2,4-D Health Summary

Gina M. Solomon, M.D., M.P.H.
Senior Scientist, Natural Resources Defense Council
Clinical Professor of Medicine, U.C. San Francisco
April 2012

2,4-Dichlorophenoxyacetic acid (2,4-D) is an herbicide that was one of the two active ingredients in Agent Orange, the Vietnam War defoliant. Although the main health effects of Agent Orange were blamed on the other component of the mixture (2,4,5-T) and dioxin contamination, the data indicate that 2,4-D has significant health risks of its own. It remains unclear whether continuing low-level dioxin contamination of 2,4-D plays a role.

2,4-D and Lymphoma

Dozens of studies in humans have reported an association between exposure to 2,4-D and non-Hodgkin's lymphoma, a cancer of the white blood cells that can be fatal.[1] The first studies linking 2,4-D with non-Hodgkin's lymphoma were published in Sweden thirty years ago.[2] Some of these studies also found an association with soft-tissue sarcoma, a rare and frequently fatal cancer.[3] More recently, studies published in Canada and Italy have supported these results, as have studies performed by researchers at the National Cancer Institute.[4, 5,6] A recent study by the Dow Chemical Company of their pesticide production workers reported a 36 percent increase in non-Hodgkin's lymphoma in workers classified as exposed to 2,4-D, but the authors concluded the result was not statistically significant.[7]

2,4-D increases lymphocyte replication in humans. One study of pesticide applicators found increasing lymphocyte proliferation of 11 to 14 percent greater than normal in the applicators in a manner that was directly related to 2,4-D absorbed dose.[8] This finding was confirmed in a follow-up study, showing a 12 to 15 percent increase in lymphocyte proliferation, with a further indication that higher-dose exposures may cause direct damage to white blood cells, thereby increasing the risk of lymphoid cancer in humans.[9] This finding is consistent with the frequently-reported epidemiologic evidence linking 2,4-D exposure to non-Hodgkin's lymphoma in humans.

Many studies have found that 2,4-D formulations are cytotoxic (i.e., damage and kill cells) and mutagenic (i.e., trigger genetic mutations). For example, in human lymphocytes—commonly known as white blood cells—2,4-D causes chromosome breakage and aberrant cells.[10] Lymphocytes are the cells that turn cancerous in lymphoma. Other studies have reported positive results in various other standardized tests of chromosome and DNA damage, including sister chromatid exchange in chick embryos and in the bone marrow and developing sperm cells of mice, and DNA damage in hamster ovary cells.[11,12,13] In the aggregate, these studies demonstrate that 2,4-D can damage chromosomes and cause mutations in numerous cell types, which could explain why this chemical has been linked to cancer in humans.

In 2010, approximately 65,540 people in the United States were diagnosed with non-Hodgkin's lymphoma. The incidence of this disease in the United States has increased to about double the rate seen in the 1970s, even when adjusted for population size and age.[14] It is reasonable to conclude, based on the

above information, that 2,4-D is likely responsible for some fraction of cases of non-Hodgkin's lymphoma each year.

2,4-D, Neuroendocrine Disruption, and Reproductive Effects

Dozens of peer-reviewed studies show that 2,4-D exhibits hormone-disrupting activity.[15,16,17] 2,4-D also affects the function of the neurotransmitters dopamine and serotonin.[18] Interference with hormones and neurotransmitters can cause serious and lasting effects during fetal and infant development, including birth defects, neurological damage in offspring, and interference with reproductive function such as suppression of sperm production.

