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### **Dichlorvos (DDVP); Order Denying NRDC's Objections on Remand; Final Order [FRL 9359-9]**

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**ENVIRONMENTAL PROTECTION AGENCY**

**40 CFR Part 180**

**[EPA-HQ-OPP-2002-0302; FRL-9359-9]**

**Dichlorvos (DDVP); Order Denying NRDC's Objections on Remand**

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

**ACTION:** Final Order.

**SUMMARY:** In this order, EPA denies an objection to a prior order denying a petition requesting that EPA revoke all pesticide tolerances for dichlorvos under section 408(d) of the Federal Food, Drug, and Cosmetic Act. The objection was filed on February 1, 2008, by the Natural Resources Defense Council (NRDC). The original petition was also filed by NRDC. Previously, in July 2008, EPA denied this same objection but the United States Court of Appeals for the Second Circuit vacated that decision, in part, and remanded the matter to EPA. This order is being issued in response to the court's remand.

**DATES:** This order is effective [*insert date of publication in the Federal Register*].

**ADDRESSES:** The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2002-0302, is available either electronically through <http://www.regulations.gov> or in hard copy at the OPP Docket in the Environmental Protection Agency Docket Center (EPA/DC), located in EPA West, Rm. 3334, 1301 Constitution Ave. NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone

number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

**FOR FURTHER INFORMATION CONTACT:** Melanie Biscoe, Pesticide Re-evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 305-7106; e-mail address: [biscoe.melanie@epa.gov](mailto:biscoe.melanie@epa.gov).

**SUPPLEMENTARY INFORMATION:**

**I. General Information**

*A. Does this Action Apply to Me?*

In this document EPA denies an objection by the Natural Resources Defense Council (NRDC) concerning EPA's denial of NRDC's petition to revoke pesticide tolerances. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to those engaged in the following activities:

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

### *B. How Can I Get Electronic Access to Other Related Information?*

You may access a frequently updated electronic version of EPA's tolerance regulations at 40 CFR part 180 through the Government Printing Office's e-CFR site at [http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab\\_02.tpl](http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl).

## **II. Introduction**

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

In this order, EPA is issuing a revised denial of an objection to an earlier EPA order, (72 FR 68662, December 5, 2007), denying a petition to revoke all tolerances established for the pesticide dichlorvos (DDVP) under the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a. Both the objection as well as the petition was filed with EPA by NRDC. (Refs. 1 and 2). EPA had previously denied this objection, (73 FR 42683, July 23, 2008), but that order was vacated, in part, by the United States Court of Appeals for the Second Circuit. (NRDC v. US EPA, 658 F.3d 200 (2d Cir. 2011)).

NRDC's petition, filed on June 2, 2006, pursuant to FFDCA section 408(d)(1), asserted numerous grounds as to why the dichlorvos tolerances allegedly fail to meet the FFDCA's safety standard. This petition was filed as EPA was completing its reassessment of the safety of the dichlorvos tolerances pursuant to FFDCA section 408(q). (Ref. 3). In response to the petition, EPA undertook an extensive review of its dichlorvos safety evaluation in the tolerance reassessment decision. Based on this extensive review, EPA concluded that dichlorvos met the FFDCA safety standard and, therefore, denied the petition. (72 FR 68695). NRDC then filed objections with EPA to the petition denial order and requested a hearing on its objections. The objections narrowed NRDC's claims to two main assertions - that, in assessing the risk to dichlorvos, EPA unlawfully reduced the statutory tenfold (10X) additional safety factor for the protection of infants and children

and EPA unlawfully relied on a human toxicity study (the Gledhill study). After carefully reviewing the objections and hearing requests, EPA determined that NRDC's hearing requests did not satisfy the regulatory requirements for such requests and that its substantive objections were without merit. (73 FR 42709-42711). NRDC sought review of EPA's decision in the United States Court of Appeal for the Second Circuit. As noted, the Second Circuit court vacated a portion of EPA's order finding that "[b]ecause 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." (658 F.3d at 218). Specifically, the court vacated "those portions of EPA's July 23, 2008 order assessing the risk of dichlorvos based on the Gledhill study . . . ." (Id.). The court remanded the matter to EPA. (Id. at 219).

On remand, EPA has carefully examined the court's opinion and has reconsidered that portion of its prior decision that relied on the Gledhill study in assessing dichlorvos risk. Because the court found this portion of EPA's order to be arbitrary and capricious due to its absence of an adequate explanation on the additional safety factor for the protection of infants and children, EPA focused on a reexamination of what additional safety factor for the protection of infants and children should be applied for the assessments based on the Gledhill study. EPA concludes, like it did in the July 23, 2008 order, that a threefold (3X) additional safety factor will protect the safety of infants and children. Accordingly, EPA again denies NRDC's objections as to those portions of the July 23, 2008 order that were vacated. Although EPA reaches the same conclusion on remand on the additional safety factor for the protection of infants and children, EPA has provided a revised, more extensive explanation for its position. Because this revised explanation addresses the court's reason for finding portions of the July 23, 2008 order to be arbitrary and capricious, EPA has not otherwise reopened or reconsidered that prior order.

*B. What Is the Agency's Authority for Taking This Action?*

NRDC petitioned to revoke the dichlorvos tolerances pursuant to the petition procedures in FFDCA section 408(d)(1). (21 U.S.C. 346a(d)(1)). Under section 408(d), EPA may respond to such a petition by either issuing a final or proposed rule modifying or revoking the tolerances or issuing an order denying the petition. (21 U.S.C. 346a(d)(4)). Here, EPA responded by issuing an order under section 408(d)(4)(iii) denying the petition. (72 FR 68622, December 5, 2007).

Orders issued under section 408(d)(4)(iii) are subject to a statutorily-created administrative review process. (21 U.S.C. 346a(g)(2)). Any person may file objections to a section 408(d)(4)(iii) order with EPA and request a hearing on those objections. (*Id.*). EPA is required by section 408(g)(2)(C) to issue a final order resolving the objections to the section 408(d)(4)(iii) order. (21 U.S.C. 346a(g)(2)(C)). NRDC filed objections to EPA's denial of its dichlorvos petition and EPA issued a section 408(g)(2)(C) order denying NRDC's objections. (73 FR 42683, July 23, 2008). EPA's order denying NRDC's objections was vacated, in part, and remanded to EPA. This revised order on remand is also being issued under section 408(g)(2)(C).

### **III. Statutory and Regulatory Background**

In this Unit, EPA provides background on the relevant statutes and regulations governing the matter on remand as well as a much-abbreviated discussion on pertinent Agency risk assessment policies. A full discussion of EPA's approach to pesticide risk assessment is included in EPA's prior order on NRDC's objections. (73 FR 42685-42688). Because the court's decision focused on the explanation offered by EPA for its use of safety factors, this Unit includes an expanded discussion on use of safety or uncertainty factors, including the additional safety factor required by the FQPA for the protection of infants and children. Further, because Benchmark Dose Methods

analysis is discussed for the first time in this revised order, a short section explaining that concept is included.

#### *A. FFDCA/FIFRA and Applicable Regulations*

1. *In general.* EPA establishes maximum residue limits, or "tolerances," for pesticide residues in food and feed commodities under section 408 of the FFDCA. (21 U.S.C. 346a). Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is "adulterated" under section 402 of the FFDCA and may not be legally moved in interstate commerce. (21 U.S.C. 331, 342). Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA). Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA), which added the provisions discussed below establishing a detailed safety standard for pesticides, additional protections for infants and children, and the endocrine disrupting substances screening program. (Public Law 104-170, 110 Stat. 1489 (1996)).

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

2. *Safety standard for pesticide tolerances.* A pesticide tolerance may be promulgated or left in effect by EPA only if the tolerance is "safe." (21 U.S.C. 346a(b)(2)(A)(i)). This standard applies when responding both to petitions to establish and petitions to revoke tolerances. "Safe" is

defined by the statute to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." (21 U.S.C. 346a(b)(2)(A)(ii)).

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

3. *Procedures for establishing, amending, or revoking tolerances.* Tolerances are established, amended, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, amend, or revoke a tolerance by means of filing a petition with EPA. (See 21 U.S.C. 346a(d)(1)). EPA publishes in the **Federal Register** a notice of the petition filing and requests public comment. (21



U.S.C. 346a(d)(3)). After reviewing the petition, and any comments received on it, EPA may issue a final rule establishing, amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition. (21 U.S.C. 346a(d)(4)).

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

#### *B. EPA Risk Assessment for Tolerances--Policy and Practice*

1. *The safety determination - risk assessment.* To assess risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps: (1) Identification of the toxicological hazards posed by a pesticide; (2) determination of the "level of concern" with respect to human exposure to the pesticide; (3) estimation of human exposure to the

pesticide; and (4) characterization of risk posed to humans by the pesticide based on comparison of human exposure to the level of concern.

Toxicological hazards posed by a pesticide are identified through use of testing in laboratory animals or humans. Generally, EPA will use the lowest “no observed adverse affect level” (NOAEL) or “lowest observed adverse effect level” (LOAEL) from the available studies or a calculated value called a Benchmark Dose as a starting point (called "the Point of Departure") in estimating the “level of concern” for human exposure to the pesticide. Points of Departure and levels of concern will be identified for all exposure routes to the pesticide (oral, dermal, and inhalation) and durations of exposure (acute, short-term, intermediate-term, and chronic). Another critical aspect of the “level of concern” determination involves the use of safety or uncertainty factors to compensate for the limitations of toxicology testing. Safety and uncertainty factors are discussed in detail in Unit III.B.2. below. Having identified a pesticide’s hazards, the Point(s) of Departure, and level(s) of concern, EPA then estimates exposure to the pesticide taking into account the various routes of exposure, how exposures vary over time, and the differences in exposure to different subpopulations. Finally, EPA combines information on hazard, level of concern, and exposure to produce a characterization of the risk posed by the pesticide. Risks are calculated for all of the various routes and durations of exposure scenarios associated with a pesticide. These risk assessment scenarios may be calculated separately for different age-based population groups (e.g., non-nursing infants) or applied to all population groups, including infants and children, depending on information on the potential for exposure and data on differential sensitivity. A more comprehensive discussion of this risk assessment process is presented in EPA’s previous order denying objections. (73 FR 42685-42689).

Before turning to a detailed discussion of safety and uncertainty factors, EPA's risk characterization process is briefly summarized because it is frequently referred to in this order. For pesticides that pose a risk over a certain threshold of exposure, EPA's characterization of risk is presented in one of two ways: Either using the Reference Dose (RfD) approach or the Margin of Exposure (MOE) approach. Importantly, these different approaches do not render substantively different results. Both approaches use the same data – the Point of Departure, the applicable safety/uncertainty factors, and human exposure to the pesticide; they just express the characterization of risk in a different metric. Under the RfD approach, EPA directly extrapolates a dose from an animal or human study to an overall safe dose for humans. An RfD is calculated by dividing all applicable safety/uncertainty factors into the level of exposure from animal or human studies determined appropriate for assessing risk (i.e., the "Point of Departure"). Estimated human exposure to the pesticide is then compared to the RfD to determine if it is excessive. Under the Margin of Exposure (MOE) approach, EPA does not calculate a safe dose in humans but rather focuses on the margin of exposure between a dose from an animal or human study and human exposure to the pesticide. A MOE is calculated by dividing human exposure to the pesticide into the Point of Departure. To determine whether that MOE is considered sufficiently protective of humans, EPA compares it to the product of all applicable safety/uncertainty factors, referred to as the target MOE. MOEs that are less than the target MOE indicate a risk of concern. At bottom, both approaches extrapolate a safe measure of human exposure from animal or human studies using a mixture of uncertainty/safety factors.

