

The Myth of Cancer in Dogs

Issue

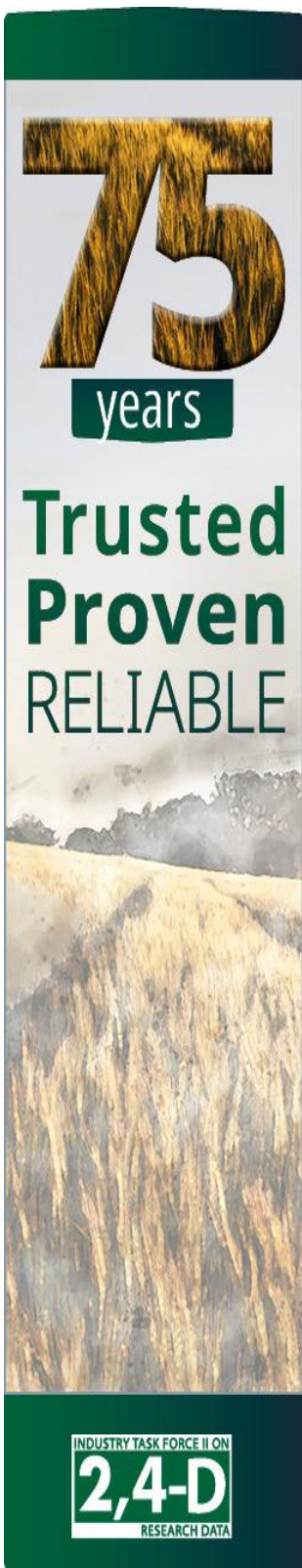
It is sometimes reported in the news media that lawn and turf herbicides containing 2,4-D are a cause of cancer in dogs. This is not supported by the simple fact that all regulatory agencies in the world that have examined the scientific data have reached the same conclusion: 2,4-D is not an animal carcinogen.

Background – NCI Study

In 1991, the Journal of the National Cancer Institute published a study which purportedly showed a positive association between canine malignant lymphoma (CML), a form of cancer in dogs, and dog owners use of the herbicide 2,4-D, (Hayes 1991)¹. The authors claimed to have demonstrated that dogs whose owners used the herbicide 2,4-D on their lawns four or more times per year were twice as likely to develop canine malignant lymphoma compared to dogs whose owners did not use 2,4-D (please note that the maximum labeled use of 2,4-D on turf is two applications per year).

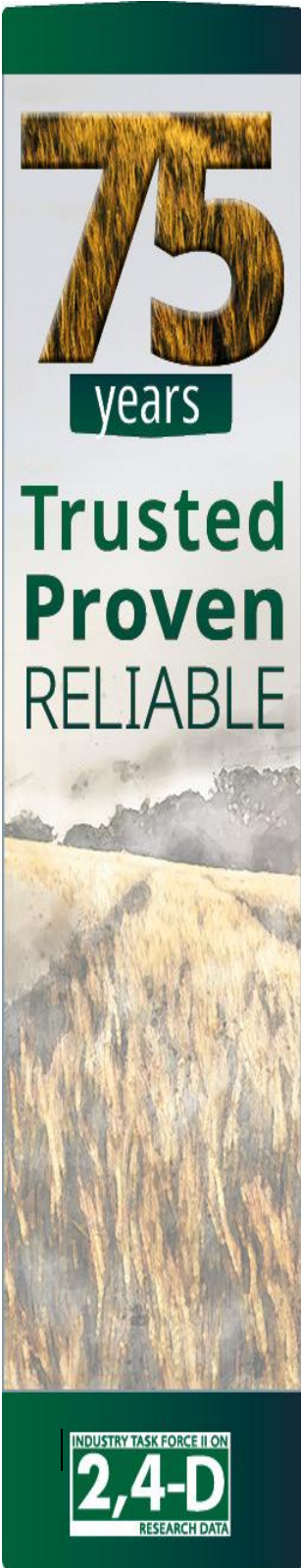
The study was immediately controversial in scientific circles since it was in direct conflict with the extensive 2,4-D toxicology database including rodent and dog feeding studies. There are also lifetime feeding bioassays in rodents (Charles, et al., 1996a)² and a chronic feeding study in the dog (Charles, et al., 1996b)³ that did not indicate oncogenic effects. These animal feeding studies were done under controlled conditions by EPA/GLP qualified laboratories. The current EPA toxicology profile shows 2,4-D to be "non-carcinogenic" in animals.⁴

The Hayes study received widespread coverage by the news media, with the story being carried by almost 200 newspapers across the United States and Canada. Today, the study is often cited by anti-pesticide groups as evidence supporting the suggested relationship of 2,4-D and non-Hodgkin's lymphoma (NHL), a human disease somewhat similar to canine malignant lymphoma. Some veterinarians advise dog owners not to use 2,4-D on their lawns.



