

EPA's Risk Assessment is Too Flawed to Proceed:

Comments from Environmental Working Group on the EPA's Proposed Decision to Register Enlist™ Herbicide Containing 2,4-D and Glyphosate

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To: The Honorable Gina McCarthy, Administrator, U.S. Environmental Protection Agency
CC: Jim Jones, Assistant Administrator, U.S. EPA Office of Chemical Safety and Pollution Prevention

Docket: EPA-HQ-OPP-2014-0195

We are submitting comments on behalf of the Environmental Working Group (EWG), a non-profit research and advocacy organization based in Washington, DC that works to protect human health and the environment.

On April 30, 2014, the Environmental Protection Agency proposed to register a double herbicide mix of 2,4-D and glyphosate (the “Enlist Duo™” herbicide) for farm field spraying in combination with a new breed of genetically engineered corn and soybeans. This latest variety of GE corn and soybeans were designed by Dow AgroSciences, a wholly owned subsidiary of the Dow Chemical Co. to tolerate 2,4-D. 2,4-D is a highly toxic herbicide, first introduced on the market in 1946; it has been linked with multiple adverse effects on human health and the environment. We strongly object to the EPA proposal on grounds that EPA has failed to conduct a thorough risk assessment for 2,4-D and has disregarded the data pointing to the risks from expansion of 2,4-D use.

Dow promotes 2,4-D-resistant corn and soybeans because the prior generation of GE corn and soybeans, engineered to tolerate the herbicide glyphosate, has resulted in accelerated herbicide resistance across a growing range of weed species. Extensive planting of glyphosate-resistant corn and soybeans, the so-called Roundup Ready® crops marketed by Monsanto, has led to the rise and spread of glyphosate-resistant weed species, significantly reducing the efficacy of both glyphosate and Roundup Ready® crops (Owen 2008; Owen 2011). Instead of delivering on the promises of lower herbicide use and lessened environmental pollution, the GE crops caused increased herbicide use (Benbrook 2012).

Now, rather than taking a step back and re-evaluating the GE crop strategy in the United States, the U.S. Department of Agriculture and the U.S. Environmental Protection Agency are rushing to approve the new GE crops which would lead to much greater use of 2,4-D and environmental pollution. It is inevitable that this technology, too, would be used to such an excess that weeds would rapidly acquire resistance to 2,4-D as well, a pattern known as the “pesticide treadmill” when farmers end up using larger amounts of increasingly toxic chemicals to control herbicide-resistant weeds. The 2,4-D experiment would roll out on a grand scale: likely tens of millions of acres.

We argue that in proposing to register a combination of 2,4-D and glyphosate for use with 2,4-D resistant GE corn and soybeans, EPA overlooked both the significant potential health risks for young children and the environmental damage that would result from large-scale 2,4-D spraying. The risk assessment documents published by EPA contain multiple inaccuracies and significantly underestimate the real harm to human health and the environment. ***Because of these basic errors, EPA cannot move forward with the registration process for 2,4-D and glyphosate herbicide combination and must conduct a new risk assessment.***

Conducting a thorough, complete risk assessment for 2,4-D is essential because of the anticipated increased uses on the fields planted with 2,4-D resistant corn and soybeans. According to the draft Environmental Impact Statement published by the USDA, if 2,4-D-resistant corn and soybeans were allowed on the market, annual 2,4-D use on crops alone could be from 3 to nearly 7 times greater by 2020 compared to 2011 levels (USDA 2013). In 2011, 25.6 million pounds of 2,4-D were used on crops in the United States. The USDA estimates that by 2020 between 77.8 and 176.2 million pounds of 2,4-D could be used on crops annually (USDA 2013). This is in addition to 38.3 million pounds used annually for non-agricultural purposes, which includes 24.3 million pounds of 2,4-D used on turf grass, lawns and ornamental plantings and 14 million pounds used on pasture, rangelands and grass management on roadsides and rights-of-ways. The USDA estimates that these non-agricultural uses of 2,4-D would stay the same between 2011 and 2020 (USDA 2013).

The national-level estimates developed by the USDA only partially reflect the extent of increased 2,4-D exposure that would impact rural communities in the vicinity of sprayed fields. As of 2011, approximately 5.4 million pounds were used on each corn and soybeans. By 2020, 32 to 85.9 million pounds of 2,4-D could be used on corn, an increase of 6-to-16-fold. On soybeans, 31 to 70.1 million pounds of 2,4-D would be used annually, an increase of 6-to-13-fold (USDA 2013). An independent assessment from the Washington State University Center for Sustaining Agriculture and Natural Resources estimated that by 2019 2,4-D uses on corn alone could increase by over 30-fold from 2010 levels (Benbrook 2012).

The increase in 2,4-D spraying on corn and soybean fields would lead to pollution of food and water and air drift of 2,4-D from the fields into nearby residential areas. Increased 2,4-D application would also worsen the problem of herbicide resistance. 2,4-D resistant weeds have been already reported in the United States (Bernards 2012; Weed Science Society of America 2014). 2,4-D approval by EPA would create conditions for the inevitable rise of resistant weeds, leading to the future loss of 2,4-D efficacy against resistant weeds.

