health of the test subjects and the failure to obtain informed consent do not render the study 'fundamentally unethical.'" Lastly, NRDC "relie[d] on and incorporate[d]" into its objections two commentaries and two letters, published in scientific journals, that specifically critiqued the scientific validity and ethics of the Gledhill study.

2.

NRDC also continued to object to EPA's failure to apply the FQPA children's safety factor, arguing that "EPA lacks reliable data to reduce the default tenfold safety factor." NRDC argued that because there was evidence of "potential pre- and post-natal toxicity" and there was "incomplete data with respect to exposure and toxicity to infants and children," EPA was compelled to apply the full 10X children's safety factor.

NRDC provided a number of examples of allegedly incomplete data. With respect to endocrine disruption, NRDC argued that EPA had not implemented an endocrine disruptor screening program, and "[t]he studies relied on by EPA were not designed to detect endocrine disruption." Further, NRDC argued that a two-generation rat reproduction study relied on by EPA was defectively designed because—as EPA acknowledged—it "did not include certain evaluations that [EPA's] 1998 [endocrine] guidelines recommended," 72 Fed. Reg. at 68676. "In the absence of

adequate data about endocrine disruption effects," NRDC argued, "EPA lacks reliable data to waive the FQPA 10X safety factor, especially in light of EPA's mandatory duty to investigate the potential of DDVP to cause endocrine disruption."

With respect to dietary exposure, NRDC alleged various weaknesses in the data regarding infant consumption, on which EPA relied in its preliminary risk assessment for dichlorvos. Acknowledging that EPA "claims to now have more infant consumption data," NRDC argued that "EPA does not assert that these data represent a statistically adequate or representative sample." Absent "reliable data about infant consumption," NRDC argued that "EPA may not depart from the 10X FQPA safety factor."

3.

Lastly, NRDC specified the disputed issues on which it would be "necessary to receive factual evidence" at a public evidentiary hearing. *See* 21 U.S.C. § 346a(g)(2)(B). In light of its above objections, NRDC requested a hearing to determine:

> (1) Whether reliable data support EPA's reduction of the FQPA tenfold safety factor. . . .
>
> (2) Whether the DDVP human study relied on by EPA is ethical, scientifically valid, or statistically meaningful.

NRDC discussed the disputed issues in greater detail when it specified its objections and concluded that "[e]ach of the disputed factual issues is sufficient either standing alone or in the aggregate to compel revocation of all DDVP tolerances."

E.

Five months later, EPA denied NRDC's objections regarding (1) the Gledhill study and (2) the FQPA children's safety factor. Order Denying NRDC's Objections and Requests for Hearing, 73 Fed. Reg. 42683, 42710-11 (July 23, 2008). EPA also denied NRDC's requests for a

hearing. *Id.*

1.

In its denial order, EPA rejected NRDC's statistical power arguments, stating that the Gledhill study showed an adverse effect and could be used to estimate a NOAEL from the study's LOAEL. 73 Fed. Reg. at 42704-06. EPA argued that the study was "sufficiently robust" to estimate a NOAEL because the study (1) extensively tested subjects before their first dose of dichlorvos; (2) used a repeated dosing and measurement approach; and (3) "showed a statistically significant effect on cholinesterase inhibition . . . that was at or near the lowest level that could be distinguished from baseline values." *Id.* at 42706.

Further, EPA "conclude[d] that it was reasonable to use the Gledhill study despite th[e] fact that it only examined adult males [because] the animal toxicology data on DDVP's cholinesterase effects consistently showed no differences between males and females and adults and the young." *Id.* at 42707.

EPA also rejected NRDC's argument that reliance on the Gledhill study violated EPA's ethical research rule, for substantially the same reasons it rejected NRDC's petition. *Id.* at 42708-09 (concluding that the consent forms clearly advised subjects that the study involved consuming an insecticide; and deficiencies in monitoring subjects did not violate the ethical research rule).

2.