2. *Safety and uncertainty factors.* i. *History.* It has long been a standard risk assessment practice to use numerical factors in conjunction with experimental toxicity data in assessing risk to humans from exposure to chemical substances. (Ref. 4). These numerical factors are designed to provide an additional margin of safety so that risks to the populations covered by an assessment are

not understated. The practice was first developed by the Food and Drug Administration (FDA) in the middle part of the last century. (Ref. 5). An influential 1954 paper by two FDA scientists called for a hundredfold margin of safety when extrapolating from long-term animal experiments to calculate safe doses in humans. (Ref. 6). The paper justified this safety factor on the basis of, among other things, potential differences in sensitivity between humans and laboratory animals as well as potential variations in sensitivity within humans. Accordingly, the paper recognized that a smaller factor would be appropriate where adequate human data are available. An explicit recommendation for a factor “as low as 10” was made by the Joint Food and Agricultural Organization/World Health Organization (FAO/WHO) Meeting on Pesticide Residues in 1965 for circumstances where human data was relied upon. (Ref. 7 at 12). Eventually, it became common regulatory practice to treat the hundredfold margin of safety as comprised of two tenfold factors: the first addressing the potential difference in sensitivity between humans and experimental animals (*i.e.*, interspecies sensitivity) and the second addressing variation within the human population (*i.e.*, intraspecies sensitivity). The rationale for these two factors is concisely summarized in a recent publication from the International Programme on Chemical Safety:

The interspecies uncertainty factor can be considered to convert the NOAEL/NOAEC [No observed adverse effect concentration] for animals (derived from a small group of relatively homogeneous test animals) into the NOAEL/NOAEC anticipated for an average representative healthy human. The uncertainty factor for human variability converts the NOAEL/NOAEC for the average human into a NOAEL/NOAEC for susceptible humans. Although adverse effect data in humans can be used directly without the need for an interspecies factor, the paucity of such data means that the vast majority of risk assessments are based on studies in experimental animals.

(Ref. 8 at 15).

EPA, as well as other Federal and international regulatory bodies, also will, where appropriate, apply additional numerical factors to take into account chemical-specific considerations affecting the risk assessment. (Ref. 9) Use of these additional factors is further explained in Unit III.B.2.v., vi, and vii.

ii. *Terminology.* Different terminology has been used to label numerical factors used in calculating safe doses of chemical substances. As noted, they were first referred to as “safety” factors. The terminology has evolved over the decades, however, such that what was once generally called a safety factor has come to be generally referred to as an uncertainty factor. (Ref. 10 at A-3). The rationale for the change was that, although the use of such factors does promote safety, there was a concern that the use of the term “safety” implied that these factors provided absolute safety. (Ref. 11). The FQPA reintroduced the term “safety” factors with its reference to a “margin of safety.” 21 U.S.C. 346a(b)(2)(C). Subsequent to the passage of FQPA, EPA’s Office of Pesticide Programs (OPP) has used the terms safety factor and uncertainty factor interchangeably. Both terms have been criticized by the National Academy of Sciences (NAS). The NAS explained that the terms safety and uncertainty imply that factors “are simply added on for safety or because of a lack of knowledge or confidence in the process.” (Ref. 12 at 132). To the contrary, according to the NAS, these factors are scientifically-based and used “to adjust for differences in individual human sensitivities, for humans’ generally greater sensitivity than test animals’ on a milligram-per-kilogram basis, for the fact that chemicals typically induce harm at lower doses with longer exposures, and so on.” (Id.).

iii. *Scientific basis for inter- and intraspecies factors.* Only limited scientific data, involving differing sensitivity of humans and animals, are cited in the 1954 article in justification of the recommendation for a hundredfold safety factor. Subsequent investigations of both animal and hu-

man toxicity data, however, have provided general support for the protectiveness of the tenfold factors for interspecies and intraspecies sensitivity differences if an adequate toxicity database is available. (Refs. 9,13, 14, and 15). The interspecies factor has been investigated through comparisons of toxicity testing in laboratory animals and humans. (Refs. 15 and 16). The protectiveness of the human intraspecies factor has been assessed through examining sub-population differences both among various human age groups (the young, adults, and elderly) as revealed in pharmaceutical trials and between juvenile and adult laboratory animals identified in toxicity testing. (Ref. 13 at 211 (“For substances other than pharmaceuticals, age-related differences in toxicity have been primarily investigated in rodent studies.”); Ref. 17 at 462-463 (describing pharmaceutical trials involving humans and comparative studies in juvenile and adult laboratory animals)). For example, the NAS, in its report “Pesticides in the Diets of Infants and Children,” looked to both human data and animal data in evaluating the potential for increased sensitivity in infants and children to pesticides. (Ref. 18 at 344-345).

iv. *Adjustment of inter- and intraspecies factors.* In addition to evaluating the protectiveness of the intra- and interspecies uncertainty factors, scientists have also examined both generic biological as well as chemical-specific factors that may affect intra- and interspecies variability with the aim of deriving more accurate uncertainty factor values than the default tenfold values.

One reason humans are considered to be potentially more sensitive to toxic agents than laboratory animals is that otherwise equivalent external doses of such agents for humans and animals on a milligram-per-kilogram of body weight basis may result in a greater internal dose for humans. This is due to species differences in general metabolic processes – commonly referred to as toxicokinetics – and “is thought to be related to species differences in exchange surfaces and distri-

bution networks that constrain concentration and flux of metabolic reactants.” (Ref. 19 at 4-35; see Ref. 15 at 228).

In addition to toxicokinetic effects on internal dose, differences between humans and laboratory animals are also driven by toxicodynamic factors. Toxicodynamics refers to the manner in which the target tissue and body respond to the toxic agent. Thus, interspecies differences are a factor of both differences in the internal dose received by humans and animals and differences in how humans and animals react to the internal dose received. Similarly, sensitivity differences between juveniles and adults, whether humans or animals, are also considered to be tied to toxicokinetic and toxicodynamic factors. Accordingly, both the inter- and intraspecies uncertainty factors are considered to have toxicokinetic and toxicodynamic components. EPA typically has considered both the tenfold (10X) inter- and intraspecies factors to be roughly equally divided on a logarithmic basis (i.e.,  $10^{0.5}$  or roughly a 3X factor) between toxicokinetics and toxicodynamics. (Ref. 19 at 4-29; *see also* Ref. 19 at 4-40 (explaining why two 3X factors [technically, 3.16X] would be equivalent to a 10X factor)). Other organizations have recommended that, while toxicokinetics and toxicodynamics play an equal role in intra-human variability, toxicokinetics has a greater effect on interspecies differences and thus recommend that the tenfold interspecies factor be divided into a fourfold factor for toxicokinetics and 2.5-fold factor for toxicodynamics. (Ref. 8 at 17; *see* Ref.14).

Of the toxicokinetic and toxicodynamic differences between humans and animals and among various human subgroups, the most is known about the toxicokinetic differences between humans and animals. For inhalation exposures, EPA has used toxicokinetic information on humans and animals to create generic dosimetric adjustment factors that replace that portion of the interspecies factor tied to toxicokinetic differences. (Refs. 19 at 4-29; 20). Where such dosimetric adjustment factor is used, the interspecies factor is reduced to 3X.

EPA guidance entitled “A Review of the Reference Dose and Reference Concentration Processes” (“RfD Guidance”) also urges that data be developed to support substitution of chemical-specific adjustment factors (sometimes referred to as data-derived factors) for the default 10X uncertainty factors for inter- and intraspecies variability. (Ref. 19 at xviii –xix, 4-47). This guidance recognizes that chemical-specific data from both humans and animals has been relied upon by EPA to adjust the human intraspecies uncertainty factor citing an article by Dourson et al. That article collects instances in which EPA has adjusted uncertainty factors on a chemical-specific basis. (Ref. 9). For example, Dourson et al. point to a 1996 EPA assessment of Aroclor that reduced the human intraspecies factor to 3X given that the Point of Departure came from a sensitive animal population – there, infant rhesus monkeys. In discussing the Dourson et al. article, the RfD Guidance notes that:

In those cases where developmental effects were the most sensitive endpoint (0 RfCs, 6 RfDs), reduction of the intraspecies [uncertainty factor] from 10 to 3 was based on data derived either from human data showing which age groups or time periods were most susceptible (e.g., methyl mercury exposure to the developing fetus) or from an animal study with support from strong human or other data (e.g., Aroclor 1016 in utero exposure in monkeys, strontium-induced rachitic bones in young rats).

(Ref. 19 at 4-43). The RfD Guidance endorsed a view similar to that expressed in an agency-wide paper prepared in development of EPA’s Children’s Safety Factor Policy. That paper also noted that there were circumstances where data from human studies or from animal studies might support reduction of the human intraspecies uncertainty factor: “The Toxicology Working Group recommends that reduction of the intraspecies uncertainty factor from a default of 10 be considered only if data are complete and the age group or window of vulnerability during development has been clear-



ly delineated, preferably based on human data or on animal data with supporting human data.” (Ref. 21 at 28). On the other hand, the RfD guidance also recognized that a 10X intraspecies factor “may sometimes be too small because of factors that can influence large differences in susceptibility, such as genetic polymorphisms.” (Ref. 19 at 4-44).

In sum, the 10X inter- and intraspecies factors are default values. Although there is substantial scientific support for these default values, chemical-specific human and animal data may be relied upon in reducing, confirming, or increasing these default values.

v. *Additional Safety/Uncertainty Factors*. In addition to the inter- and intraspecies factors, risk assessors from EPA as well as other Federal and international regulatory agencies also apply “additional” or “modifying” safety/uncertainty factors based on specific circumstances related to the toxicity data, particularly with regard to deficiencies in that data. Like the inter- and intra-species factors, these additional factors help to ensure that risks to populations covered by an assessment are not understated. Additional factors are applied to address: (1) An absence of critical toxicity data; (2) the failure of a study to identify a NOAEL; (3) the necessity of using sub-chronic data to choose a Point of Departure for estimating chronic risk; and (4) results in a study that suggest the inter- or intraspecies factors may not be sufficient (sometimes referred to as a “modifying factor”). (Ref. 10 at 9). Generally, a safety factor value of 10X or 3X (which is considered to be one-half of 10X on the logarithmic scale) is used to address these concerns.

The protectiveness of these default values has also been the subject of scientific examination. Studies have been done on the variations in the levels of NOAELs in the databases for various pesticides. They confirm the need for an additional factor when core data are lacking. (Ref. 22). Examination of the completeness of the animal database remains important even when human data are used as the Point of Departure for calculating the RfD. The latest EPA guidance on RfDs em-

phasizes that in these circumstances “[i]nformation on life stages and organ systems may come from either animal or human studies.” (Ref. 19 at 4-45). The guidance notes that “the lack of a two-generation animal reproduction study might be considered a deficiency even if the reference value is based on human data.” (Id.). Similarly, research has been conducted on existing databases to determine the adequacy of uncertainty factors used to address reliance on a LOAEL instead of a NOAEL, or subchronic data to estimate chronic risk. (Refs. 9 and 15).

Selection of particular values for these additional uncertainty values depends on what is known from the full body of information about the chemical, including both data from testing with animals and humans, about the chemical. For example, as EPA’s RfD Guidance advises: “the size of the database factor to be applied will depend on other information in the database and on how much impact the missing data may have on determining the toxicity of a chemical and, consequently, the POD [Point of Departure].” (Ref. 19 at 4-45). With regard to an additional factor for extrapolation of a NOAEL from a LOAEL, Dourson et al. report that “[a]nalysis of several data bases suggest that a factor of 10 or lower is adequate and that use of data does support a lower factor with certain chemicals.” (Ref. 9 at 112). The critical consideration, according to Dourson et al., is the severity of the effect at the LOAEL: “The data indicate that when faced with a LOAEL and not a NOAEL, the choice of uncertainty factor should generally depend on the severity of the effect at the LOAEL.” (Id.). Specifically, Dourson et al. note that “[l]ess severe effects would not require a large factor, because, presumably, the LOAEL is closer to the unknown NOAEL.” (Id.).

vi. *FQPA safety factor – integration with traditional uncertainty factors.* EPA’s safety/uncertainty factor practice with regard to pesticides was altered to a degree by the Food Quality Protection Act (FQPA). (Ref. 10). That Act established a presumptive additional “safety” factor of 10X to protect infants and children. The additional factor was designed to account for the com-

pleteness of the toxicity and exposure databases and the potential for pre- and post-natal toxicity. EPA has interpreted this legislation as both a “codification and expansion” of prior EPA practice with regard to additional safety/uncertainty factors. (Ref. 10 at A-3 – A-5). It codified EPA’s prior practice by requiring the additional presumptive factor to address toxicity data completeness issues (i.e., absence of a particular study, lack of a NOAEL in a completed study, or absence of chronic data). These traditional additional uncertainty factors became FQPA safety factors for the protection of infants and children. This accords greater protection to infants and children because for FQPA safety factors, unlike pre-FQPA additional factors, there is a presumption, which can only be overcome by reliable data, that they will be applied. At the same time, EPA concluded that Congress had not intended EPA to double-up on safety factors by, for example, applying an additional uncertainty factor due to missing data, and applying an FQPA additional safety factor as well to address the same missing data. (Ref. 10 at A-4). Congress expanded EPA’s prior practice by providing that the additional FQPA safety factor for the protection of infants and children was designed to address not just toxicity data deficiencies but exposure data deficiencies as well and by its emphasis on protecting against potential pre- and post-natal toxicity. In theory, EPA could have, prior to the enactment of the FQPA, used an “additional” or “modifying” factor to address health risks to children not otherwise protected by the interspecies, intraspecies, or data deficiency safety factors, but use of such a factor was not common. The FQPA also modified the status quo by making the additional safety factor for infants and children presumptive in nature.