The potential for great expansion of 2,4-D use requires a much greater level of scrutiny, which EPA has failed to apply in the proposed registration decision for 2,4-D and which EPA must remedy by conducting a reassessment of 2,4-D exposures and toxicity.

EWG identified the following major flaws in the EPA risk assessments:

- Incorrectly setting the No Observed Adverse Effects Level (NOAEL) for the rat study that served as the basis for the 2,4-D safety threshold at 21 mg/kg/day. By definition, a NOAEL is the exposure amount with no observed adverse effects, yet multiple toxicity

effects were observed at this dose in young animals. By choosing a NOAEL where toxicity effects actually occur, EPA contradicted standard scientific practice.

- Disregarding endocrine toxicity and immunotoxicity findings from animal studies.
- Failing to apply the additional safety factor of 10, as mandated under Food Quality Protection Act, for cases in which children are shown to be more vulnerable than adults. The animal study data clearly show that young animals are more susceptible to 2,4-D toxicity compared to adult animals. In such a case, the 10-fold safety factor, we believe, is required by law.
- Omitting 2,4-D inhalation, one of the primary routes of pesticide exposure for communities in the vicinity of sprayed fields, from aggregate exposure assessment.
- Failing to protect endangered species from 2,4-D by making an unfounded assertion that 2,4-D would stay in the sprayed fields only, an assumption that contradicts actual spraying practices and field application conditions.
- Not following the Agency's own guidance document for honeybee toxicity assessment and thereby underestimating the risks to bees and other beneficial insects.

These flaws require a completely new risk assessment for 2,4-D in which EPA should:

1. Use the 2,4-D dose of 100 ppm (corresponding to 7 mg/kg/day or lower) as the point of departure for human health risk assessment and apply the 10-fold safety factor to protect children's health as required under the Food Quality Protection Act;
2. Account for 2,4-D inhalation risks to communities near the 2,4-D sprayed fields, particularly for children in homes, day care centers and schools;
3. Conduct an aggregate exposure assessment including all sources of 2,4-D;
4. Protect endangered species from 2,4-D spraying;
5. Require a new panel of tests that would thoroughly investigate 2,4-D toxicity to honeybees in accordance with the Agency's 2011 guidelines.

Details and the rationale for these recommendations are provided below.

1. EPA should use the 2,4-D dose of 100 ppm, not 300 ppm, as the point of departure for human health risk assessment and apply an additional 10-fold safety factor to protect children's health, as required under the Food Quality Protection Act

In proposing to set a "safety threshold" for chronic 2,4-D exposures in humans, EPA relied on toxicity findings from different laboratory animal studies. For establishing the lowest 2,4-D concentration that caused toxic effects in animals, EPA used the data from a one-generation reproductive toxicity test conducted by the Dow Chemical Company (Marty 2013). In this study, adult rats were exposed to 2,4-D in feed for 4 weeks prior to mating as well as during mating, pregnancy and lactation; newborn pups were fed 2,4-D for a period from 8 weeks to over 13 weeks. The 2,4-D doses were 0, 100, 300, and 600 (females) or 800 (males) parts per million (ppm). The lowest tested dose of 100 ppm corresponds to approximately 5-7 mg/kg/day, depending on the animal body weight (Marty 2013; Saghir 2013). EPA chose a dose of 21 mg/kg/day (300 ppm) as the No Observed Adverse Effect Level or NOAEL (EPA 2014a).

To derive the level of concern for 2,4-D for human health, EPA applied an adjustment factor of 100, consisting of an initial 10-fold safety factor to extrapolate from animal to human (interspecies), and a second 10-fold safety factor to account for potential variation in sensitivity among members of the human population (intraspecies). EPA chose *not* to apply a third safety factor (of up to 10-fold) for protecting children’s health, as required under the Food Quality Protection Act. With this methodology, EPA arrived at a threshold for chronic 2,4-D exposure of 0.21 mg/kg/day.

EWG review of the animal study data found that EPA incorrectly identified 300 ppm (21 mg/kg/day) dose as the NOAEL and the basis for setting the safety threshold to 2,4-D for general population, including adults and children. Multiple toxicity effects occur in young animals fed this amount of 2,4-D and at the lowest dose tested, 100 ppm 2,4-D. Table 1 summarizes data from studies reviewed by EPA that indicate adverse health effects occurred in newborn and young laboratory rats and highlights the significance of these effects for human health.

Table 1: Toxicity effects in rats exposed to 300 ppm 2,4-D in an extended one-generation oral feeding study. Data source: EPA review of animal study results for 2,4-D in the human health risk assessment document (EPA 2014a). Page numbers from the EPA document indicated in parenthesis.