EPA also rejected NRDC's children's safety factor objections. EPA stated that "[f]or some DDVP risk assessments EPA chose to remove the children's safety factor entirely, and for others EPA reduced the safety factor to 3X." 73 Fed. Reg. at 42695. EPA explained that the 3X factor was not based on any risk to children or infants, but accounted for EPA's "failure to identify a NOAEL in the [Gledhill] study." *Id.* EPA argued that a 3X safety factor was "more than adequate" because

of "the slight adverse effect (marginal [red blood cell] cholinesterase inhibition in [the Gledhill] study) observed at the LOAEL." *Id.*; *see also id.* at 42696 ("The effects seen in [the Gledhill] study were only marginally adverse at best.").

In addition, EPA argued that even without completing the FQPA-mandated endocrine disruptor screening program, it had sufficient data bearing on endocrine effects to waive or reduce the children's safety factor. *Id.* at 42697. Although NRDC argued that "further testing of DDVP might reveal endocrine effects at levels below those at which cholinesterase inhibition has been measured," EPA rejected this argument as "speculation." *Id.* at 42698. EPA concluded that NRDC's argument "does not convince EPA that there is not a reliable basis for removing the children's safety factor as regards endocrine effects." *Id.*

Further, EPA rejected the argument that it lacked adequate consumption data for infants and children, concluding that it had "taken care to insure that its surveys of food consumption constitute a statistically valid and representative sample of infants and children." *Id.* at 42700.

3.

Lastly, EPA denied NRDC's requests for a hearing. EPA stated that "many of NRDC's claims do not present genuine and substantial questions of fact and/or are immaterial to the relief requested." 73 Fed. Reg. at 42693. Moreover, EPA stated that many of the issues "present[] purely legal or policy questions or questions involving the application of legal standards to undisputed facts," which do not require a public evidentiary hearing under FQPA. *Id.* at 42709. EPA concluded that "NRDC has failed to proffer evidence on its hearing requests which would, if established, resolve one or more issues in its favor." *Id.* at 42693.

F.

On July 30, 2008, NRDC appealed to this Court. On appeal, NRDC principally challenges

EPA's decisions to (1) waive or reduce FQPA's 10X children's safety factor when determining the safety of dichlorvos, and (2) deny NRDC's requests for an evidentiary hearing.

III. Discussion

A.

Under the Administrative Procedure Act, a reviewing court "shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). In reviewing agency action, this Court may not "substitute its judgment for that of the agency." *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). "Nevertheless, our inquiry must be searching and careful. " *Natural Res. Def. Council, Inc. v. FAA*, 564 F.3d 549, 555 (2d Cir. 2009) (internal quotation marks omitted). "The record must show that 'the agency . . . examine[d] the relevant data and articulate[d] a satisfactory explanation for its action.'" *Id.* (quoting *Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)). "Moreover, the agency's decision must reveal a 'rational connection between the facts found and the choice made.'" *Id.* (quoting *State Farm*, 463 U.S. at 43).

In addition, agency action is arbitrary and capricious "if the agency 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." *State Farm*, 463 U.S. at 43. Although we may "uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned," "[w]e may not supply a reasoned basis for the agency's action that the agency itself has not given." *Id.* (internal quotation marks omitted).

B.

1.

Pursuant to FQPA, before "establishing, modifying, leaving in effect, or revoking" a pesticide tolerance or exemption, EPA must ensure that the pesticide is "safe" for infants and children—that is, EPA must "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide." 21 U.S.C. § 346a(b)(2)(C)(ii)(I).

To make this determination, Congress required EPA to "assess the risk" of the pesticide based on available information about (1) consumption patterns of infants and children, who may eat more of certain foods with the pesticide residue; (2) the special susceptibility of infants and children to the pesticide, including neurological differences and the effects of in utero exposure; and (3) the cumulative effects of infants' and children's exposure to the pesticide and other common substances. *Id.* § 346a(b)(2)(C)(i). Unless any amount of the pesticide would cause harm, Congress required EPA to apply "an additional tenfold margin of safety . . . for infants and children." *Id.* § 346a(b)(2)(C)(ii). This tenfold margin of safety, Congress stated, was designed "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to infants and children." *Id.* EPA "may use a different margin of safety . . . only if, on the basis of reliable data, such margin will be safe for infants and children." *Id.*

Lastly, in "establishing, modifying, leaving in effect, or revoking" a pesticide tolerance or exemption, EPA must "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children." *Id.* § 346a(b)(2)(C)(ii)(II).

2.

