

IN THE
UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

Natural Resources Defense Council, Inc.)	
)	
)	
Petitioner,)	
)	
v.)	Case No. 14-73353
)	
United States Environmental Protection Agency,)	
)	
)	
Respondent.)	

Center for Food Safety, et al.,)	
)	
)	
Petitioners,)	
)	
v.)	Case No. 14-73359
)	
United States Environmental Protection Agency, et al.,)	
)	
)	
Respondents.)	

**REPLY DECLARATION OF DR. KRISTI PULLEN IN SUPPORT OF
PETITIONER NATURAL RESOURCES DEFENSE COUNCIL'S
MOTION FOR STAY PENDING REVIEW**

I, DR. KRISTI PULLEN, do hereby affirm and state:

1. This declaration is based on my personal knowledge, information, and belief.

2. I submitted a declaration in support of the Natural Resources Defense Council (NRDC)'s motion for stay pending review. *See* Pullen Decl., ECF No. 15-

3. That declaration includes a statement of my education, background, experience, and other credentials. *Id.* ¶¶ 4-5.

3. My previous declaration describes the human health impacts of 2,4-D and points out deficiencies in the U.S. Environmental Protection Agency (EPA)'s evaluation of those impacts. This declaration rebuts certain points made by EPA and Dow AgroSciences in response to my analysis.

4. First, I explained in my previous declaration that, in setting its no-observed adverse effect level (NOAEL) for 2,4-D, EPA erroneously ignored evidence of impacts to thyroid function that occurred at lower exposures. Respondents are wrong to argue that those impacts were properly disregarded because they were not adverse.

a. In the Extended One Generation Reproductive Toxicity Study of rats included in EPA's human health risk assessment for 2,4-D, thyroid effects were observed in both mothers (dams) and offspring (pups), with pups showing greater sensitivity than dams. Mother rats experienced decreases in both thyroxine (T₄) and triiodothyronine (T₃) and increases in thyroid stimulating hormone

(TSH)—changes indicative of clinical impacts to the thyroid—at exposure to 600 ppm of 2,4-D. Offspring, however, experienced similar patterns of thyroid hormone changes at 300 ppm (for 22-day old males) and 100 ppm (for 62-64 day old males and females).¹ A dose of 100 ppm is the equivalent of 5.6 mg/kg/day for males and 6.7 mg/kg/day for females. EPA set its NOAEL for thyroid impacts higher than this level, because it classified the low-dose changes in pups as adaptive, rather than adverse.

b. In making this assumption, EPA ignored advice from the authoritative National Academies of Sciences that the agency should use caution when drawing a bright line between adversity and adaptation. In its response to NRDC’s motion, EPA argues that “widely-accepted toxicology principles” require that an effect must be part of a pattern of effects to be considered adverse, citing a guidance document from 1998. EPA Opp’n, ECF No. 24, at 12. But just last year, the National Academies noted that “effects that are adaptive in some people are adverse in others.”² As the National Academies recognize, the mechanisms of adverse impacts to the thyroid in sensitive populations can differ from those in less

¹ See Pullen Decl. ¶ 10.

² *Review of the Environmental Protection Agency’s State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as They Apply to Endocrine Disruptors*, at 7 (The National Academies Press 2014), available at http://www.nap.edu/openbook.php?record_id=18608.

vulnerable populations. For example, research shows that even changes in thyroid hormone that would be deemed subclinical (for example, changes in levels of T₄ without accompanying changes in TSH levels) can result in significant damage, particularly to the developing brain.³ Decreased levels of T₄ were observed in gestating dams in the Extended One Generation Reproductive Toxicity Study at every 2,4-D dose tested. EPA should not have discounted evidence of potential harm when setting its NOAEL.

c. Given evidence that even transient changes in thyroid hormones can result in developmental effects,⁴ epidemiologic evidence that exposure to 2,4-D can result in hypothyroidism (an endocrine disorder) in humans,⁵ the importance of the thyroid in developing organs (e.g., brain, lung, heart, and kidneys), and evidence that offspring can be more sensitive than parents, EPA needed to use the

³ Gabriella Morreale de Escobar et al., *Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia?*, 85 J. Clin. Endocrinol Metab. 3975, 3975-3987 (2000), available at <http://press.endocrine.org/doi/pdf/10.1210/jcem.85.11.6961>

⁴ Mark D. Miller et al., *Thyroid-Disrupting Chemicals: Interpreting Upstream Biomarkers of Adverse Outcomes*, 117 Env. Health Perspec. 1033, 1033-1041 (2009). available at <http://www.ncbi.nlm.nih.gov/pubmed/?term=thyroid+disrupting+chemicals+interpreting+upstream+biomarkers+of+adverse+outcomes+miller>.