Effect observed	Significance for human health
Toxicity to the reproductive system	
Changes in the reproductive cycle in young female rats on postnatal day 70 (page 68); increased weight of the uterus in young female rats on postnatal days 90-139 (page 69); decreased reproductive organ weights in adult male rats (page 66).	2,4-D may disrupt the hormonal balance and affect the reproductive system.
Toxicity to the thyroid	
T4 thyroid hormone levels reduced in male and female pups on post-natal day 4 (page 67); T3 thyroid hormone levels were reduced in male pups on post-natal day 22 (page 67); TSH (thyroid-stimulating hormone) levels increased in young male and female rats on post-natal days 62-64 (page 67).	2,4-D may disrupt the thyroid function; these effects are more pronounced in offspring compared to adults.
Toxicity to the immune system	
Smaller thymus weights in young male rats on postnatal days 67-73 (page 68).	2,4-D may suppress the ability of the immune system to protect the body from pathogens.
Toxicity to kidneys	
Increased kidney weights in young female rats on postnatal day 70 (page 67); degenerative lesions in the kidneys (proximal convoluted tubule) in young male rats on postnatal day 70 (page 68) and in both male and female young rats on postnatal days 90-139 (page 69).	2,4-D may be toxic to kidneys; these effects are more pronounced in the offspring compared to adults.

As the data in Table 1 indicate, a 2,4-D dose of 21 mg/kg/day caused toxicity to the reproductive system, the thyroid, the immune system and the kidneys in young animals exposed to 2,4-D during gestation, lactation, and early life. It is therefore clear that the dose of 21 mg/kg/day cannot be considered the No Observed Adverse Effects Level, or NOAEL, for 2,4-D, precisely because adverse effects **were observed** at this dose.

Based on the data submitted to EPA for this registration, even at the dose 100 ppm, the smallest 2,4-D concentration tested in the extended one-generation reproductive toxicity study, adult female rats had increased thyroid weights (EPA 2014a, page 66). In male pups on postnatal day 22 the following statistically significant toxicity effects were observed at 100 ppm (Table 5 in Marty 2013):

- Smaller body weight;
- Smaller kidney, liver and spleen weights;
- Smaller testes weight.

Thus, the data from the study that EPA reviewed indicate that even at the dose of 100 ppm, corresponding to 5-7 mg/kg/day, treatment-related toxicity signs were observed in exposed animals. EWG finds that the dose of 100 ppm should be considered the lowest observed adverse effect dose or the LOAEL.

2,4-D studies conducted to-date point out that young individuals are more susceptible to 2,4-D toxicity than adults. While a dose of 300 ppm did not elicit a significant toxicity in adult animals, multiple toxic effects on the thyroid, the reproductive and the immune systems and the kidneys in newborn and young animals were observed at this dose. Some toxicity effects were observed in young animals even at the dose of 100 ppm. *Therefore, EPA has erred in discarding a 10-fold children's health safety factor mandated under the Food Quality Protection Act.* It does appear that 2,4-D could pose a special risk to children that warrants the full, additional safety factor.

By proposing to register 2,4-D on the basis of one generation reproductive toxicity data submitted by the manufacturer, EPA contradicted its own statement from a 2005 Reregistration Eligibility Decision for 2,4-D that a "repeat 2-generation reproduction study using the most recent protocol is required to address the concern for thyroid effects (comparative assessment between the young and adult animals) and immunotoxicity, as well as a more thorough assessment of the gonads and reproductive/developmental endpoints" (EPA 2005). In this year's (2014) proposal to register the 2,4-D-glyphosate mix, EPA has instead accepted an extended one-generation study in rats rather than requiring a full 2-generation study with detailed assessment of endocrine status in the first- and second-generation animals.

A variety of harmful effects on the reproductive system and the thyroid were observed in the newborn pups and young animals in the extended one-generation reproductive study, indicating that 2,4-D might affect the endocrine system. At the exposure dose of 300 ppm, changes in thyroid hormones T3, T4 and TSH were observed in newborn and young animals. At the dose of 100 ppm, changes in thyroid gland weights were observed in adult female animals. Data from a human epidemiological study of hypothyroidism in 2,4-D herbicide applicators (Goldner 2013) support the human health relevance of thyroid toxicity findings in studies on laboratory animals.

At the dose of 300 ppm, changes in the reproductive organ weights were observed in adult male animals as well as changes of the timing of the reproductive cycle and increased uterine weight in young female rats (EPA 2014a). At the dose of 100 ppm, a statistically significant decrease in testes weights was observed in young male rats (Marty 2013). These findings suggest that 2,4-D exposure could affect the reproductive system in males and females. The human health relevance of these animal study findings is reinforced by a study from Italy where 2,4-D decreased fertility in male farmers. Compared to healthy, unexposed men, farmers who sprayed 2,4-D had lower sperm counts, lower sperm motility and greater percentage of anomalous sperm; some of these effects persisted even after the farmers no longer had contact with 2,4-D (Lerda 1991).

The potential reproductive toxicity of 2,4-D is of great concern for children's health, since healthy development and growth depend on maintaining balanced hormonal system. The expansion of 2,4-D use would also have significant adverse effects on herbicide applicators that would be exposed to 2,4-D from inhalation and dermal contact in addition to contaminated food and water.

Additionally, as described in the EPA assessment, young male rats exposed to 2,4-D had smaller thymus weights, an indicator of 2,4-D immunotoxicity. EPA ignored these findings, even though an independent study found similar results, showing that acute oral 2,4-D exposure damaged both thymus and spleen in laboratory rats (Kaioumova 2001a). 2,4-D toxicity to the immune system was also demonstrated in studies with human immune cells grown in laboratory conditions (Kaioumova 2001b) and in studies with laboratory mice upon respiratory exposure to 2,4-D (Fukuyama 2009).