Here, NRDC argues that "EPA removed the tenfold [children's] safety factor without any rational explanation for doing so, [and thus] its decision was arbitrary and capricious." Appellant Br. 39. For dichlorvos risk assessments that relied on the Gledhill study, EPA stated that it used "a

FQPA safety factor of 3X." 72 Fed. Reg. at 68695. NRDC argues that this decision "is based upon generic assertions that unlawfully fail to take into account any dichlorvos-specific information for infants and children." Appellant Br. 37.

As an initial matter, although EPA stated that it applied a FQPA safety factor of 3X for dichlorvos risk assessments that relied on the Gledhill study, *id.*, EPA clarified that this 3X factor was not based on any evaluation of risk to infants or children. Instead, EPA stated that "[t]his additional safety factor is due to these assessments' reliance on a LOAEL rather than a NOAEL" in the Gledhill study. *Id.*; *see also* EPA, *Dichlorvos IRED* at 133-36. As EPA explained in a published final order incorporated into its denial of NRDC's petition, 72 Fed. Reg. at 68673, "[t]ypically, when a LOAEL but not a NOAEL has been identified by a study, EPA will, when the data support it, project a NOAEL for that study by dividing the LOAEL by a safety factor," 70 Fed. Reg. 46706, 46729 (emphasis added). For the risk assessments that relied on the Gledhill study, EPA determined that 3X was an appropriate safety factor to use to make the LOAEL-to-NOAEL conversion. 72 Fed. Reg. at 68673.

In EPA's IRED and two published orders, EPA consistently reiterated this position and declined to claim that the 3X factor was based on any evaluation of risk to infants or children. *See* EPA, *Dichlorvos IRED* at 133 (EPA applied 3X safety factor "for lack of a NOAEL"); 72 Fed. Reg. at 68673 (EPA applied "a safety factor of 3X [to the LOAEL] to approximate the value of a NOAEL"); 73 Fed. Reg. at 42696 ("[T]o address the uncertainty raised by the failure of the [Gledhill] human study to identify a NOAEL," EPA "chose a 3X safety factor."). Because EPA was required to explain why a children's safety factor less than 10X was designed "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to infants and children," 21 U.S.C. § 346a(b)(2)(C)(ii), its failure to provide such an explanation for the Gledhill

risk assessments was arbitrary and capricious. *See State Farm*, 463 U.S. at 43 (stating that an agency action is arbitrary and capricious if the agency does not provide "a reasoned basis" for its action); *Pub. Citizen, Inc. v. Mineta*, 340 F.3d 39, 53 (2d Cir. 2003) (same); *Natural Res. Def. Council v. EPA*, 571 F.3d 1245, 1267 (D.C. Cir. 2009) ("In order to ensure that an agency's decision has not been arbitrary, we require the agency to have identified and explained the reasoned basis for its decision." (internal quotation marks omitted)).

We note that for most of the other risk assessments—those that were not based on the Gledhill human study—EPA stated that it applied a 1X children's safety factor because, inter alia, "[i]n both rat and rabbit developmental studies," EPA found "no evidence for increased susceptibility of the rat and rabbit offspring to prenatal or postnatal exposure to dichlorvos." 72 Fed. Reg. at 68694; *see also* 73 Fed. Reg. at 42691 (same). However, EPA did not rely on this explanation to use a lower children's safety factor for the risk assessments based on the Gledhill study. Nor can we assume that EPA meant to rely on the rat and rabbit studies for the Gledhill risk assessments. When EPA did rely on the animal studies—for the non-Gledhill risk assessments—EPA said so and properly applied a safety factor of "10X for interspecies differences." EPA, *Dichlorvos IRED* at 131, 132. EPA did neither for the risk assessments based on the Gledhill study. Absent any indication by EPA that it relied on the animal studies for its decision regarding the Gledhill risk assessments, "[w]e may not supply a reasoned basis for the agency's action that the agency itself has not given." *State Farm*, 463 U.S. at 43.

