CENTER FOR FOOD SAFETY

Parkinson's Disease and 2,4-D: A Summary of the Evidence

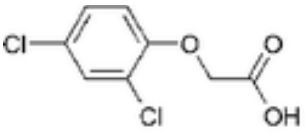
May 2013 (updated May 2014)

I. Background

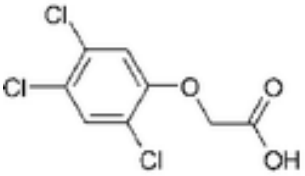
2,4-dichlorophenoxyacetic acid (2,4-D) was introduced in 1945 as one of the first chemical herbicides (Trost, pp. 22-26). It was deployed as part of a chemical weapon in the Vietnam War, and is still widely used to kill weeds in agriculture and other settings. Before addressing the evidence concerning the toxicity of 2,4-D as a stand-alone product, we briefly discuss its history of military use.

A. Military Use

Agent Orange was a 50:50 mixture of 2,4-D and the closely related compound 2,4-5-trichlorophenoxyacetic acid (2,4,5-T), which has one additional chlorine atom (see figure). Both compounds are members of the chlorophenoxy class of herbicides.



2,4-D



2,4,5-T

In what has been called the "largest chemical warfare operation in history,"[1] the U.S. military dumped 11 million gallons of Agent Orange over Vietnam from 1962-1971 (Lilienfeld & Gallo 1989), destroying rice fields and rainforests to deny the Vietnamese food and cover.

Vietnam veterans and Vietnamese suffered horribly from "Operation Ranch Hand," as it was called. The Veterans Administration (VA) regards Agent Orange exposure as associated with Parkinson's disease, as well as numerous other conditions. These include diabetes, neuropathy, heart disease, liver dysfunction, chloracne, numerous cancers (e.g. leukemia, lung, prostate, and multiple myeloma), as well as birth defects (e.g. spina bifida) in the children of exposed soldiers.[2] At least

1 Dr. Arthur Galston, Prof. Emeritus at the Yale School of Forestry & Environmental Studies, as quoted in: "Conference to 'put a human face' on the Vietnam War;" Yale Bulletin and Calendar 31(1), August 30, 2002.

2 See http://www.publichealth.va.gov/exposures/agentorange/ diseases.asp, last visited 1/23/12.

three million Vietnamese also suffered from Agent Orange, with numerous reports of birth defects in the children of exposed pregnant women (CRS 2009).

B. Domestic Use

2,4-D, 2,4,5-T and related chlorophenoxy herbicides have also been widely deployed in the domestic "war on weeds." Farmers use 2,4-D to control broadleaf weeds; the U.S. Forest Service once conducted aerial spraying with chlorophenoxys to control underbrush in national forests (Trost 1984, pp. 103-104), and the practice continues on private timberland (LoE 2012). 2,4-D is also heavily used on golf courses, playing fields and lawns. In fact, 2,4-D is the number one herbicide in the industry/commercial/ government sector and for home/garden use. 2,4-D is the fifth most commonly used herbicide in U.S. agriculture, with 27 million lbs. applied annually (EPA 2011), and is by far the most heavily used member of the chlorophenoxy group of herbicides. The planned introduction of soybeans and corn that have been genetically engineered for resistance to 2,4-D is projected to spur a three- to nearly seven-fold increase in agricultural use of the herbicide, to 77.8-176 million lbs. per year (USDA 2013, p. 134; CFS 2013a).

C. Toxicity of 2,4,5-T

There is little doubt that 2,4,5-T – which was phased out gradually in the U.S. from 1970 to 1985 – was the more toxic component of Agent Orange, and this fact is sometimes illegitimately used to obscure or deny the evidence regarding 2,4-D's toxicity (see below). Extensive testing in the 1960s and 1970s revealed that 2,4,5-T causes birth defects in the offspring of pregnant rodents fed extremely low levels of the compound, while other tests showed it to be carcinogenic (Trost 1984, Chapters 5 to 7). 2,4,5-T's toxicity is generally associated with dioxin contaminants generated during the manufacturing process. Dioxins are some of the most toxic compounds known to man. A barely visible speck of the dioxin 2,3,7,8-TCDD (less than one-millionth of a gram) is enough to kill an adult guinea pig, the most sensitive mammalian species that has been tested (Schwetz et al 1973).