The narrowly-focused and highly-prescriptive nature of the FQPA safety factor provision has required careful integration with pesticide risk assessment approaches under other statutes and, more generally, with Agency risk assessment practices. As noted above, the FQPA, with regard to the assessment of risks to infants and children, essentially codified EPA’s prior risk assessment

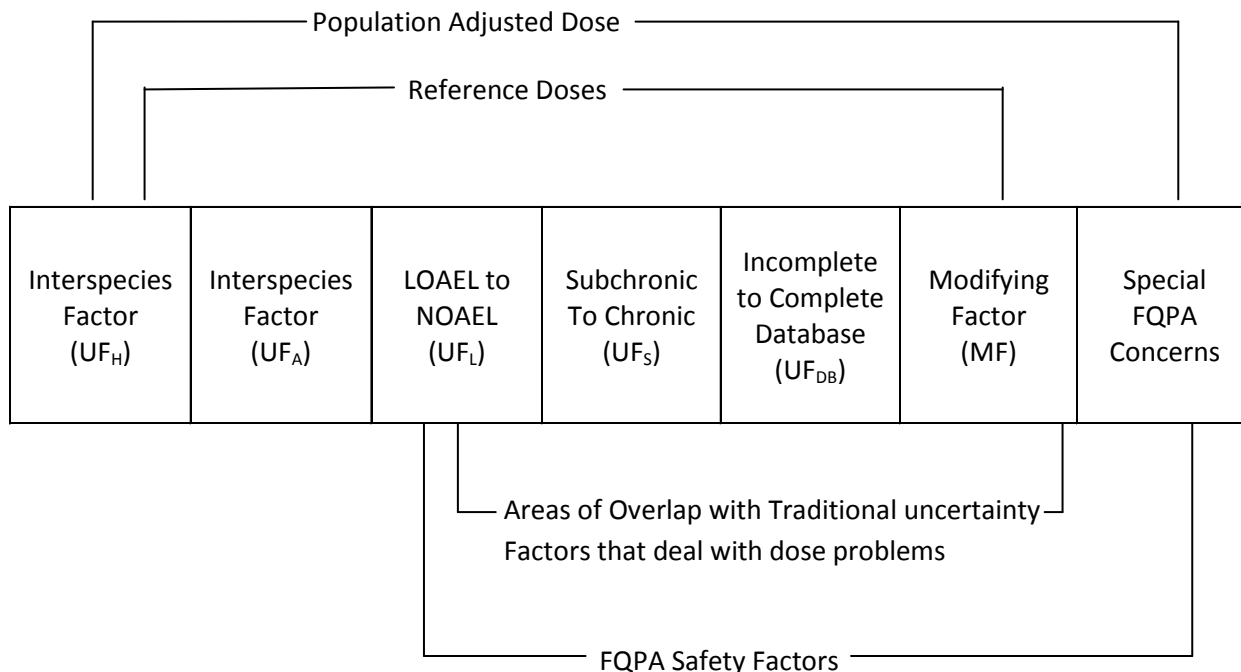
practice as to additional uncertainty factors and it expanded the use of additional uncertainty factors into new areas. The FQPA, however, did not speak to use of traditional (non-additional) uncertainty factors (i.e., the inter- and intraspecies factors). Thus, the end result was that some uncertainty factors for FFDCA pesticides remained unaffected by the new statutory requirements (the inter- and intraspecies factors), some uncertainty factors became FQPA safety factors (additional uncertainty factors that addressed toxicity data deficiencies), and some safety factors that either had previously never existed or were at least extremely rare were created as a statutory phenomenon (a factor to address exposure data base deficiencies and a factor to address potential pre- and post-natal toxicity). This selective inter-weaving of statutory requirements with Agency science policy made FFDCA risk assessments for pesticides unique compared to general Agency risk assessment practice.

Pesticide risk, however, is not regulated under a single statute. Risks to workers or the environment from pesticide use are regulated by EPA under FIFRA, not the FFDCA. Further, EPA may address risks posed by pesticide contamination of the environment under several other statutes, including the Safe Drinking Water Act, 42 U.S.C. 300f et seq., the Resource Conservation and Recovery Act, 42 U.S.C. 6901 et seq., and the Comprehensive Environmental Response, Compensation, and Liability Act, 42 U.S.C. 9601 et seq. Prior to enactment of the FQPA's specific provisions on pesticide risk assessment, a pesticide risk assessment performed by EPA's Office of Pesticide Programs under the aegis of FFDCA section 408 could generally be easily translated for use by the Office of Pesticide Programs under FIFRA, or by the other media offices within EPA for use under other statutes. However, once pesticide risk assessment under the FQPA became not simply a matter of good scientific practice but was channeled by explicit statutory requirements, it became incumbent upon the Office of Pesticide Programs to prepare its FFDCA pesticide risk assessments in

a manner that clearly delineated what aspects of the assessment were driven solely by science and what aspects primarily by FQPA statutory requirements. Specifically, the Office of Pesticide Programs had to be transparent with regard to whether it was relying on FQPA safety factors based on unique FQPA requirements (exposure database deficiencies and potential pre- and post-natal toxicity) or FQPA safety factors that are essentially a codification of prior general EPA “additional” safety/uncertainty factor practice.

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

Figure 1. Relationship between Rfd Derivation and the PAD Calculation



Special FQPA Concerns:

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

(Ref.10, Figure 3)

With regard to providing transparency on the FQPA safety factor decisions, EPA took two steps. First, it adopted a new term, the “special” FQPA safety factor, for children safety factors that were based solely on the new FQPA requirements. Second, it adopted the approach of calculating two different safe doses for a pesticide: one that excluded any “special” FQPA safety factors and one that included them. The former was referred to, in line with standard EPA policy, as a Reference Dose (RfD), and the latter as a Population Adjusted Dose (PAD). Introducing the new terminology on FQPA safety factors into long-established safety factor practice has proved challenging. EPA staff on occasion drafted documents that (1) claimed no FQPA safety factor was needed but applied an additional uncertainty factor to address the completeness of the toxicity data base or reli-

ance on a LOAEL; or (2) treated the “special” FQPA safety factor as the only type of FQPA safety factor. However, as EPA’s policy made clear, EPA interpreted FFDCA section 408(b)(2)(C) as codifying prior practice as to additional uncertainty factors such that these factors became FQPA factors. The mislabeling of uncertainty factors did not substantively change risk assessment outcomes but it did raise the confusion level on an already complex topic. Eventually, EPA determined that the term “special” FQPA safety factor caused more problems than it solved and abandoned it. However, EPA has retained the approach of continuing to calculate both a safe dose with, and without, what was once referred to as “special” FQPA safety factors.

vii. *FQPA safety factor – decision-making guidance.* In 2002, EPA issued detailed policy guidance for Agency risk assessors on decision-making under the FQPA safety factor provision. The purpose of this guidance was concisely set forth by EPA: “[T]his guidance explains how OPP intends 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’ as directed by FFDCA section 408(b)(2)(C)(i).” (Ref. 10 at ii). Although the guidance is structured around these statutory considerations, EPA also emphasizes throughout that the FQPA safety factor decision is a weight-of-the-evidence decision that must consider all available data. Thus, the policy specifies that “[b]efore any decisions are made on the appropriate FQPA safety factor applied to ensure the safety of infants and children from the use of a particular pesticide, all of the relevant submitted data for the pesticide should be assembled and reviewed by Agency scientists.” (Id. at 8).

This emphasis on the broadness of the inquiry is repeated in the discussion of the statutory consideration related to the completeness of the toxicity database. According to EPA, this consideration should not be narrowly focused on EPA’s existing database requirements. Rather, “the ‘completeness’ inquiry should be a broad one that takes into account all data deficiencies.” (Ref. 10

at 23). At the same time, the guidance stresses that “a determination of the possible need for and size of the database uncertainty factor will necessarily involve an assessment that considers the overall weight-of-evidence to evaluate the significance of the data deficiency.” (Id. at 26).

With regard to potential pre- and post-natal toxicity, the policy emphasizes that evaluation of this consideration cannot be divorced from the existing process for choosing levels of concern (i.e., RfDs, PADs, and target MOEs). Thus, EPA instructs risk assessors to evaluate the concern with data showing pre- and post-natal toxicity by considering, among other things, “the degree to which protection for infants and children is provided by the standard approach for deriving RfDs through the application of traditional uncertainty factors.” (Id. at 29). The guidance stresses that “[i]n particular, the risk assessor should consider the protection accorded infants and children by the intraspecies uncertainty factor.” (Id.). EPA notes that the scientific literature as well as the National Academy of Sciences has concluded that the intraspecies factor is generally adequate to protect infants and children; however, the policy points out that certain chemicals may display greater than 10X age-related variability. For this reason, EPA reiterates that “[t]he adequacy of the standard intraspecies factor to address the potential for greater sensitivity or susceptibility of children should be considered in the context of evidence on potential pre- and post-natal toxicity as discussed below.” (Id.; *see also* Id. at 51-52). The policy paper went on to provide numerous examples of weight-of-the-evidence considerations relevant to evaluation of human and animal data on pre- and post-natal toxicity. (Id. at 30-33).

The discussion on the completeness of the exposure database focuses on whether the various approaches EPA uses to assess exposure are likely to understate it. Risk assessors are to evaluate whether their assessments “have addressed all significant exposure routes” and whether “there may



be uncertainty about whether OPP's approach to estimating exposure for a particular use pattern, pathway, or aggregate exposure is sufficiently health protective." (Id. at 48).

3. *Benchmark dose approach.* As indicated above, EPA has traditionally used a NOAEL or LOAEL as a Point of Departure in estimating an exposure level of concern for a pesticide or other substance. Increasingly, however, EPA uses a more sophisticated modeling tool known as the Benchmark Dose approach as an alternative to using NOAELs or LOAELs for Point of Departure selection. (Refs. 23). A benchmark dose, or BMD, is a point estimate along a dose-response curve that corresponds to a specific response level. For example, a BMD<sup>10</sup> represents a 10% change from the background level (the background level is typically derived from the control group). In addition to a BMD, a confidence limit may also be calculated. Confidence limits express the uncertainty in a BMD that may be due to sampling and/or experimental error. The lower confidence limit on the BMD is termed the benchmark dose limit (BMDL). Use of a BMD or BMDL for deriving the Point of Departure allows more precise estimates of the Point of Departure, resulting in tighter confidence intervals. Use of the BMDL also helps ensure with high confidence (e.g., 95% confidence) that the selected percentage of change from background is not exceeded. Numerous scientific peer review panels over the last decade have supported the Agency's application of the BMD approach as a scientifically supportable method for deriving Point of Departures in human health risk assessment, and as an improvement over the historically applied approach of using NOAELs or LOAELs. (Refs. 24, 25, and 26). The NOAEL/LOAEL approach can look at the dose response at only the few doses used in a study, and is therefore limited by the characteristics of the study design, such as dose selection, dose spacing, and sample size. (Ref. 23 at 3-5). With the BMD approach, all the dose response data are used to derive a dose response curve. For all of these reasons, BMD analysis is preferred by EPA to the NOAEL/LOAEL approach of selecting a Point of Departure from studies

when the available data are amenable to BMD modeling consistent with the biological processes relevant to the study in question.