Some human studies have been done on the hormonally-related effects of 2,4-D, and these support the results of the animal studies. Male farm sprayers exposed to 2,4-D have lower sperm counts and more spermatic abnormalities compared to men who are not exposed to this chemical.[19] In Minnesota, higher rates of birth defects have been observed in wheat-growing areas of the state with the highest use of 2,4-D and other herbicides of the same class. This increase in birth defects was most pronounced among infants who were conceived in the spring, the time of greatest herbicide use.[20] A larger study in agricultural counties in Minnesota, Montana, North Dakota, and South Dakota found significant increases in birth malformations of the circulatory and respiratory systems, especially among infants conceived in April-June in wheat-growing counties (this is the time period and zone of greatest 2,4-D use).[21] In the same study, infant deaths from birth defects among males were significantly elevated in high-wheat-growing counties. A recent epidemiological study found increased odds of Parkinson's disease in those with occupational exposure to 2,4-D.[22]

Exposure to 2,4-D

2,4-D blows in the wind from the point of application, so the chemical may contaminate soil and water for many miles downwind. 2,4-D is classified by the EPA as a hazardous air pollutant and by the State of California as a toxic air contaminant. 2,4-D lingers in the soil for over a month after it is applied (the half-life of 2,4-D in soil is one week, with virtual elimination defined as about five half-lives).[23] Numerous studies have demonstrated that 2,4-D that was applied outdoors is commonly tracked into homes on shoes or pet paws, and that 2,4-D degrades very slowly when it is not exposed to direct outdoor sunlight, persisting for many months or even a year in household carpets.[24, 25] Residues of 2,4-D on children's hands and in their urine have been shown to correlate closely with the levels of 2,4-D in carpet dust, demonstrating that the contamination from the dust enters children's bodies.[26]

Studies in homes in Iowa within about a half-mile of agricultural fields where 2,4-D was applied detected the chemical in house dust in 95 percent of nearby homes.[27] 2,4-D has been found as a contaminant in surface water samples in the United States, and has also been detected in groundwater, according to the United States Geological Survey.[28] 2,4-D has also been detected in drinking water and it is a regulated contaminant in the National Primary Drinking Water Regulations.[29] Human exposure to 2,4-D is widespread, including among children. A 2008 study, for example, found 2,4-D in 83 percent of household dust samples in North Carolina and 98 percent of homes sampled in Ohio, despite the fact that only one homeowner in this study of 135 homes reported recent use of the pesticide.[30]

REFERENCES

1 *See, e.g.*, Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer 85:1353-1360, 1999. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256:1141-1147, 1986. McDuffic HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 10(11):1155-63, 2001.

2 Hardell L, Eriksson M, Lenner P, et al. Malignant lymphoma and exposure to chemicals especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br J Cancer 43:169-176, 1981.

3 Hardell L, Sandstrom A. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39:711-717, 1979.

4 McDuffie HH, Pahwa P, Robson D, Dosman JA, Fincham S, Spinelli JJ, McLaughlin JR. Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med 47(8):806-16, 2005.

5 Miligi L, Costantini AS, Veraldi A, Benvenuti A; WILL, Vineis P. Cancer and pesticides: an overview and some results of the Italian multicenter case-control study on hematolymphopoietic malignancies. Ann N Y Acad Sci 1076:366-77, 2006.

6 Chiu BC, Blair A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. J Agromedicine 14(2):250-5, 2009. Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 1;52(19 Suppl):5485s-5488s, 1992.

7 Burns C, Bodner K, Swaen G, Collins J, Beard K, Lee M. Cancer Incidence of 2,4-D Production Workers. Int J Environ Res Public Health 8:3579-3590, 2011.

8 Figgs LW, Holland NT, Rothmann N, Zahm SH, et al. Increased lymphocyte replicative index following 2,4-dichlorophenoxyacetic acid herbicide exposure. Cancer Causes Control 11(4):373-80, 2000.

9 Holland NT, et al., Micronucleus frequency and proliferation in human lymphocytes after exposure to herbicide 2,4-dichlorophenoxyacetic acid in vitro and in vivo. Mutat Res 521(1-2):165-78, 2002.

10 Zeljezic D, Garaj-Vrhovac V. Chromosomal aberrations, micronuclei and nuclear buds induced in human lymphocytes by 2,4-dichlorophenoxyacetic acid pesticide formulation. Toxicology 200:39-47, 2004.