D. Toxicity of 2,4-D

2,4-D has been studied extensively in its own right, and many studies demonstrate a range of adverse impacts on human health (see CFS 2012b for documented discussion). 2,4-D has been linked in numerous studies to non-Hodgkin's lymphoma, an often-fatal immune system cancer that is particularly prevalent in farmers. 2,4-D is banned in Norway, Sweden and Denmark largely on the basis of such epidemiology. Other studies reveal high rates of birth anomalies (e.g. malformations of the circulatory and respiratory systems) in the children of pesticide applicators in regions where 2,4-D is heavily used. 2,4-D also has liver toxicity, and high-level exposure elicits a broad range of neurological and neuromuscular symptoms (CFS 2013b). 2,4-D also contains dioxin contaminants, though at lower levels than 2,4,5-T did. Even so, 2,4-D is the 7th largest source of dioxins in America (EPA 2005). And while the EPA, based on industry tests and assurances, claims that dioxin

levels in 2,4-D have declined since the early 1990s, independent scientists have found comparable levels (Holt et al 2010). It is not clear if dioxin contaminants or 2,4-D itself is responsible for its adverse impacts (Pearce & McLean 2005), and some may be attributable to one and/or the other.

II. 2,4-D and Parkinson's Disease

Two different types of evidence are brought to bear when exploring potential environmental causes of disease: epidemiology in humans and mechanistic studies in animals. Epidemiology is the science that investigates the factors that determine the frequency of disease in a given population, such as exposure to a pesticide and cancer in farmers. Because it is unethical to conduct experimentation on human beings, epidemiology is the most important tool medical science has to explore environmental causes of human disease.

Mechanistic research explores the biological mechanisms by which toxins cause disease, and utilizes experimental animals as surrogates for humans. EPA relies almost entirely on mechanistic research in evaluating pesticides, while virtually ignoring epidemiology. Weaknesses of mechanistic studies include the following. It is often difficult to apply the results of animal studies to humans, who can be more or less sensitive than animals. Most animal studies involve only the pesticide formulation's active ingredient, and so cannot detect any adverse effects of formulation additives. Such additives (e.g. surfactants) are sometimes toxic in their own right, or can synergize with the active ingredient and make it more toxic. Animal studies evaluate only one pesticide at a time, and so can miss adverse effects triggered by real-world exposures to multiple pesticides. Finally, the EPA approves pesticides with known toxicity to applicators, depending upon personal protection equipment and other exposure reduction measures to mitigate risk, despite clear evidence that many farmers do not make use of such equipment. Epidemiology bypasses these weaknesses to deliver evidence on real world outcomes.

Below, we summarize some of the epidemiological and mechanistic evidence for the proposition that exposure to pesticides and herbicides in general, and 2,4-D in particular, increases the risk of contracting Parkinson's disease.

A. **Epidemiology Studies**

There have been numerous epidemiology studies that associate Parkinson's Disease (PD) with exposure to pesticides,[3] herbicides, and 2,4-D. Gorell et al. (1998) found a significant association between PD and herbicide exposure, which increased after controlling for other confounding factors (OR = 4.10[4]). Residential herbicide exposure, which presumably occurs at a lower level than occupational exposure, was not associated

3 Pesticides encompass all pest-killing chemicals: insecticides, fungicides, and herbicides, among other classes. In the U.S., herbicides comprise two-thirds of all pesticide use.

4 OR = "odds ratio." Compares the likelihood of disease in an exposed population to that of a control group of unexposed individuals. OR's > 1.0 indicate a higher probability of disease in the exposed population. An OR of 2.0 indicates double the probability, 3.0 triple the probability, 4.0 quadruple the probability, etc., of contracting the disease. See http://practice.sph.umich.edu/micphp/epicentral/odds_ratio.php.

with increased risk of PD. In contrast, the risk of PD was substantially increased in subjects who reported 10 years or more of occupational herbicide exposure (OR = 5.8). Tanner et al (2009) found that "[o]ccupational use of pesticides was associated with an almost 80% greater risk of parkinsonism. Growing evidence suggests a causal association between pesticide use and parkinsonism."

Priyadarshi et al (2000) conducted a meta-analysis[5] of 19 studies published between 1989 and 1999, and found that the majority of the studies reported a "consistent elevation in the risk of PD with exposure to pesticides" and that "the risk of PD increased with increased duration of exposure." Based on a comprehensive review, Brown et al (2006) concluded that: "From the epidemiological literature, there does appear to be a relatively consistent relationship between pesticide exposure and PD. This relationship appears strongest for exposure to herbicides and insecticides, and after long durations of exposure." A more recent assessment came to similar conclusions: "This review affirms the evidence that exposure to herbicides and insecticides increase the risk of PD" (van den Mark 2012).