Studies in laboratory mice also found that exposure to 2,4-D in combination with herbicide propanil exacerbated the effects on the immune system, suggesting that a mixture of herbicides is more toxic than an individual herbicide tested alone (De La Rosa 2003; De La Rosa 2005).

Early-life exposure to chemicals that damage the immune system can lead to decreased resistance to pathogens, allergies, autoimmune diseases and inflammatory diseases in adolescence and adulthood (DeWitt 2012). The human health relevance of 2,4-D immunotoxicity in laboratory animals is supported by a 1996 Italian study of farmers who handled and applied 2,4-D. This study found that 2,4-D suppressed human immune function by reducing both the numbers of different types of white blood cells and their ability to respond to stimulation (Faustini 1996). 50-to-70 days after the exposure to 2,4-D the numbers of immune cell subpopulations returned to normal but their functional capacity was not restored (Faustini 1996).

EWG review of overall data from human and animal studies finds that the FQPA safety factor of 10 must be applied for 2,4-D. A true safety threshold for 2,4-D must be derived by the following methodology:

- Starting with a departure point of 100 ppm corresponding to 7 mg/kg/day or lower;
- Applying three safety factors: a factor of 10 for extrapolation from animal study to humans (interspecies); a factor of 10 to account for variability within the human population (intraspecies); and a FQPA safety factor of 10 to account for greater sensitivity of young individuals compared to adults;

- Establishing a chronic exposure population-adjusted dose (cPAD) of 0.007 mg/kg/day or lower, rather than EPA's flawed proposal for a cPAD of 0.21.

EWG recommendations are consistent with the 2,4-D risk assessment conducted by the California Office of Environmental Health Hazard Assessment (OEHHA 2009). For establishing the Public Health Goal for 2,4-D in drinking water, OEHHA used a NOAEL of 5 mg/kg/day, derived from a 1996 study in rats (Charles 1996). OEHHA applied an overall uncertainty factor of 1,000 "to account for interspecies extrapolation (10), probable variability among humans (10), and potential susceptibility of infants and children associated with the developmental effects noted in the limited available studies, with a lack of more in-depth studies (10)" (OEHHA 2009). This methodology resulted in the acceptable daily dose for chronic 2,4-D exposure of 0.005 mg/kg/day, 42 times lower than the EPA flawed chronic exposure benchmark of 0.21 mg/kg/day.

In the 2,4-D assessment, OEHHA also highlighted the fact that numerous epidemiological studies have connected 2,4-D to non-Hodgkin's lymphoma among farmers (OEHHA 2009). Although these studies are confounded by exposure to multiple pesticides and different preparations of 2,4-D, there is a large and compelling body of data that demonstrates the link between occupational exposure to herbicides and insecticides and non-Hodgkin's lymphoma (reviewed in Schinasi and Leon 2014).

EWG believes that the scientific arguments presented above clearly establish that EPA must restart the risk assessment process and derive a truly protective safety threshold for 2,4-D that safeguards children's health.

2. EPA must account for 2,4-D inhalation health risks to communities near the 2,4-D sprayed fields, particularly for children in homes, day care centers and schools.

Herbicides and pesticides sprayed over large areas pose significant inhalation risks during the application process and due to the drift from sprayed fields to nearby residential areas such as homes, day care centers and schools. In the 2005 risk assessment for 2,4-D, EPA recognized that "chemicals tend to be more toxic by the inhalation route than by the oral route due to rapid absorption and distribution, bypassing of the liver's metabolic protection, and potentially serious portal-of-entry effects, such as irritation, edema, cellular transformation, degeneration, and necrosis" (EPA 2005). At the time, EPA required 2,4-D manufacturers to conduct a 28-day inhalation study in laboratory animals. *This study has now been conducted and revealed severe toxicity of 2,4-D to the respiratory system (EPA 2014a). Yet, inexplicably, EPA chose to ignore the inhalation toxicity risks in conducting the aggregate exposure assessment for expanded uses of 2,4-D that would result from planting 2,4-D-resistant GE corn and soybeans.*

EWG review of the 2,4-D inhalation toxicity study discovered that adverse effects occurred at all 2,4-D doses tested, starting with the lowest tested dose of 0.05 mg/L. After breathing in 2,4-D, animals developed squamous metaplasia, epithelial hyperplasia and inflammation in the larynx (EPA 2014a, Human health risk assessment Section A.3.6). The severity of these effects increased in a dose-related manner and the effects persisted following the 4-week recovery period after the 2,4-D exposure was terminated. Metaplasia and hyperplasia of the respiratory

system could be a precursor to tumor development and cancer and therefore should be considered a severe adverse health effect. EPA must require detailed follow-up inhalation toxicity studies before registration approval can be granted for 2,4-D-glyphosate mix for use with GE corn and soybeans.

Even though adverse effects on thyroid hormones were observed in the oral feeding study, suggesting that such effects could also occur following 2,4-D inhalation, the 2,4-D manufacturer who commissioned the tests chose not to measure thyroid hormone and thyroid gland weights in the inhalation toxicity study. EPA disregarded this potentially wide gap in data submitted by the manufacturer, stating that inhalation effects would not be systemic in the absence of any data to support such a conclusion. This flaw is another reason that EPA must re-do the risk assessment.