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The 2,4-D Task Force was curious how the dose-response of frequency of 2,4-D use was calculated. Since the Hayes dog study was publicly funded, the data file was given to Dr. John B. Kaneene, Director, Population Medicine Center, School of Veterinary Medicine, Michigan State University (MSU), for independent analysis. Neither the Task Force nor MSU were able to obtain additional information from the NCI investigators regarding exposure criteria or the dose response algorithm.

Dr. Kaneene, using NCI's own data, found that the data would not support the CML conclusions reached by the author, and that there was no association between 2,4-D and cancer in dogs. Dr. Hayes was offered an opportunity to defend his study, which he declined. The MSU re-analysis was then published in the peer-reviewed journal (Kaneene, et al., 1999)⁵. Subsequently, a second more recent epidemiological case-control study (Gavazza et al., 2001)⁶ failed to show any association between dogs whose owners used lawn care herbicides and canine malignant lymphoma. This study concluded, "Variables describing animal care and pesticide use were either not associated with the disease [CML] or were uninformative."

Regulatory decisions around the world confirm that 2,4-D is not an animal carcinogen (WHO 1996⁷, EU 2001⁸, PMRA 2005⁹, EPA 2005, EFSA 2015¹³).

Reprints for "Re-Analysis of 2,4-D Use and the Occurrence of Canine Malignant Lymphoma" (Kaneene 1999), are available through this Task Force. For information on other NCI epidemiologic case-control studies involving 2,4-D, see the Epidemiology page on this web site.

Background – Scottish Terriers Study

In 2004, the Journal of the American Veterinary Medical Association¹⁰ published a study which purportedly showed a positive association between transitional cell carcinoma (TCC) of the urinary bladder in Scottish Terriers, a form of urinary tract cancer in dogs. The authors concluded the results suggest that exposure to lawns or gardens treated with herbicides was associated with an increased risk of TCC in Scottish Terriers and exposure to pesticides.

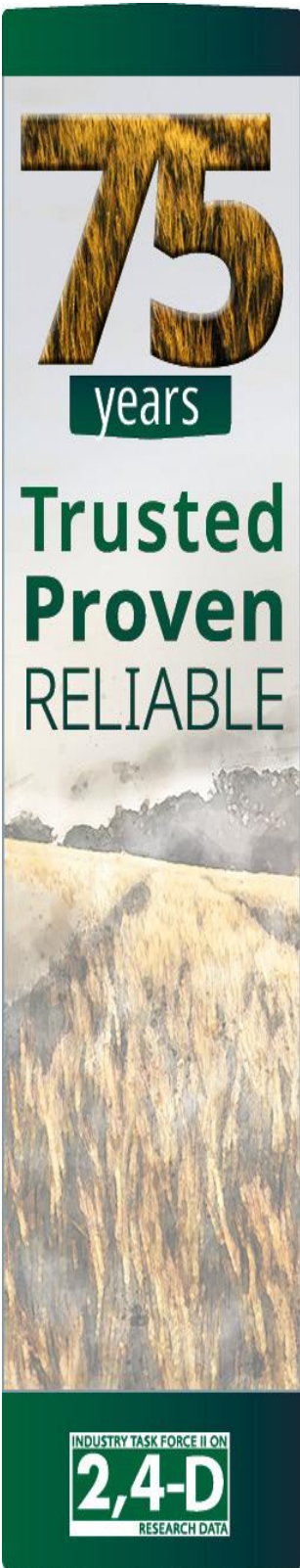
The authors speculate that "dogs with daily or weekly exposure to lawns treated with 2,4-D might be expected to chronically excrete 2,4-D in their urine where it would come in constant contact with bladder epithelium [cell wall]." The logical question: how could a dog in this study possibly be exposed daily? The labeled rate is maximum of two applications per year.

The conclusions reached by Glickman, et al. are NOT supported by the data. The results are not adequate to differentiate a risk of phenoxy herbicide from other pesticides. The exposure to pesticides is overestimated and the findings are not consistent with other studies. Further, the author's recommendation that owners "decrease their dogs' access to lawns or gardens that have been treated with pesticides, particularly phenoxy herbicides" is not supported by their data.