#### **IV. Dichlorvos**

Dichlorvos is a chlorinated organophosphate pesticide that inhibits plasma, red blood cell (RBC), and brain cholinesterase in a variety of species. (Ref. 3 at 122-123). Cholinesterase inhibition is a disruption of the normal process in the body by which the nervous system chemically communicates with muscles and glands. Although cholinesterase inhibition in the nervous system is not itself regarded as a direct adverse effect, it is "generally accepted as a key component of the mechanism of toxicity leading to adverse cholinergic effects." (Ref. 27 at 25; see 73 FR 42688-42689). Inhibition of blood cholinesterase "is not an adverse effect, but may indicate a potential for adverse effects on the nervous system" and thus serves as a "surrogate" for cholinesterase inhibition in the nervous system (Ref. 27 at 28). Subchronic and chronic oral dichlorvos exposures to rats and dogs as well as chronic inhalation dichlorvos exposure to rats resulted in significant decreases in plasma, RBC, and/or brain cholinesterase activity. Repeated, oral subchronic dichlorvos exposures in male humans were associated with statistically and biologically significant decreases in RBC cholinesterase inhibition. These cholinesterase effects occurred at dose levels below levels at which any other adverse effect was seen. Generally, there was no evidence of increased sensitivity to young animals following exposure to dichlorvos. No evidence of increased sensitivity to young animals was seen following *in utero* dichlorvos exposure to rat and rabbit fetuses as well as pre/post natal dichlorvos exposure to rats in developmental, reproduction, and comparative cholinesterase studies. The only evidence of sensitivity in the young was seen in one parameter, auditory startle amplitude, in a developmental neurotoxicity study; however, the effects in the rat pups in that study were at levels well above levels that result in RBC cholinesterase inhibition.

Because inhibition of cholinesterase activity was identified as the most sensitive effect, it was selected as the toxicity endpoint for assessment of risks for all acute and chronic dietary exposures, as well as short-, intermediate-, and long-term (chronic) dermal, inhalation, and incidental oral residential exposures. For each risk assessment scenario, EPA selected a Point of Departure based on either an animal or human study taking into account the duration of the study and the route of exposure used in the study. (Ref. 3 at 130-135). These Points of Departure were used in calculating RfD/PADs and acceptable MOEs. Due to the lack of sensitivity differences between adults and juveniles, the resulting RfD/PADs and acceptable MOEs were designated as applicable to all population subgroups, including infants and children. Animal studies were used in choosing levels of concern for evaluating risk from acute and chronic dietary exposure; acute dermal exposure; and acute and chronic inhalation exposure. A human study (the Gledhill study) was used in evaluating risk from short-term incidental oral exposure; short-, intermediate-, and long-term dermal exposure; and short- and intermediate-term inhalation exposure. All of the studies from which a Point of Departure was selected were conducted in adults (adult humans or adult animals). (See Table 1).

Safety factor determinations used in determining the level of concern for each risk assessment scenario differed based on whether EPA relied on one of several different animal studies or a human study for the Point of Departure for that scenario. For levels of concerns derived from a Point of Departure from an animal study, EPA generally applied a 100X safety factor (10X for interspecies variability and 10X for intraspecies variability). Based on a weight-of-the-evidence evaluation, EPA removed the 10X FQPA safety factor for risk assessments based on an animal study. (See Table 1). EPA's weight-of-the-evidence evaluation concluded that (1) the toxicity database was complete; (2) most of the data indicated no increased sensitivity in the young and the only evidence of increased sensitivity occurred at levels well above the Points of Departure used for es-

establishing the levels of concern; and (3) its estimate of human exposure to dichlorvos was not understated.

For levels of concerns derived from a Point of Departure from the human study, EPA applied a 10X safety factor for intraspecies variability and a 3X FQPA safety factor. (72 FR 68694-68695). No interspecies factor was applied because EPA was not extrapolating a level of concern in humans from a dose in an animal study. The weight-of-the-evidence balance for the FQPA safety factor was slightly different for risk assessments relying on the Gledhill human study for the Point of Departure. In addition to all of the considerations pertaining to the assessments with an animal-derived Point of Departure, the Gledhill-based risk assessments introduced another factor to consider – namely, that the Gledhill study raised a data completeness issue due to the fact that it only identified a LOAEL. This latter factor convinced EPA to retain a portion of the FQPA safety factor when relying on the human study for the Point of Departure. EPA concluded, however, that reliable data supported reduction of the 10X factor to 3X because the effect seen at the LOAEL in that study was so marginal (16 percent RBC cholinesterase inhibition) that a lower dose would have been unlikely to detect any adverse effect. (72 FR 68694-68695; see Table 1).

**Table 1.--Summary of Risk Assessment Scenarios, Population Groups, and Uncertainty/Safety Factors for Dichlorvos**

Scenario	Study from which Point of Departure taken	Age and Species of Study Subjects	Population Groups Covered by Risk Assessment	Uncertainty/Safety Factors
Acute Dietary	Rat acute oral cholinesterase study	Adult rats	All population groups, including infants and children	Interspecies – 10X Intraspecies – 10X FQPA – 1X

Chronic Dietary	1-year dog study	Adult dogs	All population groups, including infants and children	Interspecies – 10X Intraspecies – 10X FQPA – 1X
Short-term Incidental Oral	Human 21-day oral study	Adult humans	All population groups, including infants and children	Interspecies – 1X Intraspecies – 10X FQPA – 3X
Acute Dermal and Acute Incidental Oral	Rat acute oral cholinesterase study	Adult rats	All population groups, including infants and children	Interspecies – 10X Intraspecies – 10X FQPA – 1X
Short-, Intermediate- and Long-term Dermal	Human 21-day oral study	Adult humans	All population groups, including infants and children	Interspecies – 1X Intraspecies – 10X FQPA – 3X
Acute Inhalation	Rat acute oral cholinesterase study	Adult rats	All population groups, including infants and children	Interspecies – 10X Intraspecies – 10X FQPA – 1X
Short- and Intermediate-term Inhalation	Human 21-day oral study	Adult humans	All population groups, including infants and children	Interspecies – 1X Intraspecies – 10X FQPA – 3X
Long-term Inhalation	2-year rat inhalation study	Adult rats	All population groups, including infants and children	Interspecies – 10X Intraspecies – 3X FQPA – 1X

## **V. NRDC's Petition to Revoke Dichlorvos Tolerances and the Administrative Proceedings on the Petition**

### *A. NRDC's Petition and EPA's Denial of the Petition*

On June 2, 2006, the NRDC filed a petition with EPA which, among other things, requested that EPA conclude the dichlorvos tolerance reassessment process by August 3, 2006, with a finding that the dichlorvos tolerances do not meet the FFDCA safety standard and issue a final rule by August 3, 2006, revoking all dichlorvos tolerances. NRDC's petition contained dozens of claims as to

why dichlorvos' FFDCA tolerances should be revoked. After carefully considering all of NRDC's claims, the public comment received on the petition, and a revised risk assessment EPA conducted in response to the petition, EPA issued an order pursuant to FFDCA section 408(d)(4)(iii) denying the request to revoke dichlorvos' FFDCA tolerances. (72 FR 68662, December 5, 2007).

*B. NRDC's Objections and EPA's Denial of the Objections*

On February 1, 2008, NRDC filed, pursuant to FFDCA section 408(g)(2), objections to EPA's denial of its tolerance revocation petition and requested a hearing on those objections. NRDC's objections and requests for hearing included two main claims: (1) that EPA has unlawfully failed to retain the full 10X safety factor for the protection of infants and children; and (2) that it was unlawful for EPA to rely on a toxicity study for dichlorvos (the Gledhill study) that was conducted with humans. Because NRDC did not seek judicial review on EPA's substantive conclusions on the latter issue but only challenged EPA's denial of a hearing on the issue, and because the Second Circuit court on review did not reach the hearing issue, the Gledhill study is further discussed only to the extent it bears on the FQPA safety factor decision.

NRDC cited several grounds for its assertion that EPA unlawfully lowered the 10X children's safety factor. However, only two of its arguments were later raised in NRDC's judicial challenge to EPA's decision. First, NRDC claimed that EPA lacked adequate data on dichlorvos' potential effects on the endocrine system because EPA had not received data on endocrine effects through the Endocrine Disruptor Screening Program. Second, NRDC argued that EPA's choice of a 3X additional safety factor was based on generic data and "not [ ] on any data specific to DDVP." (Ref. 1 at 5).

EPA denied both of NRDC's reasons for its objection to the choice of a 3X FQPA factor. EPA rejected NRDC's endocrine data argument on both legal and factual grounds. EPA concluded that the statute gave it broad discretion to determine what data are needed in making a determination on the FQPA safety factor and that nothing in section 408(p), creating the Endocrine Disruptor Screening Program, overrode that broad discretion. As a factual matter, EPA found that it had adequate data on endocrine effects from the existing dichlorvos database. (73 FR 42697-42698)

EPA also rejected NRDC's claim that it relied on wholly generic data, rather than dichlorvos-specific data, in choosing a 3X FQPA factor. NRDC's argument here was that EPA chose 3X because EPA considers 3X to be a half-value of a 10X factor rather than on data pertaining to dichlorvos. In response, EPA noted that its petition denial order had comprehensively restated its basis for its FQPA safety factor decision, and that restatement focused in great detail on the toxicology data for dichlorvos, particularly, the data on the sensitivity of the young. (73 FR 42695). EPA further pointed out that although the statutory considerations underlying the FQPA safety factor generally supported removal of the 10X additional factor, the reason EPA chose to retain a 3X FQPA safety factor for some assessments was directly tied to a deficiency in a dichlorvos study (the Gledhill study) that is critical to those assessments. (*Id.*). Thus, there was no basis for NRDC's claim that EPA had not relied on dichlorvos-specific data in making its FQPA safety factor decision.

## **VI. Judicial Review of EPA's Denial Order**

### *A. NRDC's Petition for Judicial Review and the Matters Presented on Review*

NRDC petitioned the Second Circuit court for review of EPA's denial of certain of its objections and hearing requests. As to its hearing requests, NRDC argued that EPA improperly denied

its request for a hearing on statistical and informed consent issues presented by the Gledhill study. As to its objections, NRDC asserted (1) that, as a legal matter, EPA was required to retain the 10X FQPA factor if it did not have data from the Endocrine Disruptor Screening Program; and (2) that EPA's choice of a 3X FQPA factor was arbitrary and capricious because EPA had relied upon "generic assertions that unlawfully fail to take into account any dichlorvos-specific information for infants and children." (Ref. 28 at 37). NRDC supported the latter argument in the following fashion. First, it argued that EPA chose 3X solely because it was half of 10X. Second, NRDC asserted that EPA's consideration of the Gledhill study did not constitute "dichlorvos-specific information for infants and children" because the Gledhill study was conducted with adults. Third, NRDC dismissed EPA's reliance on dichlorvos developmental studies in animals on the ground that a prior case had held that EPA had not, in that particular case, offered an adequate explanation of how the data on developing animals supported the FQPA factor chosen.

In response, EPA explained that NRDC's focus on EPA's discussion of why 3X is considered half of 10X ignored the central part of EPA's analysis: an assessment of whether the dichlorvos data showed 3X would be safe. EPA responded to the claim of a failure to consider "dichlorvos-specific information for infants and children" by noting that the Gledhill study had not been considered in isolation in the decision on the FQPA safety factor but in the context of "the animal data showing no difference in adult-young sensitivity" because it was "that very data that shows why the Gledhill study is appropriate for the entire population . . . ." (Ref. 29 at 63). Further, EPA noted that NRDC's argument that EPA reliance on animal sensitivity data does not justify a choice of 3X contradicted the core of NRDC's claim – that EPA had not considered "dichlorvos-specific information for infants and children." (Id. at 62).

#### *B. The Second Circuit Court's Decision on Review*



On review, the Second Circuit court addressed three issues: (1) was EPA legally compelled to retain the 10X FQPA safety factor in the absence of obtaining data from the Endocrine Disruptor Screening Program; (2) did EPA adequately explain its decision on the FQPA safety factor; and (3) was NRDC entitled to an evidentiary hearing with regard to its claims regarding the alleged statistical and informed consent deficiencies in the Gledhill study.

1. *Endocrine data.* The court held that EPA was not statutorily required to retain the 10X FQPA factor in circumstances where it has not obtained the data required under the Endocrine Disruptor Screening Program. (658 F.3d at 219). The court found “no indication in the statute or legislative history that Congress . . . intended the children's safety factor to be mandatory in assessing the risks of all pesticides until EPA completed the estrogen disruptor screening program . . . .” (Id.). According to the court, “Congress allowed EPA to determine, based on all available data, whether there was ‘reliable data’ supporting a reduced or waived children's safety factor . . . .” (Id.).

2. *FQPA safety factor.* Contrary to the narrow FQPA safety factor issue presented to EPA in NRDC’s objections – did EPA’s decision on the FQPA safety factor rely on “a generic assertion [instead of being] based on any data specific to DDVP”? – the court framed the issue on the FQPA factor more broadly: “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.” (Id. at 201).