Thyroid toxicity of 2,4-D was observed in the Agricultural Health Study, an on-going large-scale epidemiological study funded by the National Cancer Institute and the National Institute of Environmental Health Sciences that involves 89,000 farmers and their spouses in Iowa and North Carolina (AgHealth 2014). In the 2013 publication from this study, the use of 2,4-D was associated with a greater risk of hypothyroidism in male pesticide applicators (Goldner 2013). For pesticide applicators, inhalation and dermal contact are the primary routes of exposure, indicating that adverse effects on thyroid could occur not only from ingestion of 2,4-D with contaminated food and water but from other sources as well, especially by breathing in contaminated air.

The risks of 2,4-D inhalation would be of greatest concern for children in nearby residential areas, including homes, day care centers and schools. With the expansion of 2,4-D-treated acreage, children in agricultural areas would end up breathing in a lot of 2,4-D. Such exposures were previously associated with residential lawn and turf herbicide treatments (Morgan 2008), which led to calls to ban such applications to protect children's health (Sears 2006). If 2,4-D-resistant corn and soybeans were planted on tens of millions of acres of American farmland, children in many states would end up breathing 2,4-D-contaminated air. Recent studies from the U.S. Geological Survey report detections of glyphosate in air far removed from spraying locations (Majewski 2014). EPA should plausibly assume that the dramatically expanded use of 2,4-D contemplated in the registration request would result in similar, widespread air contamination.

Dow Chemical Co. publishes numerous promotional statements asserting that the 2,4-D formulation in the Enlist herbicide duo has "ultra-low volatility" and "minimized potential for physical drift" (Dow 2014). The claim of "low volatility" is also repeated in the EPA assessment (EPA 2013; EPA 2014a). However, the 2,4-D data reviewed by EPA only indicate that the estimated volatility of 2,4-D choline salt, the form of 2,4-D in the Enlist herbicide, is lower than the volatility of 2,4-D ethylhexyl ester and 2,4-D dimethylamine salt, two other 2,4-D formulations tested by Dow (EPA 2013). In fact, field studies found that volatilization of 2,4-D choline formulation from treated crops does occur and could result in bystander exposure to vapor phase 2,4-D (EPA 2014a).

EPA discarded the evidence of 2,4-D volatilization and potential for drift into nearby areas by stating that, according to air distribution modeling, airborne concentrations of 2,4-D at the edge

of the treated fields are “not of concern” (EPA 2014a). EWG strongly disagrees with this conclusion. As described in sections 2 and 3 of our comments, EPA does not have a well-done inhalation toxicity study in laboratory animals for determining the true No Observed Adverse Effects Level for 2,4-D inhalation exposure. The Agency did not include inhalation exposures in the exposure assessments; did not adequately consider the risks of 2,4-D exposure for children who live, play and study in the vicinity of 2,4-D treated fields; and disregarded the potential risks of 2,4-D inhalation to the thyroid. Finally, no inhalation toxicity studies have been done for the Enlist Duo™ pesticide itself, with simultaneous exposure to both 2,4-D and glyphosate, although research suggests that exposure to herbicide and pesticide combinations could be more toxic than exposure to individual chemicals.

The fact that the 2,4-D choline formulation has lower volatility compared to some other 2,4-D formulations does not mean that the risks of 2,4-D inhalation exposure from spraying 2,4-D-resistant genetically engineered corn and soybeans can be discarded in the absence of sufficient safety data and without a comprehensive exposure assessment.

EWG concludes that EPA has failed to appropriately assess 2,4-D inhalation toxicity and the potential inhalation risks of Enlist herbicide combination. EWG believes that EPA must conduct a new risk assessment for 2,4-D, which would:

- Require a new 2,4-D inhalation toxicity study with both adult and young animals in order to establish the true No Observed Adverse Effects Level where no toxicity would occur in the respiratory system;
- Require an inhalation toxicity study for the Enlist Duo™ herbicide with simultaneous inhalation exposure to both 2,4-D choline and glyphosate;
- Assess the potential risks of metaplasia, hyperplasia and respiratory tract tumors from 2,4-D inhalation;
- Require an assessment of thyroid hormone function and thyroid weights in animals exposed to 2,4-D and Enlist Duo™ by inhalation;
- Include the exposure via air and herbicide drift from sprayed fields in the acute and chronic aggregate exposure assessments for Enlist Duo™ herbicide.