⁵ Whitney S. Goldner et al., *Hypothyroidism and Pesticide Use Among Male Private Pesticide Applicators in the Agricultural Health Study*, 55 J. Occupational Envtl. Med. 1171, 1171-78 (2013), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3795845/pdf/nihms-491361.pdf>.

most protective NOAEL possible, in addition to the tenfold Food Quality Protection Act (FQPA) uncertainty factor, to adequately account for the effects of 2,4-D exposure. It did neither in approving Enlist Duo.

5. I also explained in my previous declaration that EPA's Response to Public Comments erred in concluding that, even if EPA used a NOAEL of 100 ppm and applied the FQPA tenfold uncertainty factor, it would not have found that Enlist Duo caused any unsafe 2,4-D exposures. Respondents are wrong to defend EPA's statement.

a. In its Response to Public Comments, EPA purported to evaluate the impact on its risk assessment of adopting a NOAEL of 100 ppm and applying the tenfold FQPA safety factor, as NRDC suggested it should. EPA stated that these inputs would still result in only acceptable risks for all age groups.⁶ EPA's math is wrong.

b. A NOAEL of 100 ppm is equivalent to a NOAEL of 5.6 mg/kg/day in male rats and 6.7 mg/kg/day in female rats. Using a NOAEL of 5.6-6.7 mg/kg/day, and dividing by the two tenfold uncertainty factors that EPA did use (one to account for uncertainties regarding interspecies variability and one to account for uncertainties regarding intraspecies variability) results in a chronic

⁶ EPA, Response to Public Comments Received Regarding New Uses of Enlist Duo on Corn and Soybeans (Oct. 15, 2014), ECF No. 15-14 at 8.

reference dose (cRfD), or chronic population adjusted dose (cPAD) (i.e., the level that exposure should not exceed) of 0.056-0.067 mg/kg/day. Dividing by ten once again to account for the FQPA tenfold uncertainty factor yields a cPAD of 0.0056 – 0.0067 mg/kg/day, as shown in the equation below.

$$\text{cRfD} = \text{cPAD} = \frac{\text{NOAEL (mg/kg/day)}}{\text{UF}_{\text{inter}} * \text{UF}_{\text{intra}} * \text{UF}_{\text{FQPA}}}$$

$$\text{cRfD} = \text{cPAD} = \frac{5.6 - 6.7 \text{ (mg/kg/day)}}{10 * 10 * 10}$$

$$\text{cRfD} = \text{cPAD} = 0.0056 - 0.0067 \text{ (mg/kg/day)}$$

c. As shown in the table below, EPA’s own chronic dietary exposure estimates for every population group (see column two) exceed the cPAD derived above. Therefore, every population group’s projected dietary exposure to 2,4-D presents an unacceptable risk compared to that cPAD. The most exposed population group (children one to two years old), would be exposed to levels of 2,4-D that are 460-551% of the cPAD: in other words, more than four times the level of acceptable risk.

Summary of Chronic Dietary Exposure and Risk for 2,4-D (adapted from Table 5.4.6.) ⁷				
Population Subgroup	Dietary Exposure (mg/kg/day)	% cPAD with cPAD = 0.21	% cPAD With cPAD = 0.0056	% cPAD With cPAD = 0.0067
General U.S. Population	0.009882	4.7	176	147
All Infants (< 1 year old)	0.008879	4.2	159	133
Children 1-2 years old	0.030838	15	551	460
Children 3-5 years old	0.025920	12	463	387
Children 6-12 years old	0.015028	7.2	268	224
Youth 13-19 years old	0.009103	4.3	163	136
Adults 20-49 years old	0.007842	3.7	140	117
Adults 50+ years old	0.007282	3.5	130	109
Females 13-49 years old	0.007453	3.5	133	111

d. In light of the above, if it had done the math correctly, EPA would have found that Enlist Duo results in unacceptable exposure to 2,4-D, if the agency had adopted a NOAEL of 100 ppm and applied the FQPA tenfold safety factor.

⁷ EPA, 2,4-D Human Health Risk Assessment for a Proposed Use of 2,4-D Choline on Herbicide-Tolerant Corn and Soybean at 26 (2013).

I declare under penalty of perjury that the foregoing is true and correct. Executed
this 16 of February, 2015 in Washington, D.C.



Dr. Kristi Pullen