At least three high-quality studies associated PD with exposure to chlorophenoxy herbicides and/or 2,4-D in particular. As noted above, 2,4-D is by far the most widely used of the chlorophenoxy group. The following descriptions are based closely on the National Academy of Science's most recent review of the scientific and medical evidence on the health impacts of Agent Orange compounds on Vietnam veterans (NAS 2012).[6]

Brighina et al. (2008) performed a large case–control study of 844 case–control pairs, and found that exposure to chlorophenoxy acid or esters chemical class was associated with increased risk of PD in younger subjects (OR = 1.52); 2,4-D was the most commonly reported of the chlorophenoxy herbicides. "In total, our subjects reported exposure to 44 different chemical subclasses of pesticides, but no other chemical subclass of pesticides was significantly associated with PD."

Another well-controlled study was performed investigating 224 PD cases and 557 controls drawn from an agricultural area in France with a high degree of pesticide/herbicide use (Elbaz et al 2009). Farming as an occupation as well as professional pesticide use were significantly associated with an increased risk of PD. Exposure to chlorophenoxy herbicides was associated with a trend toward higher risk of PD (OR = 1.8, 95% CI 0.9–3.3), which became statistically significant when age of onset was restricted to greater than 65 years (OR = 2.9, 95% CI 1.1–7.3).

Tanner et al. (2009) performed a case–control study recruiting consecutive subjects from eight large movement disorders clinics in North America; 519 cases and 511 controls were recruited. Subjects whose occupation included frequent pesticide use had an increased risk of PD (OR = 1.90). Those exposed to 2,4-D in particular also had significantly increased risk of PD (OR = 2.59). The strengths of this study were the multicenter recruitment strategy and the careful job ascertainment.

---

5 A meta-analysis is a study of studies that seeks to identify statistically significant patterns across similar studies.

6 By law, a committee of the Institute of Medicine of the National Academy of Sciences (NAS) conducts such reviews every two years to inform the Veterans Administration concerning the long-term effects of exposure to Agent Orange on Vietnam veterans. The NAS assesses studies on what it terms "chemicals of interest," which include 2,4-D, 2,4,5-T and dioxins, as well as several other compounds used in other Vietnam War defoliants.

B. Mechanistic Studies

According to the National Academy of Sciences' most recent review of the medical and scientific evidence:

"A number of the studies suggest that there are neurologic effects, both neurochemical and behavioral, of the chemicals of interest, ***primarily 2,4-D***, in animal models if exposure occurs during development or in cultured nerve cells (Konjuh et al., 2008; Rosso et al., 2000a,b; Sturtz et al., 2008); older references described behavioral effects of developmental exposure of rodents to a 2,4-D–2,4,5-T mixture (Mohammad and St. Omer, 1986; St. Omer and Mohammad, 1987)" (NAS 2012, p. 636, emphasis added).

"In addition, although they dealt with hepatocytes and not cells of the nervous system, earlier studies have indicated that 2,4-D affected aspects of mitochondrial energetics and mitochondrial calcium flux (Palmeira et al., 1994a,b, 1995a,b); if these effects can also occur with nervous system cell mitochondria, which is feasible, then the energy balance and pathways of cells in the nervous system could be affected, with later damage to nervous system function" (NAS 2012, pp. 636-637).

Aggregation and fibrillation of a common brain protein, α-synuclein, is associated with Parkinson's and other neurodegenerative diseases. One *in vitro* study found that a number of pesticides, including 2,4-D, induced α-synuclein to form fibrils characteristic of Parkinson's Disease (Uversky et al 2002).

C. Conclusion

Numerous epidemiology studies have demonstrated a link between Parkinson's Disease and exposure to herbicides in general and 2,4-D in particular. While the biological mechanisms underlying this link have not yet been definitively identified, numerous animal studies have shown that 2,4-D exposure has neurological effects – both neurochemical and behavioral.

2,4-D is already a heavily used herbicide. However, the introduction by Dow AgroSciences of corn, soybeans and cotton genetically engineered to withstand heavy and repeated applications of this herbicide would at least quadruple use of 2,4-D from 27 million lbs. to over 100 million lbs. per year. Given the evidence recounted above, the large rise in 2,4-D use with these 2,4-D-resistant crops could well lead to increasing rates of Parkinson's Disease in the American population.

References

Brighina L, Frigerio R, Schneider NK, Lesnick TG, de Andrade M, Cunningham JM, Farrer MJ, Lincoln SJ, Checkoway H, Rocca WA, Maraganore DM (2008). "Alpha-synuclein, pesticides, and Parkinson disease: A case–control study," Neurology 70(16 pt 2): 1461–1469.

Brown, TP et al (2006). "Pesticides and Parkinson's Disease – Is There a Link?" Environmental Health Perspectives 114(2): 156-164.