11 Gonzalez M, Soloneski S, Reigosa MA, Larramendy ML. Genotoxicity of the herbicide 2,4-dichlorophenoxyacetic and a commercial formulation, 2,4-dichlorophenoxyacetic acid dimethylamine salt. I. Evaluation of DNA damage and cytogenetic endpoints in Chinese Hamster ovary (CHO) cells. Toxicol In Vitro 19(2):289-97, 2005.

12 Madrigal-Budhaidar E, et al. Induction of sister chromatid exchanges by 2,4-dichlorophenoxyacetic acid in somatic and germ cells of mice exposed in vivo. Food Chem Toxicol 39(9):941-6, 2001.

13 Arias E. Sister chromatid exchange induction by the herbicide 2,4-dichlorophenoxyacetic acid in chick embryos. Ecotoxicol Environ Saf 55(3):338-43, 2003.

14 Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

15 Duffard R, Bortolozzi A, Ferri A, Garcia G, Evangelista de Duffard AM. Developmental neurotoxicity of the herbicide 2,4-dichlorophenoxyacetic acid. Neurotoxicology 16(4):764, 1995.

16 Stürtz N, Jahn GA, Deis RP, Rettori V, Duffard RO, Evangelista de Duffard AM. Effect of 2,4-dichlorophenoxyacetic acid on milk transfer to the litter and prolactin release in lactating rats. Toxicology 271(1-2):13-20, 2010.

17 Charles JM, Cunny HC, Wilson RD, Bus JS. Comparative subchronic studies on 2,4-dichlorophenoxyacetic acid, amine, and ester in rats. Fundamental & Applied Toxicol 33:161-165, 1996.

18 Bortolozzi AA, Evangelista DeDuffard AM, Duffard RO, Antonelli MC. Effects of 2,4-dichlorophenoxyacetic acid exposure on dopamine D2-like receptors in rat brain. Neurotoxicol Teratol 26(4):599-605, 2004.

19 Lerda D, Rizzi R. Study of reproductive function in persons occupationally exposed to 2,4-D. Mutation Research 262:47-50, 1991.

20 Garry VF, Schreinemachers D, Harkins ME, et al. Pesticide appliers, biocides, and birth defects in rural Minnesota. Environ Health Perspect 104:394-399, 1996.

21 Schreinemachers DM. Birth malformations and other adverse perinatal outcomes in four U.S. wheat-producing states. Environ Health Perspect 111(9):1259-1264, 2003.
22 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.
23 Extension Toxicology Network. 1993. http://extoxnet.orst.edu/pips/24-D.htm (citing Howard, Philip H. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Lewis Publishers Chelsea, Michigan.
24 Nishioka MG, et al. Measuring lawn transport of lawn-applied herbicide acids from turf to home: Correlation of dislodgeable 2,4-D turf residues with carpet dust and carpet surface residues. Environmental Science and Technology 30:3313-3320, 1996.
25 Nishioka MG, Lewis RG, Brinkman MC, Burkholder HM, Hines CE, Menkedick JR. Distribution of 2,4-D in air and on surfaces inside residences after lawn applications: comparing exposure estimates from various media for young children. Environ Health Perspect 109(11):1185-91, 2001.
26 *Ibid*
27 Ward MH, Lubin J, Giglierano J, Colt JS, Wolter C, Bekiroglu N, Camann D, Hartge P, Nuckols JR. Proximity to crops and residential exposure to agricultural herbicides in Iowa. Environ Health Perspect 114(6):893-897, 2006.
28 The Quality of Our Nation's Waters, Pesticides in the Nation's Streams and Ground Water, 1992-2001. United States Geological Survey. Accessed February 2012.
29 Pesticide Data Program, Annual Summary, Calendar Year 2009. United States Geological Survey. Accessed February 2012.
30 Morgan MK, Sheldon LS, Thomas KW, Egeghy PP, Croghan CW, Jones PA, Chuang JC, Wilson NK. Adult and children's exposure to 2,4-D from multiple sources and pathways. J Expo Sci Environ Epidemiol 18(5):486-94, 2008.