The court found that, for risk assessments relying on the Gledhill study in deriving the Point of Departure, EPA had provided essentially no explanation with regard to the FQPA safety factor. The court noted that EPA had retained an additional 3X safety factor for these risk assessments but

the court concluded that it was EPA's express position that this factor was not based on any evaluation of the risks to infants and children but rather was intended to address the lack of NOAEL in the Gledhill study only. According to the court, "[i]n 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 the risk to infants and children." (Id. at 216). Further, the court concluded that, unlike the risk assessments that were not based on the Gledhill study, EPA did not rely on the developmental animal studies showing no differential sensitivity between adult and juvenile animals. According to the court, "EPA explicitly stated that it did not rely on any animal studies." (Id. at 217). The court thought this abnegation of reliance of animal studies was confirmed by EPA's decision not to apply an interspecies factor to the Gledhill-based assessments. (Id.). Although the court noted that EPA called the 3X factor a FQPA factor, the court found that label to be insufficient absent an explanation "[i]n [e]ither its IRED [or] its two orders [of] 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.'" (Id.). The court held that EPA's reasoning concerning the marginal effects seen at the LOAEL in the Gledhill study did not constitute a sufficient explanation because EPA did not relate that reasoning "to 'potential pre- and post-natal toxicity and completeness of the data with respect to infants and children.'" (Id.). Finally, the court questioned EPA's analysis that the effects at the LOAEL were marginal suggesting that EPA had not done a proper statistical analysis. (Id. at 218).

Accordingly, the court concluded that, as to risk assessments that used the Gledhill study to derive the Point of Departure, EPA's order was arbitrary and capricious due to EPA's failure to provide an adequate explanation with regard to its decision on the FQPA safety factor. (Id.). Given this conclusion, the court vacated the aspect of EPA's order pertaining to risk assessments based on the Gledhill study and remanded the matter to EPA. (Id. at 220).

3. *Evidentiary hearing.* With regard to NRDC’s request for an evidentiary hearing on issues it raised concerning the Gledhill study, the court determined that it did not need to resolve this question given its disposition of the FQPA safety factor issue. As the court pointed out, “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.” (Id. at 219).

## **VII. FQPA Safety Factor Determination for Gledhill-based Assessments**

### *A. Introduction*

FFDCA section 408(b)(2)(C) expressly requires EPA to apply a default additional 10X safety factor for the protection of infants and children unless EPA determines, based on reliable data, that a different factor would be safe. Under the terms of the statute, this additional safety factor is imposed “to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.” (21 U.S.C. 346a(b)(2)(C)). To implement these statutory commands, EPA has released detailed guidance that advises EPA risk assessors in making decisions on the FQPA safety factor to focus on potential pre- and post-natal toxicity and the completeness of the toxicity and exposure databases. In the dichlorvos IRED and the two orders responding to NRDC’S dichlorvos petition, EPA devoted several pages to explaining how its decision to apply a 3X FQPA safety factor complied with the statutory directives on the FQPA safety factor and was consistent with its policy guidance document. (See Ref. 3 at 128-132; 72 FR 68694-68695; 73 FR 42695-42696). From start to finish this discussion centered on the issues of completeness of the toxicity and exposure databases for dichlorvos and the potential increased sensitivity of infants and children to dichlorvos from pre- and post-natal toxicity.

Nevertheless, in vacating, in part, EPA's dichlorvos order, the Second Circuit court held that there was a complete absence of an explanation from EPA as to how EPA's choice of a safety factor protected infants and children. As the court repeatedly stated, "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.'" (658 F.3d at 217). In fact, the court rejected EPA's claim to have applied any FQPA safety factor at all. According to the court, the additional safety factor applied by EPA could not be considered a FQPA safety factor given what the court viewed as EPA's denial that the additional safety factor had anything to do with infants and children. (Id. at 211, 216).

Following a close review of EPA's prior explanations and the court's opinion, EPA now recognizes that the discussion of the FQPA safety factor in its dichlorvos IRED and orders was less than transparent. EPA's explanation for its position on the FQPA safety factor used, at times, a form of short-hand that hid rather than elucidated its reasoning. In particular, EPA's short-hand appears to have led the court to the following two misunderstandings: (1) That EPA's use of a 3X safety factor to address the lack of a NOAEL in the Gledhill study had nothing to do with the safety of infants and children; and (2) that EPA did not consider the animal developmental data in making a determination on the FQPA safety factor for assessments relying on the Gledhill study. Clarification of EPA's position on these two issues is critical to an understanding of EPA's FQPA safety factor decision. Accordingly, on remand, EPA has first addressed how the Gledhill-based assessments relate to protection of infants and children and how EPA used animal developmental data in these assessments. Only then does EPA offer its explanation as to how, in light of the court's opinion, its choice of a FQPA safety factor for the Gledhill-based risk assessment is protective of the safety of infants and children, as required by FFDCA section 408(b)(2)(C).

## *B. Clarifications*

### *1. Applying a FQPA safety factor to address the lack of a NOAEL in the Gledhill Study.*

Numerous times in the IRED as well as its dichlorvos orders, EPA stated that an additional 3X safety factor was applied in risk assessments using the LOAEL in the Gledhill study as the Point of Departure due to a “lack of a NOAEL” in the study. (Ref. 3 at 133; 658 F.3d at 217 (collecting cites)). EPA explained that the safety factor was used to project a NOAEL for the study. The court interpreted these statements as meaning the 3X factor had nothing to do with the protection to infants and children. According to the court, “EPA explained that the 3X factor [used in conjunction with the Gledhill study] 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. at 214). Certainly, the narrow issue addressed by the use of the 3X factor was the lack of a NOAEL in the Gledhill study. However, extrapolating a NOAEL through use of a safety factor is not an end in itself. Rather, the safety factor was used to ensure that dichlorvos risk assessments relying on the LOAEL in the Gledhill study adequately protect the population groups covered by those assessments. Importantly, the population groups covered by the Gledhill-based assessments include infants and children. Thus, the 3X factor to account for the lack of a NOAEL in the Gledhill study was critical to protecting infants and children. However, EPA’s orders and IRED failed to make this linkage between the 3X factor and the safety of infants and children clear. That linkage is fleshed out in detail below.

As discussed in Unit III.B.2.v., prior to the passage of FQPA, EPA had applied an additional uncertainty factor to address a data deficiency such as when adverse effects were seen in the lowest dose of a toxicological study (*i.e.*, when the study did not provide a NOAEL). Such a factor is used to essentially extrapolate a NOAEL for the study. Without an additional safety factor, there is uncertainty as to whether reliance on the LOAEL as a Point of Departure in calculating a RfD/PAD or

MOE is adequately protective of the populations covered by the risk assessment scenario relying on that RfD/PAD or MOE.

EPA has interpreted the FQPA as codifying this LOAEL-to-NOAEL uncertainty factor as a FQPA safety factor when the factor is used in a portion of a risk assessment (i.e., in a particular exposure scenario) that assesses, at least in part, the risk to infants and children. (Ref. 10 at 11-16, A-3 – A-4). The logic here is straightforward. A study that fails to produce a NOAEL is considered to be a data deficiency that affects the completeness of the toxicity database. The statute specifically references completeness of the toxicity database as a reason for requiring an additional safety factor for the protection of infants and children. Thus, when the LOAEL from a study that lacks a NOAEL is chosen for the Point of Departure for a risk assessment applying to infants, children, or women of child-bearing age (for the purpose of protecting fetuses), the safety factor used to address this data deficiency is a FQPA safety factor for the protection of infants and children. This is the case whether or not the Point of Departure is used for infants, children, or women of child-bearing age *only* or for both adults and all other population groups, including infants and children. Many risk assessments for particular exposure scenarios use the same Point of Departure for both adults and infants and children because frequently the relevant toxicity data show a lack of differential sensitivity between adults and the young. However, use in a risk assessment of the same Point of Departure for both adults and the young does not make the FQPA safety factor provision inapposite. EPA's position is that any assessment of risk for a particular exposure scenario that includes, at least in part, an assessment of risks to infants and children triggers the FQPA safety factor provision. Nothing in section 408(b)(2)(C) limits the safety factor provision only to situations where infants or children are more sensitive than adults. For similar reasons, it is also irrelevant to application of the FQPA safety factor provision whether the Point of Departure is from a study involving

juveniles or adults. Points of Departure for assessing risks to infants and children are based on the studies showing the most sensitive effects, whether the studies are conducted in adults or juveniles. (See Ref. 17 at 452 (“[C]hronic and subchronic tests in [adult animals] have value in assessing potential risks to children by, for example, identifying target sites for toxicity and providing dose-response information that may be useful for human safety assessment, irrespective of life stage.”)). The critical factor for the FQPA safety factor provision is whether the study is being used for a Point of Departure for assessing risk to infants and children.

With this background, the connection between the use of a 3X safety factor to address the Gledhill study LOAEL and the protection of the infants and children can now be explicated. Because the Gledhill study produced cholinesterase effects at the lowest level in the subchronic studies in the dichlorvos database and the database showed no age-related sensitivity, (see discussion in Unit VII.C.), EPA chose the Gledhill LOAEL as the Point of Departure for assessing risks for short- and intermediate-term exposure scenarios to all population groups, including infants and children. In other words, the Gledhill LOAEL was selected as the Point of Departure for all population groups for these exposure scenarios because the dichlorvos database demonstrated that the Gledhill study not only provided the best measure of cholinesterase inhibition for protecting adults but that it was the best measure for protecting infants and children. Nonetheless, EPA also recognized that the data deficiency in the Gledhill study – the failure of the Gledhill study to identify a NOAEL – raises uncertainty as to what that study indicates regarding the threshold below which exposure to dichlorvos will not result in cholinesterase inhibition. To address this uncertainty and thus protect the safety of all population groups covered by the risk assessments, including infants and children, EPA chose to apply an additional safety factor of 3X. This choice of a safety factor was made under the rubric of the FQPA safety factor provision because the uncertainty raised by reliance on a

LOAEL both (1) affected the assessment of the risk to infants and children; and (2) was driven by a data deficiency affecting the completeness of the toxicity database. (73 FR 42695; 72 FR 68694-68695; Ref. 3 at 133, 134). Thus, the additional 3X safety factor used in assessments relying on the Gledhill study was not simply to address the lack of a NOAEL in that study but rather to ensure the protection of infants and children (among others) given that a LOAEL was used as the Point of Departure for assessing risk to infants and children for several exposure scenarios. Regrettably, the connection between a safety factor used to address the lack of a NOAEL in a study in adults and the protection of infants and children was not transparent in EPA's IRED or its denial of NRDC's petition and objections. That linkage should now be clear.

2. *Reliance on animal developmental data.* EPA's FQPA safety factor policy emphasizes the importance of considering the "weight-of-evidence analyses for the completeness of the toxicity database, the degree of concern for pre- and postnatal toxicity, and results of the exposure assessments" in making a safety factor determination. (Ref. 10 at 50). In particular, the policy stresses "taking into account all pertinent information in evaluating potential pre- and postnatal toxicity." (Id. at 29). The policy recognizes that human data on pre- and postnatal toxicity is "difficult to obtain" and for that reason discusses, in detail, how animal developmental data should be considered in evaluating the potential for pre- and post-natal toxicity in humans. (Id. at 28-31). Although EPA did discuss the animal data on juvenile sensitivity in its FQPA safety factor determination, (72 FR 68694-68695), the court concluded that EPA had not considered that data in making a determination on the FQPA safety factor for assessments relying on the Gledhill study for the Point of Departure.

To support this conclusion, the court opined that EPA's orders specifically referenced the animal developmental studies in conjunction with the safety factor determination for the non-Gledhill-based assessments but had not done so as to the Gledhill-based assessments. The court is



correct that EPA did not clearly explain that its discussion of the animal developmental data related both to the assessments based on a Point of Departure from animal data as well as the assessments relying on the Gledhill study for the Point of Departure. EPA's discussion of the Gledhill study, and the data deficiency therein, followed the analysis of the animal developmental data but did not directly reference that data or the statutory considerations bearing on the FQPA safety factor decision. (Id.). To avoid this error in its revised safety factor finding below, EPA has included a discussion of the data deficiency in the Gledhill study under the topic of "completeness of the data with respect to . . . toxicity" and also explicitly discussed how the statutory consideration pertaining to the potential for pre- or post-natal toxicity, and the animal data bearing on this issue, was considered in the context of the Gledhill-based assessments.