3. EPA must conduct an aggregate exposure assessment including all sources of 2,4-D, including food, water, air, and accidental (non-dietary) ingestion

Based on a risk assessment approach that protects children’s health and incorporates the FQPA 10-fold safety factor, EWG recommends a safety threshold of 0.007 mg/kg/day for 2,4-D *or lower*. ***Comparing this safety threshold with EPA findings on chronic aggregate 2,4-D exposures, EWG finds that EPA approval of 2,4-D and glyphosate combination (the “Enlist Duo™” herbicide) for GE corn and soybeans would pose a significant health risk for children 12 and younger (Table 2).***

EWG also compared 2,4-D exposures with a second threshold of 0.021 mg/kg/day, which is derived by applying the FQPA safety factor of 10 to the EPA’s flawed safety threshold of 0.21 mg/kg/day, for which EPA failed to include the FQPA factor. As Table 2 demonstrates,

independently of whether a 2,4-D safety threshold might be established at 0.007 mg/kg/day or 0.021 mg/kg/day, **children aged 1-to-5 years are at risk of excessive exposure.**

Young children could ingest 2,4-D from food and water; breathe in 2,4-D drifting from treated fields or even from elevated levels in ambient air; and accidentally swallow, through hand-to-mouth exposure, 2,4-D that might end up on lawns, in residential areas, and in places such as schools and day care centers as a result of turf grass spraying and other non-agricultural uses.

Table 2: Comparison between anticipated chronic 2,4-D exposures to children and adults with EWG-recommended threshold of 0.007 mg/kg/day and a threshold of 0.021 mg/kg/day.

Population subgroup	EPA estimate for future chronic 2,4-D exposure from food and drinking water, mg/kg/day*	Comparison to a 2,4-D safety threshold of 0.021 mg/kg/day	Comparison to a 2,4-D safety threshold of 0.007 mg/kg/day
General U.S. Population	0.009882	Smaller than the safety threshold	Exceeds the safety threshold by 41%
All Infants (< 1 year old)	0.008879	Smaller than the safety threshold	Exceeds the safety threshold by 26%
Children 1-2 years old	0.030838	Exceeds the safety threshold by 47%	Exceeds the safety threshold by 340%
Children 3-5 years old	0.025920	Exceeds the safety threshold by 23%	Exceeds the safety threshold by 270%
Children 6-12 years old	0.015028	Smaller than the safety threshold	Exceeds the safety threshold by 115%
Youth 13-19 years old	0.009103	Smaller than the safety threshold	Exceeds the safety threshold by 30%
Adults 20-49 years old	0.007842	Smaller than the safety threshold	Exceeds the safety threshold by 12%
Adults 50+ years old	0.007282	Smaller than the safety threshold	Exceeds the safety threshold by 4%
Females 13-49 years old	0.007453	Smaller than the safety threshold	Exceeds the safety threshold by 6%

* Source: Summary Table 5.4.6; EPA. April 30, 2014. Human Health Risk Assessment for a Proposed Use of 2,4-D Choline on Herbicide-Tolerant Corn and Soybean. Docket EPA-HQ-OPP-2014-0195.

EPA also conducted a “short-term” aggregate risk assessment for residential bystander exposure, which included food, water and accidental oral exposure for 1-to-2-year-old children through routes such as hand-to-mouth ingestion and soil ingestion; the inhalation exposure was excluded. According to EPA, “short-term” refers to exposures 1 to 30 days in length. Including accidental oral exposure *doubles* the overall exposure for toddlers, to a total of 0.062338 mg/kg/day (EPA 2014a, Human health risk assessment Table 6.2.1 and Table 7.2). ***This level of daily exposure is 9 times greater than the safety threshold of 0.007 mg/kg/day recommended by EWG, highlighting the risks of 2,4-D to young children.***

Based on our review, the actual risks to children and adults from increased spraying of 2,4-D are likely even higher than those indicated in Table 2, which leads us to conclude that the Agency has incorrectly and inappropriately omitted inhalation exposures from aggregate exposure estimates. Inhalation and accidental, non-dietary ingestion are important routes of pesticide exposure for children (Curwin 2005; Morgan 2014). Under the Food Quality Protection Act, EPA must consider aggregate exposures in its decision-making about pesticide safety.

EPA's argument that 2,4-D "oral and inhalation endpoints are not the same and cannot be aggregated" (EAP 2014a) is inconsistent with the weight of scientific evidence. This argument is also inconsistent with the Agency's previous statements on the subject. As EPA wrote in a response to a petition "Pesticides in the Air – Kids at Risk: Petition to EPA to Protect Children from Pesticide Drift", in the past the Agency has interpreted "aggregate exposure" to refer to the "combined exposures to a single chemical across multiple routes (oral, dermal, inhalation) and across multiple pathways (food, drinking water, residential)" (EPA 2014b). Thus, inhalation exposure cannot be omitted.

As summarized by OEHHA, "farm children may come in contact with 2,4-D through residues from contaminated soil in areas where they play, their parents' clothing, dust tracked into their homes, food eaten directly from the fields, drift from aerial spraying, contaminated well water, and breast milk. In addition, farm children may accompany their parents to work in the fields, further increasing their pesticide exposure" (OEHHA 2009). These multiple routes of exposure must all be included in the overall exposure assessment.

A 2007 study of Minnesota and North Carolina farm families in which at least one adult was a licensed pesticide applicator found that 4-to-12-years-old children had nearly three times higher than 2,4-D levels in urine samples compared to children 12 or older (Alexander 2007). These findings support EWG conclusion that young children would be most at risk from increased 2,4-D use on 2,4-D resistant crops. Although 2,4-D does not bioaccumulate, more extensive exposure for children younger than 12 results in higher levels of this toxic herbicide in the bodies of young children, a fact that must be taken into account in the overall risk assessment.