CFS (2013a). Comments to USDA APHIS on Dow AgroSciences LLC; Draft Environmental Impact Statement for Determination of Nonregulated Status of Herbicide Resistant Corn and Soybeans: Science Comments I. Center for Food Safety, March 11, 2014. http://www.centerforfoodsafety.org/files/cfs-enlist-draft-eis-science-comments-i_77655.pdf.

CFS (2013b). "Comments to EPA on Registration Review of the Herbicide 2,4-D," Center for Food Safety, February 12, 2013, pp. 9-11. http://www.centerforfoodsafety.org/files/cfs-24-d-registration-review-comments-final_82266.pdf.

CFS (2012a). "Comments to USDA APHIS on Draft Environmental Assessment and Draft Plant Pest Risk Assessment for Dow AgroSciences Petition (09-349-01p) for Determination of Nonregulated Status of Event DAS-68416-4: 2,4-D- and glufosinate-resistant soybean," Center for Food Safety, September 11, 2012, pp. 6-10. http://www.centerforfoodsafety.org/files/cfs-24-d-soy-science-comments-final-9-11-12_11171.pdf.

CFS (2012b). "Comments to EPA on Notice of Receipt of Applications to Register New Uses of 2,4-D on Enlist AAD-1 Corn and Soybean," Center for Food Safety, June 22, 2012, pp. 53-65. http://www.centerforfoodsafety.org/files/cfs-24-d-comments-to-epa-final-6-22-12.pdf.

CRS (2009). "Vietnamese victims of Agent Orange and U.S.- Vietnam Relations," Congressional Research Service, May 28, 2009.

Elbaz A, Clavel J, Rathouz PJ, Moisan F, Galanaud JP, Delemotte B, Alperovitch A, Tzourio C. (2009). "Professional exposure to pesticides and Parkinson disease," *Annals of Neurology* 66(4): 494–504.

EPA (2011). "Pesticide Industry Sales and Usage: 2006 and 2007 Market Estimates," Environmental Protection Agency, Feb. 2011, Tables 3.6, 3.7 and 3.8.

EPA (2005). "Reregistration Eligibility Decision for 2,4-D," Environmental Protection Agency, EPA 738-R-05-002, June 2005, p. 83.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. (1998). "The risk of Parkinson's dis- ease with exposure to pesticides, farming, well water, and rural living," *Neurology* 50: 1346–1350.

Holt, E. et al (2010). "Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) Impurities in pesticides: a neglected source of contemporary relevance," Environ. Sci. Tech. 44: 5409-15.

Lilienfeld, DE & Gallo, MA (1989). "2,4-D, 2,4,5-T and 2,3,7,8- TCDD: An Overview," Epidemiologic Reviews 11: 28-58.

LoE (2012). "Clearcut Chemicals," Living on Earth, Week of May 4, 2012. http://www.loe.org/shows/segments.html?programID=12-P13-00018&segmentID=3

NAS (2012). *Veterans and Agent Orange: Update 2010,* Institute of Medicine, National Academy of Sciences, The National Academies Press, Washington, DC, 2012.

Pearce, N and McLean, D (2005). "Agricultural exposures and non-Hodgkin's lymphoma," Scand J Work Environ Health 31, suppl. 1: 18-25.

Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S (2000). "A meta-analysis of Parkinson's disease and exposure to pesticides," Neurotoxicology 21(4): 435-40.

Schwetz, BA et al (1973). "Toxicology of chlorinated dibenzo-p- dioxins," Adv. Chem 120: 55-69. A single 0.6 mcg/kg dose killed 50% of male guinea pigs tested; typical weight of male guinea pig = 1 kg.

Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. (2009). "Occupation and risk of Parkinsonism: A multicenter case–control study," *Archives of Neurology* 66(9): 1106–1113.

Trost, C. (1984). *Elements of Risk: The Chemical Industry and its Threat to America,* Times Books, 1984.

USDA (2013). Draft Environmental Impact Statement on Dow AgroSciences Petitions (09-233-01p, 09-349-01p, and 11-234-01p) for Determinations of Nonregulated Status for 2,4-D-Resistant Corn and Soybean Varieties. Animal and Plant Health Inspection Service, USDA, 2013. http://www.aphis.usda.gov/brs/aphisdocs/24d_deis.pdf.

Uversky V, Kiowa Bower JL, Fink AL. (2002). "Synergistic effects of pesticides and metals on the fibrillation of α-synuclein: Implications for Parkinson's disease," *Neurotoxicology* 23: 527–536.

van den Mark, M et al (2012). "Is pesticide use related to Parkinson Disease? Some clues to heterogeneity in study results," Environmental Health Perspectives 120(3): 340-347.