The court also concluded that "EPA explicitly stated that it did not rely on any animal studies" in connection with the Gledhill-based assessments, (658 F.3d at 217), citing to language in the IRED that specified that where the Point of Departure was chosen from the Gledhill study "there was no need to account for interspecies extrapolation . . . [s]ince the study was conducted in human subjects." (Ref. 3 at 133, 134). According to the court, "[w]hen EPA did rely on the animal studies . . . [it] properly applied a safety factor of '10X for interspecies differences.'" (658 F.23d at 217). The court appears to have drawn the conclusion that the interspecies factor should be applied whenever EPA considers animal studies in any aspect of the risk assessment. Thus, the court reasoned that because EPA did not apply an interspecies factor for the Gledhill-based assessments, it could not have considered the animal developmental data in the FQPA safety factor determination for dichlorvos.

The court has misapprehended the reason EPA uses an interspecies factor in risk assessments. The factor is not automatically applied whenever animal data are considered in any aspect

of a risk assessment. Rather, as explained in Unit III.B.2., the interspecies factor is used when extrapolating from a dose in an animal study (generally a NOAEL or LOAEL) on a milligram-per-kilogram of body weight basis to a dose in humans. (See Ref. 10 at 10 (an interspecies factor is used “if animal data have been used as the basis for deriving the hazard values”). The interspecies factor is designed to account for possible toxicokinetic and toxicodynamic differences in humans and laboratory animals that may result in differences in internal dose and organ sensitivity between humans and animals. Thus, in the dichlorvos animal assessments in which EPA relied on animal data for the Point of Departure, EPA did apply an interspecies factor. For those assessments, EPA was either extrapolating a RfD for humans from animal data or comparing the margin between human exposure and the dose in animals that was judged to be a NOAEL. No interspecies factor was necessary in assessments based on the LOAEL from the Gledhill study because EPA was not extrapolating from a NOAEL or LOAEL in laboratory animals to humans or comparing human exposure to a dose from an animal study. Rather, EPA had data in humans – the Gledhill study – and was relying on that data for the Point of Departure. There was no need to account for the toxicokinetic and toxicodynamics differences between humans and animals when deriving a safe dose for humans from a study conducted with humans.

EPA, however, did rely on the animal developmental data in the FQPA safety factor determination for the Gledhill-based assessments. But that reliance was for a purpose distinct and separate from use of the data for extrapolating a dose from animals to humans. In accordance with Agency FQPA safety factor policy, EPA considered the dichlorvos animal developmental data with regard to the important information it provides on whether the 10X intraspecies factor for dichlorvos is protective of infants and children. (Ref. 10 at 29). A primary focus of the animal developmental data (the rat and rabbit developmental studies, the rat reproduction study, the rat devel-

opmental neurotoxicity study, and comparative cholinesterase studies) is on the relative sensitivity of adult and juvenile animals. Because EPA would rarely have data on the relative sensitivity among different age groups of humans to a pesticide, these animal data help inform, as EPA policy makes clear, whether the 10X intraspecies factor is sufficiently protective of infants and children. (Id.).

Considering animal developmental data in evaluating the intraspecies factor is a standard part of EPA's risk assessment process. As discussed in Unit III.B.2 and above, animal developmental data are central both to establishing the justification for the 10X default value for the intraspecies factor and for evaluating the protectiveness of this default value for specific chemicals. Although broad-based surveys of data on adult/juvenile sensitivity in both humans and animals generally support the use of a 10X default value for the intraspecies factor, there is wide recognition that the possibility of heightened sensitivity in infants and children warrants obtaining particularized data on juvenile/adult animal sensitivity for individual chemical risk assessments. When these data are available, they may indicate that there is no heightened concern warranting an additional safety factor or that an additional factor is necessary above and beyond the default 10X value for the intraspecies factor. In a few cases, EPA has even relied, at least in part, on animal data as supporting a reduction in the default 10X intraspecies factor.

Yet, despite the centrality of animal data to the justification for and selection of the intraspecies factor, EPA is not aware of any instance where an interspecies factor has been applied solely for reliance on animal data on adult-juvenile sensitivity to evaluate the protectiveness of the human intraspecies factor. For example, EPA's long-established and consistent practice is not to apply an interspecies factor when relying on a human study for the Point of Departure even though a decision on the intraspecies factor is still an essential part of such assessments. Dourson et al. col-

lected a summary of all EPA's RfDs on EPA's Integrated Risk Information System (IRIS) as of May 2000 that used human data for the Point of Departure. (Ref. 17). All 24 such assessments identified used an interspecies factor of 1X (*i.e.*, no factor). EPA has identified 9 additional such risk assessments on IRIS post-dating May 2000, and each one of those also does not apply an interspecies factor. (Ref. 30). Even more on point are EPA pesticide risk assessments relying on human data. Since the promulgation of the 2006 Human Research Rule, EPA has accepted 10 human studies for use in pesticide risk assessments other than the Gledhill study. (*Id.*). A Point of Departure was selected from 9 of those 10 studies.<sup>1</sup> Yet, in none of those assessments did EPA apply an interspecies factor in conjunction with a Point of Departure from a human study even though the assessments do not focus on the human data exclusively. Animal developmental data play a critical part in these assessments, particularly where a FQPA safety factor analysis is required.

The FQPA safety factor analysis in the tolerance reassessment document for the pesticide ethephon provides a good example of this. With ethephon, “[t]he conventional UF of 10X for interspecies extrapolation was not applied because the endpoint selected for the risk assessment was from a human study.” (Ref. 31 at 6). At the same time, EPA noted that:

The Agency concluded that no FQPA Safety Factor is necessary to protect the safety of infants and children in assessing ethephon exposure and risks because the toxicology database for ethephon contains ac-

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<sup>1</sup> The one human study that was not used for selection of a Point of Departure was conducted with the pesticide oxamyl. The oxamyl human study was submitted for the purpose of justifying a reduction of the 10X interspecies factor despite use of an animal study for the Point of Departure. The Human Studies Review Board concluded that the “intentional human dosing study of oxamyl was sufficiently robust to be used for reducing the 10x inter-species (*i.e.* animal to human) uncertainty factor in the cumulative risk assessment for the N-methyl carbamates.” (Ref. 36 at 28). Thus, it is not even a given that a full interspecies factor will be applied when an animal study is relied upon to extrapolate a dose in humans.

ceptable guideline developmental and reproductive studies as well as acute and subchronic neurotoxicity studies. [Guideline studies are conducted in animals. (40 CFR 158.500)]. The Agency also concluded that there is no quantitative or qualitative evidence of increased susceptibility following in utero or postnatal exposure in any of the developmental or reproductive studies. The RfDs and toxicity endpoints established are protective of pre/postnatal toxicity following acute and chronic exposures.

(Id.). A variation on the approach in ethephon is the safety/uncertainty factors chosen in assessing the risk of the pesticide methomyl. (Ref. 32 at 5). For the methomyl risk assessments that relied on a human study for the Point of Departure, the Agency applied a 10X intraspecies, a 1X interspecies factor (no extrapolation from a dose in animals to humans), and a 2X (data-derived) FQPA safety factor. The 2X FQPA factor was chosen because, unlike dichlorvos, the adult/juvenile comparative cholinesterase data in rats showed that juveniles were approximately twice as sensitive to methomyl as adults. Thus, a 2X FQPA safety factor was applied to ensure that the 10X intraspecies factor was sufficiently protective. However, just as with dichlorvos and ethephon, no interspecies factor (1X) was used because the Point of Departure was derived from a human, not animal, study. A final example illustrating that consideration of animal data in conjunction with choice of a Point of Departure from a human study does not result in use of a 10X interspecies factor is the assessment of the pesticide chloropicrin. With chloropicrin, EPA relied upon a human study for the Point of Departure and thus no interspecies factor (1X) was applied. However, EPA's consideration of the data from humans and animals also led EPA to conclude that no intraspecies factor (1X) was needed ei-

ther. (Ref. 33). No interspecies factor was applied as a result of consideration of animal data in evaluating the need for an intraspecies factor.

Use of a 10X interspecies factor for reliance on animal developmental data to evaluate the protectiveness of the intraspecies factor would also lead to illogical results. For example, animal developmental data are now considered so critical to evaluating pre- and post-natal toxicity that the FQPA imposes a presumptive 10X safety factor in their absence. Yet, once the data are submitted, it does not make sense to replace the 10X safety factor that addressed their absence with a safety factor of equivalent value to address their mere use for evaluation of pre- and post-natal toxicity. Leaving aside what the animal developmental data show, there cannot be equal need for safety factors both in the absence and presence of adequate animal developmental data.

In sum, it would not only be unprecedented, but inconsistent with well-established safety factor practice, to suggest that the mere consideration of animal data in evaluating the protectiveness of the intraspecies factor triggers application of an interspecies factor. Importantly, under the FFDCA section 408, EPA is only authorized 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.” 21 U.S.C.

346a(b)(2)(D)(ix).

Unfortunately, EPA’s short-hand description of its FQPA determination misled the court regarding EPA’s consideration of the animal developmental data. Further, EPA’s brief explanation for why it did not apply an interspecies factor did not clarify the situation. This, in turn, resulted in confusion regarding the role of the interspecies factor. EPA’s revised FQPA safety factor explanation attempts to avoid such pitfalls.

### *C. Revised FQPA Safety Factor Decision*

1. *Introduction and background.* The Second Circuit court has vacated that portion of EPA's order on NRDC's objections "assessing the risk of dichlorvos based on the Gledhill study . . ." (658 F.3d at 220). The court found that EPA had "failed to explain why it did not use a 10X children's safety factor" for those assessments. (*Id.*).

In the IRED, EPA relied on the Gledhill human study for selection of the Point of Departure for assessing dermal (short-, intermediate-, and long-term), incidental oral (short-term), and inhalation (short- and intermediate-term) risk for all population subgroups, including infants and children. Agency-wide guidance on Reference Dose selection emphasizes that human data provides the best source for assessing human risk: "Adequate human data are the most relevant for assessing risks to humans. When sufficient human data are available to describe the exposure-response relationship for an adverse outcome(s) that is judged to be the most sensitive effect(s), reference values should be based on human data." (Ref. 19 at 4-12; *see* Ref. 10 at 33 ("human data are the most relevant data for assessing health risks")). EPA chose the Gledhill study, in particular, for determination of the Point of Departure because it evaluated cholinesterase inhibition, the most sensitive effect for dichlorvos as shown by animals studies, and because the Gledhill study has "the lowest LOAEL established for RBC cholinesterase inhibition in a repeated oral exposure to dichlorvos." (Ref. 3 at 133). Specifically, it was the lowest LOAEL considering both the human and animal studies and cholinesterase effects in adults and juveniles. EPA's determination that the Gledhill study "is sufficiently robust for developing a Point of Departure for estimating dermal, incidental oral, and inhalation risk from exposure to DDVP," was concurred in by the Human Studies Review Board, an independent expert panel of scientists. (72 FR 68675).

The level of concern for the risk assessments relying on the Gledhill study for the Point of Departure was expressed in terms of a target MOE of 30. That value was based on an intraspecies uncertainty factor of 10X and a FQPA safety factor of 3X. Although EPA concluded that neither the data on pre- or postnatal toxicity or on exposure to dichlorvos showed a need for a FQPA safety factor, EPA found that the data deficiency with regard to the Gledhill study – namely, its lack of a NOAEL – justified the retention of a 3X FQPA safety factor.

2. *FQPA safety factor decision.* In making a FQPA safety factor determination, EPA follows a weight-of-the-evidence approach that focuses on the three considerations explicitly noted in FFDCA section 408(b)(2)(C): the completeness of the toxicity database; the potential for pre- and post-natal toxicity; and the completeness of the exposure database. (Ref. 10 at iv). Each of those considerations is discussed below.

i. *Completeness of the toxicity database.* In ruling on NRDC's petition, EPA concluded that it had a complete toxicity database under the pesticide data requirements in 40 CFR part 158. This included all required data specifically pertaining to effects on the young – developmental studies in two species (rat and rabbit); a two-generation reproduction study in rats; and a developmental neurotoxicity study in rats. EPA also had comparative cholinesterase inhibition data in adult and juvenile rats. EPA did not have data submitted pursuant to the Endocrine Disruptor Screening Program, but for the reasons explained in its order denying NRDC's petition, EPA has concluded that it has adequate data on dichlorvos' endocrine effects for the purposes of its FQPA safety factor decision. (73 FR 42697-42698).