In addition to the risks to children's health, inhalation exposure would be also of great concern for farmers and farm workers. Studies of exposed farmers demonstrate that occupational contact with 2,4-D could disrupt the thyroid function and affect the reproductive system (Faustini 1996; Lerda 1991).

Therefore, EPA must conduct a comprehensive 2,4-D exposure assessment, including inhalation and dermal exposure in addition to exposures from food and water. Until a comprehensive exposure assessment is completed, EPA cannot, on scientific and statutory grounds, register 2,4-D for use in combination with 2,4-D-resistant corn and soybeans.

4. EPA must restrict 2,4-D uses and application levels to protect endangered species from 2,4-D spraying.

Genetically engineered crops have been promoted as a way to reduce herbicide use and to decrease environmental damage from pesticide spraying. That promise is now in doubt. Since the time that herbicide-resistant GE crops were introduced in 1996, farmers and agri-businesses growing these crops shifted to a blanket herbicide application (Givens 2009; Prince 2012). The overall herbicide use has increased, not decreased (Benbrook 2012).

If the 2,4-D resistant crops were approved for large-scale planting, the first target of 2,4-D toxicity would be plants, insects, birds and mammals in the vicinity of treated fields. In the post-GE crop world, herbicide applicators commonly engage in large-scale spraying of glyphosate over vast areas, rather than the targeted spraying that more toxic herbicides such as 2,4-D require (Owen 2011). This blanket mode of application would contaminate and poison plants and animals in the vicinity of sprayed fields, leading to economical and environmental damage. EPA needs to conduct a thorough label review for increased uses of 2,4-D, as well as for 2,4-D in combination with other pesticides, since farmers and pesticide applicators often mix different chemicals together during pesticide application.

EPA identified 53 listed endangered species, including 4 mammals and 5 birds, that would be potentially at risk of direct or indirect effects from the increased uses of 2,4-D in the six states where 2,4-D resistant crops would be likely planted (Illinois, Indiana, Iowa, Ohio, South Dakota, Wisconsin) (EPA 2014c). In the environmental risk assessment published by EPA, the Agency reported that 2,4-D is toxic to birds and mammals. However, EPA claimed that the listed endangered species would not be at risk because the sprayed 2,4-D would remain on the fields only and not extend to off-field areas. The Agency has not indicated exactly how the 53 endangered plants and animals listed in its 2,4-D assessment would be informed of these field boundaries, nor how they would be instructed with respect to appropriate re-entry intervals.

The Dow Chemical Co. claims that 2,4-D formulation in the Enlist herbicide duo has “minimized potential for physical drift” (Dow 2014). However, there are multiple gaps in the 2,4-D volatilization and spray drift data that Dow submitted to the EPA. The data that do exist indicate that there may be risks for terrestrial plants and for endangered species of mammals and birds from 2,4-D drift off the treated fields (EPA 2013).

As the EPA itself has stated, the vapor-phase effects data submitted by Dow were “limited in scientific soundness” because they did not include controls and did not measure growth and weight parameters in terrestrial plants in the vicinity of sprayed fields. In fact, the 2,4-D volatilization studies conducted by Dow did not fit the EPA guidelines for such studies. EPA also noted that the manufacturer has failed to conduct the necessary environmental tests for simultaneous exposure to 2,4-D and glyphosate. EPA acknowledges that, “there could be additional toxicological effects (synergistic or additive) because of the presence of two herbicides” (EPA 2013). Yet, all of these data gaps and environmental toxicity concerns were disregarded by the Agency in its proposal to register the Enlist Duo™ herbicide.

Clearly, arbitrary assumptions underlie the Agency's claim that of the 53 species potentially at risk of 2,4-D, 49 species would not be affected, meaning that EPA would not take any steps to protect those listed plants and animals from 2,4-D (EPA 2014c).

Contrary to the EPA's unrealistic assertion that sprayed 2,4-D would stay only on the treated fields, numerous scientific studies and research on pesticide application practices show that pesticide drift off the treated fields can and does occur (Kegley 2003; Lee 2011; LeNoir 1999; Owens and Feldman 2004; Tupper 2012; Washington State Department of Health 2014). EPA itself acknowledges this fact by stating on its website that "the drift of spray and dust from pesticide applications can expose people, wildlife, and the environment to pesticide residues that can cause health and environmental effects and property damage" (EPA 2014d). Since EPA's assertion that the sprayed 2,4-D would stay on the treated fields contradicts the actual scientific data and Agency's own statements on the issue, EPA must re-do the endangered species assessment for 2,4-D taking into account the likelihood of 2,4-D drift to non-sprayed areas as well as the cumulative environmental toxicity of multiple pesticides and herbicides that may be used together with 2,4-D.

5. EPA must require a new panel of tests to investigate 2,4-D toxicity to honeybees in accordance with the Agency's 2011 guidelines.