Moreover, EPA foreclosed reliance on the animal studies for the risk assessments based on the Gledhill study. For those risk assessments, EPA explicitly stated that it did not rely on any animal studies. EPA, *Dichlorvos IRED* at 133, 134. As a result, EPA concluded that "[s]ince the study was conducted in human subjects, there was no need to account for interspecies

extrapolation." *Id.* EPA thus avoided applying the 10X interspecies safety factor. Such a factor would have increased the safe margin of exposure for risk assessments based on the Gledhill study to 300, even without the children's safety factor. Further, it would have prevented numerous currently-allowed uses of dichlorvos, which have an actual MOE less than 300. *Id.* at 133-35, 165, 182, 185. Absent the animal studies, on which EPA relied for only the non-Gledhill risk assessments, EPA did not explain why a children's safety factor less than 10X would "take into account potential pre- and post-natal toxicity and completeness of the data with respect to infants and children." *See* 21 U.S.C. § 346a(b)(2)(C)(ii). The lack of such an explanation, as noted above, is arbitrary and capricious.

Even we were to assume, contrary to EPA's explanations, that the safety factor EPA labeled as a "FQPA safety factor" was designed "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to infants and children," *id.* § 346a(b)(2)(C)(ii), EPA failed to explain why it did not apply FQPA's presumptive factor of 10X. In neither its IRED nor its two orders did EPA explain how the 3X factor was designed "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to infants and children." *See id.* Nor did EPA identify "reliable data" and explain how that data showed that a safety factor less than 10X "will be safe for infants and children." *See id.* Therefore, EPA failed to provide "a reasoned basis" for its decision to use a children's safety factor less than 10X. *See State Farm*, 463 U.S. at 43. Thus, those risk assessments based on the Gledhill study are arbitrary and capricious. *Id.*

To the extent EPA argues that a 3X safety factor was "more than adequate" because of "the slight adverse effect (marginal [red blood cell] cholinesterase inhibition in [the Gledhill] study) observed at the LOAEL," 73 Fed. Reg. at 42695, we reject that argument as well. *See also id.* at 42696 ("The effects seen in [the Gledhill] study were only marginally adverse at best."). As noted

above, EPA did not explain how this conclusion related to "potential pre- and post-natal toxicity and completeness of the data with respect to infants and children." *See* 21 U.S.C. § 346a(b)(2)(C)(ii). FQPA requires such an explanation if a 10X children's safety factor is not used.

Moreover, while the Gledhill study may have had sufficient statistical power to detect a cholinesterase inhibition greater than 0, EPA did not explain whether the 9-person study (six dosed subjects, 3 placebo subjects) had sufficient power to determine with any level of precision the magnitude of the cholinesterase inhibition. *See* Fed. Judicial Center., *Reference Manual on Scientific Evidence* 116 (2d Ed. 2002) ("Precision can be expressed using the 'standard error' or a 'confidence interval.'"). That is, although EPA may have been able to conclude that the cholinesterase inhibition was greater than 0, EPA did not explain whether it could statistically conclude that magnitude of the inhibition was "large" or not. *See also* 72 Fed. Reg. at 68691 (comparing the 6 subjects' "group mean" of cholinesterase inhibition to a population's 20-percent level of cholinesterase inhibition, without explaining the precision of the group mean).

In sum, EPA did not rely on animal studies in its dichlorvos risk assessments based on the Gledhill study, nor did it rely on human data regarding the special susceptibility of infants and children to dichlorvos. Because EPA failed to explain why it did not use a 10X children's safety factor for dichlorvos risk assessments that relied on the Gledhill study, EPA acted in an arbitrary and capricious manner. Accordingly, we vacate those portions of EPA's July 23, 2008 order assessing the risk of dichlorvos based on the Gledhill study, as it was not "reliable data" on which EPA could base its decision to choose a lower children's safety factor..

C.

NRDC also challenges the dichlorvos risk assessments that were not based on the Gledhill study. However, for these assessments, NRDC argues only that EPA could not waive or reduce the

10X children's safety factor because it had not implemented an endocrine disruptor screening program. Appellant Br. 34-37. Although at the administrative level NRDC alleged numerous other deficiencies with these risk assessments, NRDC did not raise these challenges on appeal and we do not consider them here. We focus only on whether, as NRDC argues, "EPA unlawfully waived the children's safety factor . . . because the agency has never conducted the endocrine testing required by statute to identify harmful health effects to children." Appellant Reply Br. 17-18.