In addition to these standard animal toxicity studies, the dichlorvos registrant had submitted one toxicity study in humans, the Gledhill study, that EPA had determined was in compliance with its Human Research Rule. (40 CFR part 26). As discussed below, there is a data deficiency issue



with this study that is pertinent to the completeness of the toxicity database consideration. Although this study was conducted in adults, it is highly relevant to the protection of infants and children because EPA has, for the reasons explained in Units VII.B.1. and VII.C.1, selected the Gledhill study for identifying a Point of Departure for as to several risk assessment scenarios for all population groups, including infants and children. Thus, how EPA addresses the data deficiency in the Gledhill study will directly affect how it assesses risks to infants and children.

The Gledhill study was a repeat dose study measuring RBC cholinesterase inhibition in control and dichlorvos- treated human subjects. Only a single dose level (7 mg) was used in the study. Cholinesterase inhibition in the treated subjects reached a level of 16 percent by day 18 of treatment (i.e., cholinesterase activity levels declined to 84 percent of the pre-dose mean by day 18). As shown in Table 2 below (reprinted from EPA's Data Evaluation Record of the Gledhill study and the Gledhill study report), the statistical analysis of the results of the Gledhill study shows a high level of statistical significance (at the 1 percent level)<sup>2</sup> for cholinesterase activity levels both between controls and treated subjects and between pre- and post-dosing cholinesterase levels for treated subjects for most days post-dosing.

**Table—2. Results of the Gledhill study**

Timepoint	Placebo (n = 3)			Dosed (n = 6)		
	Mean	SD	% pre-dose mean	Mean	SD	% pre-dose mean

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<sup>2</sup> Statistical significance is a term used to describe observed data that differ from the overall distribution of values by a level that is unlikely to be due to random error. Statistical significance is examined in terms of the probability of the observed differences occurring. By convention, observed values that have a 5 or 1 percent chance of occurring are treated as statistically significant, with 1 percent being the more rigorous standard. (Ref. 43).

Pre-dose	18483.52	1346.91	100	17738.33	1713.50	100
Day 1	17930.00	1404.24	97	17628.33	1914.45	99
Day 2	18180.00	1564.7	98	16816.67*	1546.63	95
Day 4	18740.00	1771.13	101	16933.33**	1597.33	95
Day 7	18530.00	1888.36	100	16181.67**( <sup>††</sup> )	1759.48	91
Day 9	18460	1007.03	100	16708.33	2504.97	94
Day 11	19210.00	1035.95	104	16036.67**( <sup>††</sup> )	1654.38	90
Day 14	18490.00	1642.35	100	15333.33**( <sup>††</sup> )	1250.34	86
Day 16	17706.67	2470.15	96	15191.67**( <sup>††</sup> )	1062.59	86
Day 18	18260.00	2298.87	99	14855.00**( <sup>††</sup> )	1198.51	84

\* Statistically significant difference from pre-dose at the 5% level (paired t-test)

\*\* Statistically significant difference from pre-dose at the 1% level (paired t-test)

<sup>††</sup> Statistically significant difference between placebo and dose groups at the 1% level (t-test, based on repeated measures of analysis of covariance).

(Refs. 34 and 35).

EPA found these statistical results to be sufficiently “robust” to support use of the Gledhill study as the Point of Departure. This judgment was concurred on by the Human Studies Review Board. (Ref. 36). The Board relied upon the following aspects of the study: 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. at 39). The HSRB concluded that “[a]lthough a study using a single dose level is not ideal for establishing a LOAEL, there was general consensus that RBC cholinesterase is a well-characterized endpoint for compounds that inhibit acetylcholinesterase activity and therefore, because the decreased activity in RBC 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." (Id. at 41).

There is one significant deficiency with the Gledhill study, however. Because the study used a single dose level, and that dose was found to cause an adverse effect on RBC cholinesterase activity, the study does not identify a NOAEL. As discussed earlier, this type of deficiency is incorporated and addressed as part of the FQPA safety factor because it relates to the first consideration noted in FFDCA section 408(b)(2)(C) – completeness of the toxicity database. (*See* Unit III.B.2.vi.).

In deciding what level of safety factor is necessary to address this data deficiency, EPA is guided by EPA science policy on use of uncertainty factors, the scientific literature on safety factors, and EPA prior practice with regard to FQPA safety factor decisions. EPA's RfD policy recommends a default value of 10X for an uncertainty factor addressing the lack of a NOAEL but makes clear that "[t]he size of the LOAEL-to-NOAEL uncertainty factor may be altered, depending on the magnitude and nature of the response at the LOAEL." (Ref. 19 at 4-44). Further, as discussed in Unit III.B.2.v, Dourson et al. concluded that "[t]he data indicate that when faced with a LOAEL and not a NOAEL, the choice of uncertainty factor should generally depend on the severity of the effect at the LOAEL." (Ref. 9). In specific FQPA safety factor decisions, the magnitude of the response has frequently been an important consideration supporting use of a 3X FQPA safety factor to address reliance on a LOAEL for the Point of Departure. (*See, e.g.*, 75 FR 22245, 22249, April 28, 2010 (selecting a 3X FQPA safety factor for lack of a NOAEL where "[t]he neurotoxic effects in this study showed a good dose response which resulted in minimal effects on motor activity and locomotor activity at the LOAEL."); 74 FR 67090, 67094, December 18, 2009 (selecting a 3X FQPA safety factor for lack of a NOAEL where "[t]he gastric lesions (most sensitive effect)

are due to the direct irritant properties of endothall (i.e., portal effects) and not as a result of frank systemic toxicity; the severity of the lesions were minimal to mild; and there was no apparent dose-response for this effect.”); 74 FR 53172, 53177, October 16, 2009 (“The concern is low for the use of a LOAEL to extrapolate a NOAEL, given the relatively insignificant nature of the effect (transient diarrhea seen in the rat); the fact that diarrhea was only seen in studies involving gavage dosing in the rat but not in repeat dosing through dietary administration in rats, mice, rabbits, and dogs; the very high dose level needed to reach the acute oral lethal dose (LD)<sub>50</sub> (>5,000 milligrams/kilogram (mg/kg)), and the overall low toxicity of azoxystrobin.”); 74 FR 26536, 26541, June 3, 2009 (selecting a 3X FQPA safety factor for lack of a NOAEL where “[t]he response was marginal at the LOAEL.”); 72 FR 41224, 41228, July 27, 2007 (“The uncertainty factor of 3X for use of the LOAEL instead of the NOAEL is considered appropriate because an increased incidence and severity of epithelial hyperplasia, hyperkeratosis and ulceration of the non-glandular region of the stomach in females were seen in few animals and were minimal in severity and observed in one sex only.”); 72 FR 33901, 33905, June 20, 2007 (“The 3X factor is considered to be protective because the incidence of the effects at the lowest dose tested was only marginally higher than the historical controls.”); 71 FR 71052, 71056, December 8, 2006 (“A 3x safety factor (as opposed to a 10x) for the lack of a NOAEL in this critical study is adequate because the magnitude of the response was low (low incidences without dose response) and the effect of concern was seen in an unusual strain (Chinchilla) of rabbits and not in the New Zealand strain commonly used in developmental toxicity studies.”)).

EPA’s policy on cholinesterase inhibition provides important guidance on characterizing the magnitude of a RBC cholinesterase finding. The policy explains that cholinesterase activity data is treated “like most continuous endpoints (*i.e.*, graded measures of response such as changes in organ

weight, hormone levels or enzyme activity),” in that “no fixed generic percentage of change from the baseline is considered to separate adverse from non-adverse effects.” (Ref. 27 at 14). Given the continuous nature of the inhibition response, “OPP has used statistical significance, rather than a fixed percentage of response from baseline, as the primary, but not exclusive, determinant of toxicological and biological significance in selecting Points of Departure.” (Id.) Nonetheless, the policy advises that, in examining what level of cholinesterase inhibition will be judged an adverse effect, the level of inhibition must be critically evaluated “in the context of both statistical *and* biological significance.” (Id. at 37) (emphasis in original). Although the policy notes that “[n]o fixed percentage of change (e.g., 20% for cholinesterase enzyme inhibition) is predetermined to separate adverse from non-adverse effects,” (Id.), it explains that “OPP’s experience with the review of toxicity studies with cholinesterase-inhibiting substances shows that differences between pre- and post-exposure of 20% or more in enzyme levels is nearly always statistically significant and would generally be viewed as biologically significant.” (Id. at 37-38). The policy recommends that “[t]he biological significance of statistically-significant changes of less than 20% would have to be judged on a case-by-case basis, noting, in particular the pattern of changes in the enzyme levels and the presence or absence of accompanying clinical signs and/or symptoms.” (Id. at 38). The policy notes that similar or higher levels of cholinesterase inhibition are used “in monitoring workers for occupational exposures (even in the absence of signs, symptoms, or other behavioral effects).” (Id. at 31). For example, the policy points out that the California Department of Health Services requires that workers exposed to toxic chemicals such as organophosphate pesticides be removed from the workplace if “red blood cell cholinesterase levels show 30% or greater inhibition,” and that the World Health Organization “has guidelines with the same RBC action levels (i.e., 30% or greater inhibition).” (Id.). In conducting Benchmark Dose analyses for dichlorvos, as well as other organophosphate pesti-

cides, EPA generally has used a 10 percent inhibition level as indicating an adverse effect for both RBC and brain compartments given that both of these compartments were used for developing Points of Departure. (Ref. 37 at I.B p.17). A close examination of the cholinesterase inhibition data for dichlorvos, however, has shown that, while both brain and RBC compartments have similar levels of inhibition for acute or very short-term exposures, for longer-term exposures brain cholinesterase inhibition is much less sensitive than RBC inhibition and thus 20 percent RBC inhibition would be adequately protective. (72 FR 68691; Ref. 38). RBC cholinesterase inhibition is not itself an adverse effect; rather, it is used as a surrogate for effects on the nervous system.

In the Gledhill study, the average level of RBC cholinesterase inhibition of the final day of treatment was 16 percent. Although the level of RBC cholinesterase inhibition was relatively low and not accompanied by clinical signs, EPA concluded, contrary to the study's author, that the 7 mg dose did produce an adverse effect. In reaching this conclusion, EPA relied on the uniform nature of the results in the subjects that showed a clear pattern of increasing response over time and a high level of statistical significance in the differences in cholinesterase inhibition both between treated and control subjects and between pre-treatment and post-treatment of individual subjects. Nonetheless, consistent with its cholinesterase policy and its conclusions in regard to other dichlorvos cholinesterase data, EPA found the magnitude of the change in cholinesterase levels to be marginal. The Human Studies Review Board agreed both with EPA's determination on adversity and the marginality of the response. As to the marginality of the response, the Board specifically noted that "because the decreased activity in RBC 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." (Ref. 36 at 41). Under EPA's cholinesterase policy, the level of cholinesterase inhibition in the Gledhill study falls at the low end

of the scale of what might be considered an adverse effect and the policy recommends a case-by-case inquiry into the adversity determination for inhibition at this level. Accordingly, EPA determined previously, and reaffirms in this order, that a full 10X safety factor is not needed to address the lack of a NOAEL in the Gledhill study. When a full order of magnitude of additional protection (i.e.  $10^1$ ) is unnecessary, EPA will generally use a half of that value (i.e.  $10^{-5}$  or approximately 3X) if that value is protective. Here, EPA determined, and in this order reaffirms, that the marginal nature of the cholinesterase response shows that a 3X factor is safe.

In reaching its determination, EPA placed, and continues to place, great weight on the view of the Human Studies Review Board. This Board was created by EPA in response to a congressional mandate. (71 FR 6138 (February 6, 2006)). It is comprised of non-EPA scientists, overwhelmingly from academia, who are specialists in the field of bioethics, biostatistics, human health risk assessment, and human toxicology. (73 FR 42690). The members of the Board at the time the Gledhill study was considered are listed in Appendix 1 to EPA's prior denial order. (73 FR 42713). The Board is charged with reviewing both the ethics and scientific merit of intentional exposure human studies. Its proceedings are conducted in public and it accepted three rounds of public comment on review of the Gledhill study: (1) Written comment submitted prior to its open meeting on dichlorvos; (2) oral comments at the open meeting; and (3) oral comments at a telephone conference on its proposed decision. (73 FR 42692). No comments were submitted prior to the Board's review suggesting that the cholinesterase response was greater than a marginal response and no meaningful comments were submitted to the Board or EPA, following release of the proposed and final Board opinions, contesting the conclusions of this independent and expert scientific panel on this point. The Board's conclusion with regard to the marginality of the cholinesterase inhibition effects in the Gledhill study are strongly supportive of EPA's choice of a 3X factor to address the

lack of a NOAEL in the Gledhill study. After all, the Board concluded that “it was unlikely that a lower dose would produce a measurable effect in RBC cholinesterase activity.” (Ref. 36 at 41).