The 2,4-D toxicology and biomonitoring studies in dogs do not show sustained exposure or resulting cancer. There are two studies which reviewed the chronic toxicity of 2,4-D in beagles. The first fed groups of dogs between 0 and 55 ppm of 2,4-D for 2 years¹¹. No cases of bladder cancer were reported. The second was conducted under Good Laboratory Practice standards¹². Charles et al. concluded that after a year of observation, there was no indication of any immunotoxic or oncogenic response. These dogs were fed 2,4-D daily for the one- or two-year chronic study observations. Glickman, et al. also used a one-year criteria for relevant exposure in their study.

Background – Household Chemicals Exposure

Another study frequently linked by alarmist internet articles is a 2011 study by Takashima-Uebelhoer et al. There are a number of methodological strengths and weaknesses to the study, and it finds that increased usage of lawn chemicals might be related to increased rates of the cancer canine malignant lymphoma (CML). While there is some unusual methodology in this study, the main limitation is that it is an epidemiological study; a study examining the broader trends of a disease in a population, conducted through surveys and questionnaires. Epidemiological studies are an extremely important part of the scientific process; they can raise important questions. But they are just the first step; toxicological studies examining the chemistry and biology of a substance are needed to answer these questions. If 2,4-D did not have such a robust body of evidence demonstrating no association with cancer in dogs, this study would indeed be cause for concern. But with so much 'test tube and Petri dish' science showing the non-association, surveys filled out by 200 dog owners just do not make a very compelling case that there is a connection after all.



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Background – 2,4-D in Urine of Dogs Study

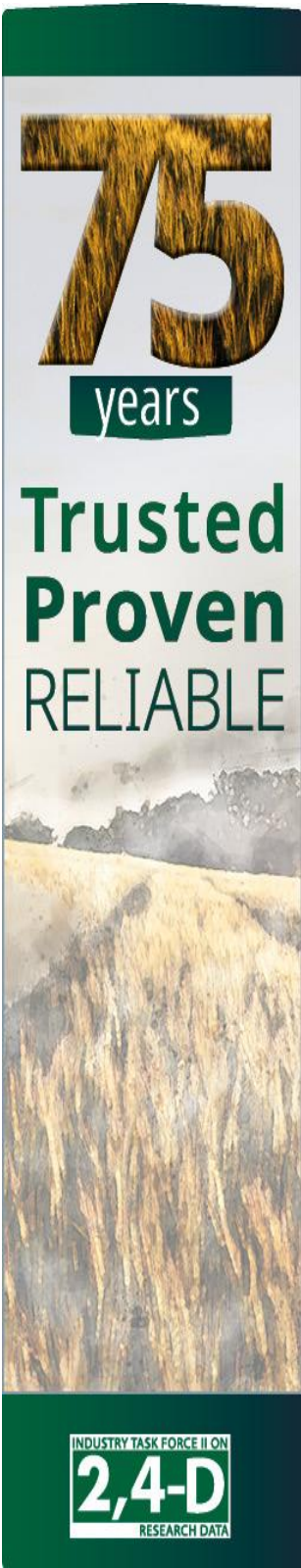
In 2013, the journal ‘Science of the Total Environment’ published a study¹³ by Knapp et al. This study described the concentration of several herbicide compounds – including 2,4-D – in the urine of dogs at various stages before and after application. It also examined the dislodgeable residues of these compounds on turf grasses in various states. The study treats the relationship between 2,4-D and various cancers in dogs as established fact; however, as detailed above strong evidence indicates 2,4-D is not an animal carcinogen. It should also be remembered that the presence of 2,4-D in the urine of any animal following exposure is a good sign; it means the compound is properly being removed from the body rather than stored.

Knapp et al provide interesting data on the residues of herbicide compounds on turf grasses at various timepoints after application. Detectable residues of 2,4-D on plain green grass started at ~100 $\mu\text{g}/\text{m}^2$ (0.1mg) at a few minutes after application, and declined to ~30 $\mu\text{g}/\text{m}^2$ (0.03mg) after 48 hours. For context, assuming residues of 70 $\mu\text{g}/\text{m}^2$ (0.07mg) and using the 1mg/kg/day No Observable Adverse Effects Level (NOAEL) established by Charles et al, calculations show that an average-sized dog (21.58 kg in the Knapp study) would need to fully absorb all available 2,4-D residues from 308.3 m^2 (3308 ft^2) of lawn on a daily basis for an entire year to show any negative health effects. Additionally, multiple studies previously discussed have failed to replicate any findings of 2,4-D causing any forms of cancer in dogs.