EWG found that EPA has mistakenly discounted the potential risks of 2,4-D to bees and other beneficial insects, thereby contradicting the Agency's own Interim Guidance on Honey Bee Data Requirements. EPA has not yet published a final guidance for quantifying risks to beneficial insects, particularly honeybees. However, in the interim guidance EPA recommends a panel of tests to examine the risks to honeybees from pesticides and herbicides (EPA 2011):

- Potential for direct and indirect exposures;
- Differential sensitivity of larvae compared to adult bees;
- Sub-lethal effects that may affect brood and colony health;
- Differences in sensitivity when exposed via the contact or oral route.

None of these recommended tests have been conducted by the 2,4-D manufacturer and made available to EPA. The only data reviewed by EPA in the Environmental Risk Assessment are the acute exposure contact toxicity study on adult bees. No chronic tests of 2,4-D toxicity to honeybees have been conducted so far; no tests of bee larvae and bee colonies; and no tests of oral exposure of 2,4-D even though bees are highly likely to ingest 2,4-D sprayed on foliage. These tests must be completed before 2,4-D-resistant crops are allowed on the market, to prevent economic losses for commercial and recreational beekeepers and for farmers who depend on honeybees and other pollinators to grow their crops.

In the acute contact toxicity tests reviewed by the EPA, the Agency used the phrase supplied by Dow, describing 2,4-D as "practically non-toxic" to honeybees (EPA 2013). EWG review of the EPA assessment found that even in short-term tests, *a variety of toxic effects were in fact observed in honeybees*, including "lethargy, immobility, loss of equilibrium and hyper excitability"; additionally, some bees died while others had slow response to stimuli and reduced coordination (EPA 2013, Environmental Risk Assessment, Section 4.2.3). ***Such effects clearly***

show that the honeybees are affected by 2,4-D exposure even upon brief contact. The effects of 2,4-D ingestion and chronic 2,4-D exposure would likely be more severe. EPA description of 2,4-D as “practically non-toxic” to bees contradicts the data and the Agency’s own Interim Guidance on Honey Bee Data Requirements.

The sub-lethal signs of 2,4-D toxicity to honeybees are particularly worrisome given the phenomenon of colony collapse disorder. Since 2006, reports from all parts of United States brought attention to declining honeybee populations (National Research Council 2007). The bee colony collapse is often associated with pesticide exposure and poor nutrition as well as pathogen infections (USDA 2012); but the reasons why the bees’ immune system is unable to fight off the pathogens are not well understood (Dainat 2012).

As the EPA itself states, in addition to direct effects on terrestrial invertebrates, 2,4-D could have potential indirect effects (EPA 2013). Bees or other beneficial insects could be exposed to 2,4-D from herbicide left on treated plants, herbicide carried over to nearby areas, as well as during the spraying itself over the tens of millions of acres contemplated in the Agency’s analysis. For example, 2,4-D herbicide activity against non-target terrestrial plants, which includes most plants other than 2,4-D resistant corn and soybeans and 2,4-D resistant weeds, would destroy the flowering plants essential for the survival and thriving of the pollinator colonies and further affect pollinating insects. In addition to impacting honeybees, 2,4-D could affect other important insect species such as monarch butterflies (Pleasants and Oberhauser 2012). Direct and indirect toxicity of 2,4-D to beneficial insects and honeybees could cause significant environmental and economic damage.

In summary, EPA must reassess the 2,4-D effects on bees and other pollinator insects. This assessment would only be possible after the 2,4-D manufacturer completes the full panel of testing recommended in the EPA guidance documents in order to examine 2,4-D toxicity at all stages of bee life cycle and for all routes of exposure.

Conclusion

The promotion of 2,4-D-resistant corn and soybeans undercuts the argument that GE crops would reduce chemical pollution. Instead, more pesticides would be applied to the fields and drift to nearby communities and sensitive environmental habitats. The introduction of 2,4-D-resistant GE corn and soybeans would significantly increase 2,4-D spraying all across the agricultural areas of the United States, particularly in the Midwest, leading to much greater 2,4-D exposures via food, drinking water, and air. The communities near 2,4-D-resistant GE corn and soybean fields would receive the heaviest brunt of 2,4-D. The risks in these communities would be highest to young children in homes, day care centers and schools.

EPA’s proposal to register the 2,4-D with glyphosate mixture for use with the new GE crops does not meet the statutory and scientific criteria for pesticide registration because of multiple arbitrary and capricious oversights and inaccuracies in human and environmental risk assessments done by the Agency. ***EPA must halt the ongoing registration process and conduct***

a thorough risk assessment, accounting for risks from all routes of exposure, and protecting the health of young children, who might be especially vulnerable to 2,4-D. Moreover, although EPA chose to classify 2,4-D as below the level of concern for honeybees, this decision is scientifically incorrect in light of the bee colony collapse disorder and contradicts the Agency's own guidance on data requirements for pesticide toxicity testing in honeybees. EPA must conduct a serious label review for 2,4-D and take steps to protect the beneficial insects, birds and mammals, as well as listed endangered species, in the sprayed agricultural areas from direct and indirect effects of 2,4-D.

Until a new assessment is completed, EPA lacks a sufficient scientific and legal basis to allow the 2,4-D and glyphosate herbicide duo on the market. EPA must completely re-do the human and environmental risk assessments taking into consideration the increased uses of 2,4-D and new data on toxicity of this herbicide.

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