Use of a 3X factor is protective because it represents a choice of not simply of any lower dose (decreasing the dose by 10 percent fits this criterion) but of a significantly lower dose than that in the Gledhill study for estimating risk (by applying a 3X factor EPA was essentially dividing the dose by a factor of 3).

The court suggested in its opinion that EPA had not conducted an adequate statistical analysis to determine the accuracy of the 16 percent cholinesterase inhibition figure and thus had no basis for making a conclusion “with any level of precision [as to] the magnitude of the cholinesterase inhibition.”<sup>3</sup> 658 F.3d at 218. Although EPA scientists and the scientists on the Human Studies Review Board, including the three biostatisticians, found the statistical analysis sufficient to support their conclusion on the marginality of the cholinesterase effect, EPA agrees that a precision analysis, i.e., the calculation of confidence intervals, conveys valuable information on the plausible range in which, within a certain degree of probability, the true value lies. Accordingly, EPA has calculated the confidence intervals for the mean cholinesterase inhibition levels. (Ref. 39). For the days 14, 16, and 18 which had average cholinesterase inhibition levels of 14 percent, 14 percent, and 16 percent, respectively, this calculation shows a 95 percent confidence that average inhibition is be-

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<sup>3</sup>The court stated that EPA had found the Gledhill study to “have had sufficient *statistical power* to detect a cholinesterase inhibition greater than 0, [but] 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.” (Ref. at 218) (emphasis added). To clarify, EPA did not do a “statistical power” calculation because statistical power is a way of determining the probability of whether a study would detect an effect of a given size if such an effect is there to find. The concern is that a study may indicate that there is no effect when, in fact, the study missed the effect because it had a low probability of finding it (i.e., the study gives a false negative). Because the Gledhill study identified the positive effect it was looking for (cholinesterase inhibition), EPA dismissed NRDC’s arguments regarding statistical power as irrelevant. (73 FR 42704-42706). What EPA’s statistical analysis of the Gledhill study did show was that there was a statistically significant difference (at the level of 1 percent) in cholinesterase inhibition between control and treated subjects and between pre- and post-dosing for treated subjects on most days of treatment. That is, the differences in cholinesterase inhibition between controlled and treated subjects and between pre- and post-dosing of treated subjects were very unlikely to have been due to chance.



tween 9- and 18 percent, 9- and 19 percent, and 8- and 24 percent, respectively. Because these ranges of RBC cholinesterase inhibition consistently fall at the low end of what might be found to be a statistically and biologically significant effect on RBC cholinesterase activity, EPA reaffirms its conclusion that the RBC cholinesterase inhibition seen in the Gledhill study was marginal.

Finally, the determination to retain a FQPA safety of 3X for assessments for which the Point of Departure was selected from the Gledhill study is also supported by two BMD analyses on the dose levels causing cholinesterase inhibition in animals performed in conjunction with the IRED. As explained earlier, BMD analysis is preferred by EPA to the NOAEL/LOAEL approach of selecting a Point of Departure from studies because all of the data from a study can be used in deriving a dose response curve. (Ref. 23). In the absence of the Gledhill study, these analyses would substitute for the LOAEL in the Gledhill study for selection of the Point of Departure for short- and intermediate-term risk assessments because they define the most sensitive effect for these exposure durations. The first of these analyses is a BMD analysis of comparative cholinesterase studies conducted in adult and juvenile rats. (This BMD analysis is discussed in more detail immediately below in the section on “pre- and post-natal toxicity.”) The lowest BMDL from that analysis (focusing on pooled historical controls) is 0.38 mg/kg/day. (Ref. 42). The second BMD analysis is an analysis of the cholinesterase inhibition results of the subchronic toxicity rat study. (Ref. 40). There, the BMDL was calculated as 0.4 mg/kg/day. The only other potential animal study for use in selecting a Point of Departure for short- and intermediate-term exposures, the subchronic neurotoxicity study, had a significantly higher LOAEL (7.5 mg/kg/day) and produced percentage inhibition levels consistent with, or lower than, the other animal cholinesterase studies. (Ref. 41). A 100X safety factor to address interspecies extrapolation and interspecies variability would be used with these BMDLs if they were chosen as Points of Departure. No additional FQPA factor would

be needed for the same reasons that a FQPA factor was not applied to the other assessments relying on animal data. (72 FR 68694-68695). Reliance on the BMD analyses for the Point of Departure with a 100X safety factor produces a level of concern that is comparable to using the Gledhill study for the Point of Departure with a 30X safety factor. This is most easily seen if alternative RfD/PADs are calculated using the BMD analyses from the comparative cholinesterase studies and the subchronic study and from the LOAEL in the Gledhill study. With Gledhill study, the LOAEL of 0.1 mg/kg/day would be divided by 30 (10X for intraspecies and 3X for FQPA) yielding a RfD/PAD of 0.0033 mg/kg/day. With the BMD analyses, the BMDL of 0.38 mg/kg/day or 0.4 mg/kg/day would be divided by 100 (10x for interspecies and 10X for intraspecies) for a RfD/PAD of 0.0038 mg/kg/day or 0.004 mg/kg/day, respectively. The similarity of these results, whether extrapolating from the animal or human data, provides extra confidence in EPA's FQPA safety factor decision. Additionally, EPA notes that reliance of the Gledhill study produces a marginally lower and thus more protective level of concern.

Thus, the completeness of the toxicity database consideration indicates that an additional safety factor of no greater than 3X is needed to protect the safety of all populations, including infants and children, due to a data deficiency in the Gledhill study. This decision is consistent with EPA policies on RfD selection, the FQPA safety factor, and cholinesterase inhibition, and with the scientific literature on safety/uncertainty factors. It is also consistent with long-established practice in making FQPA safety factor decisions in circumstances where a LOAEL-to-NOAEL extrapolation is necessary. Finally, EPA's scientific conclusions underlying this determination have been concurred in by the Human Studies Review Board, an independent panel of scientific experts in the field of toxicology and bio-statistics.

ii. *Pre- and post-natal toxicity.* There was no evidence for increased susceptibility of rat and rabbit offspring to prenatal or postnatal exposure to dichlorvos. In both rat and rabbit developmental studies, no developmental effects were observed. In the rat reproduction study, the parental/systemic NOAEL/LOAEL was 2.3/8.3 mg/kg/day, which was identical to the reproductive/offspring NOAEL/LOAEL. The developmental neurotoxicity study showed evidence of sensitivity in one parameter, auditory startle amplitude. However, there are no residual concerns for sensitivity from this parameter because the effects in pups were seen at a dose well above the Points of Departure upon which EPA is regulating and a clear NOAEL for the effect (again, well above the Points of Departure) was identified.

In addition, EPA evaluated the relative sensitivity of adult and juvenile animals to cholinesterase inhibition from dichlorvos exposure using a Benchmark Dose (BMD) analysis. For dichlorvos, EPA did a BMD analysis of the rodent toxicity studies for adult and juvenile cholinesterase inhibition (in both brain and RBC) in acute and repeated dose scenarios. (Refs. 3 at 129; 42). EPA analyzed for a BMD showing a 10 percent inhibition of cholinesterase. EPA found similar results for BMDs and BMDLs for cholinesterase inhibition in both the acute and repeated dose scenarios for compartments (brain or RBC), sex, and age. In other words, this analysis indicated that there was no significant sensitivity difference with regard to cholinesterase inhibition between adults and juveniles.

These data showing a lack of sensitivity of juvenile animals relative to adults indicate a low level of concern that the intraspecies factor applied to the Point of Departure from the Gledhill study will fail to protect infants and children. Therefore, the potential pre- and post-natal toxicity consideration, by itself, indicates that risks to infants and children can be safely assessed absent an additional safety factor.

iii. *Completeness of the exposure database.* EPA has extensive data for estimating human exposure levels to dichlorvos. Although NRDC objected to portions of EPA's dietary exposure assessment, after a careful re-analysis of that assessment EPA concluded that its dichlorvos exposure estimate from food, if anything, overstates dichlorvos exposure given the many conservatisms retained in the food exposure assessment and dichlorvos' documented volatility and rapid degradation. (73 FR 42699; 72 FR 68686). Further, EPA concluded that drinking water exposure to dichlorvos was also likely to have over-estimated exposure because of conservative assumptions. (72 FR 68679-68680). A similar conclusion was reached as to residential exposure to dichlorvos after EPA revised this assessment taking into account concerns raised by NRDC. (72 FR 68691). Thus, the completeness of the exposure base consideration, by itself, also does not indicate a need for an additional safety factor to protect infants and children.

3. *Conclusion.* The FQPA safety factor provision requires EPA to presumptively retain an additional 10X safety factor for the protection of infants and children. EPA may apply a different factor only if reliable data show that factor to be safe. Under EPA policy, EPA considers whether the *additional* FQPA safety factor is warranted taking into account the other safety factors being applied.

For the Gledhill-based risk assessments, EPA has applied a 10X intraspecies safety/uncertainty factor to account for the potential for variable sensitivity among humans. EPA has not applied an interspecies factor in these risk assessments because the Point of Departure is drawn from a study in humans, not laboratory animals. (See Unit VII.B.2). Thus, the precise question under the FQPA safety factor provision for dichlorvos is whether EPA should retain the presumptive additional 10X factor for the protection of infants and children or whether there are reliable data showing that a different additional factor will, in conjunction with the 10X intraspecies factor, pro-

protect the safety of infants and children. As the above discussion of the all-important FQPA safety factor considerations indicates, there are (1) reliable data from animal studies on adult/juvenile sensitivity showing that the standard 10X intraspecies factor will be protective of potential pre- and post-natal toxicity to infants and children; (2) reliable data on human exposure to dichlorvos demonstrating that an additional safety factor is not needed to protect infants and children due to exposure concerns; and (3) reliable data with regard to the one toxicity data deficiency identified to show that a 3X additional factor will be protective of all human populations, including infants and children, as to the only toxicity data completeness issue. Therefore, EPA reaffirms its selection of a 3X FQPA safety factor for Gledhill-based assessments.

### *C. Conclusion*

For all of the reasons set forth above, EPA denies NRDC's objection to the use of a 3X FQPA safety factor for assessments relying on the Gledhill study for a Point of Departure. Based on the revised explanation provided in this order, EPA concludes, like it did in the July 23, 2008 order, that a 3X additional safety factor will protect the safety of infants and children. Because this revised explanation addresses the court's reason for finding portions of the July 23, 2008 order to be arbitrary and capricious, EPA has not otherwise reopened or reconsidered that prior order.

## **VIII. Statutory and Executive Order Reviews**

This action, denies an objection to a denial of a petition to revoke tolerances, is in the form of an order and not a rule. (21 U.S.C. 346a(g)(2)(C)). Under the Administrative Procedure Act (APA), orders are expressly excluded from the definition of a rule. (5 U.S.C. 551(4)). Accordingly, the regulatory assessment requirements imposed on a rulemaking do not apply to this action, as explained further in the following discussion.

### *A. Executive Order 12866 and Executive Order 13563*

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

*B. Paperwork Reduction Act*

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

*C. Regulatory Flexibility Act*

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

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

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

mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1531-1538).

*E. Executive Orders 13045, 13211 and 12898*

As indicated previously, this action is not a "regulatory action" as defined by Executive Order 12866. As a result, this action is not subject to Executive Order 13045, entitled "Protection of Children from Environmental Health Risks and Safety Risks", (62 FR 19885, April 23, 1997) and Executive Order 13211 entitled "Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use", (66 FR 28355, May 22, 2001). In addition, this order also does not require any special considerations under Executive Order 12898 entitled "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" (59 FR 7629, February 16, 1994).

*F. National Technology Transfer and Advancement Act*

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

**IX. Congressional Review Act**

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

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41. Office of Pesticide Programs, U.S. EPA. (June 20, 1994). Memorandum from Brigid Lowery to Jocelyn E. Steward, Dichlorvos (DDVP). Review of Subchronic Neurotoxicity Study in Sprague-Dawley Rats.

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43. National Research Council, Reference Manual on Scientific Evidence 249-252 (3<sup>rd</sup> ed. 2011).

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

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

Dated: 8/29/12

A handwritten signature in black ink, appearing to read "Steve Beall", written over a horizontal line. The signature is fluid and cursive, with a long horizontal stroke extending to the right.

*Director, Office of Pesticide Programs.*