Under FQPA, EPA was required 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." 21 U.S.C. § 346a(p)(1). Pursuant to this screening program, Congress required EPA to test "all pesticide chemicals," including dichlorvos. *Id.* § 346a(p)(3). Moreover, Congress required EPA to report on its findings regarding the existence of estrogen-like effects within four years—by August 2000. *Id.* § 346a(p)(7).

In its order rejecting NRDC's petition, EPA acknowledged that it has not completed the screening program, explaining that it only recently "published a draft list of the first group of chemicals that will be tested." 72 Fed. Reg. at 68669; *see also* 73 Fed. Reg. at 42690 (providing no further update). Despite the absence of any data from EPA's estrogen disruptor screening program, EPA stated that its dichlorvos risk assessments relied on other studies that "provide[d] information relevant to potential endocrine disruption." 72 Fed. Reg. at 68676. In particular, EPA stated that it relied on "data bearing on potential endocrine effects from a two-generation [rat] reproduction study [from 1992] as well as other chronic data in which effects on [rat, mouse, and dog] reproductive organs were examined." *Id.* at 68677. In addition, EPA stated that cholinesterase inhibition is dichlorvos's "most sensitive mechanism of toxicity" and such inhibition occurred in animals even at low levels at which potential endocrine-related effects did not occur. *Id.* Therefore,

EPA concluded that it had "adequate data to make a safety finding as to [dichlorvos'] potential endocrine-related effects." *Id.*

NRDC challenges neither the data on which EPA relies, nor the way in which the data relate to infants and children. Instead, NRDC argues that regardless of other evidence of potential endocrine-related effects, EPA must apply the 10X children's safety factor unless it relies on data from its estrogen disruptor screening program. We reject this argument.

FQPA specifies that EPA may apply a children's safety factor of less than 10X if it determines, "on the basis of reliable data," that a margin lower than 10X "will be safe for infants and children." 21 U.S.C. § 346a(b)(2)(C)(ii). Given this standard, EPA may conclude, if it has a basis to do so, that the results of its estrogen disruptor screening program provide such "reliable data." However, such data are not the only possibly reliable data. In the time before EPA receives results from its screening program, Congress did not bar EPA from concluding that it has "reliable data" regarding potential endocrine-related effects. EPA may show that data from other studies provide reliable evidence that a lower than 10X safety factor will be safe for infants and children. There is no indication in the statute or legislative history that Congress, which required EPA to test "all pesticide chemicals," *id.* § 346a(p)(3), intended the children's safety factor to be mandatory in assessing the risks of all pesticides until EPA completed the estrogen disruptor screening program in four years (in fact it has lasted much longer to complete). *See id.* § 346a(b)(2)(C), (p); H.R. Rep. No. 104-669 at 41 (1996). Rather, Congress allowed EPA to determine, based on all available data, whether there was "reliable data" supporting a reduced or waived children's safety factor, 21 U.S.C. § 346a(b)(2)(C)(ii), with subsequent review by the courts of appeals, *id.* at § 346a(h).

Thus, even before completing its endocrine disruptor screening program, EPA may conclude that it has "reliable data" for purposes of the children's safety factor. NRDC does not argue on

appeal that the endocrine-related data generated outside the program are not reliable. Nor does NRDC does not challenge the non-Gledhill risk assessments on any other basis. Therefore, we deny NRDC's request to find arbitrary and capricious the risk assessments not based on the Gledhill study.

D.

Lastly, NRDC requests a public evidentiary hearing under FQPA to determine (1) whether "the results of the [Gledhill] human study were statistically invalid"; and (2) whether "test subjects [gave] their informed consent to participate in [the Gledhill] human study." Appellant Br. 21, 27. In light of our above conclusion that EPA's risk assessments based on the Gledhill study are arbitrary and capricious, we need not decide whether a public evidentiary hearing is required on those matters relating to the Gledhill study. Nor is such a ruling appropriate at this time. EPA may decide, on remand, not to rely on the Gledhill study or to rely on the study in a different manner or for different reasons. Thus, we decline to resolve the issue here.

IV. Conclusion

For the foregoing reasons, we **GRANT** in part and **DENY** in part NRDC's petition to review EPA's July 23, 2008 order. We **VACATE** those portions of EPA's order assessing the risk of dichlorvos based on the Gledhill study and **REMAND** for further proceedings consistent with this opinion.