Together these studies indicate that 2,4-D is not associated with bladder cancer or any other cancers. In addition, other phenoxy herbicide chronic dog studies show phenoxies are not carcinogenic to dogs.

About the Task Force

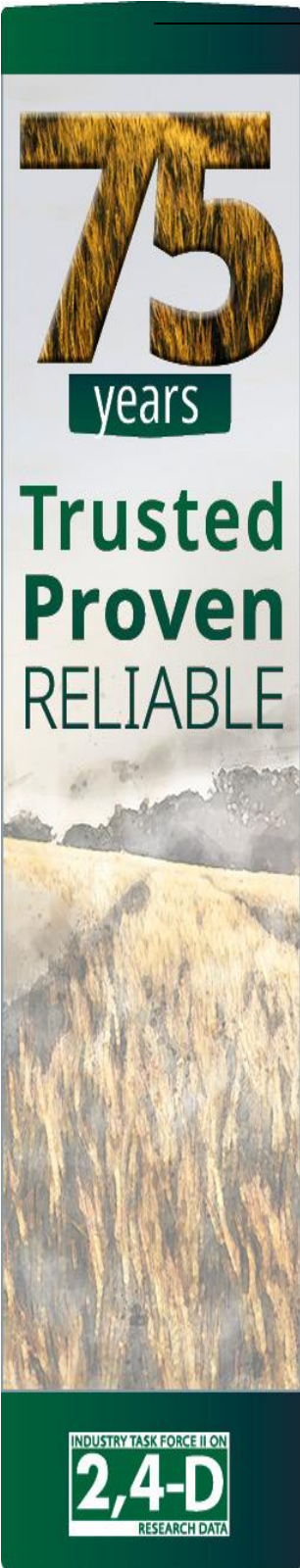
The Industry Task Force II on 2,4-D Research Data is organized to provide funding for the on-going Good Laboratory Practice (GLP) research studies required to respond to the US EPA registration review and PMRA pesticide re-evaluation programs. The 2,4-D Task Force is comprised of those companies holding technical 2,4-D registrations: Corteva Agriscience (U.S.), Nufarm USA, Inc. and Agro-Gor Corp., a U.S. corporation jointly owned by Albaugh, LLC. (U.S.) and PBI-Gordon Corp. (U.S.).



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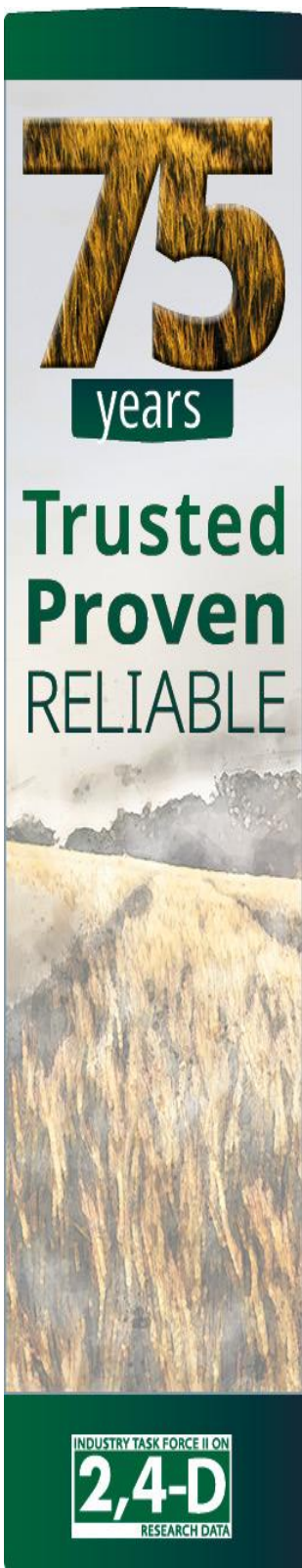
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- ² Charles, JM, Bond, DM, Jeffries, TK, Yano, BL, Stott, WT, Johnson, KA, Cunny, HC, Wilson, RD and Bus, JS. 1996a. Chronic Dietary Toxicity/Oncogenicity Studies on 2,4-Dichlorophenoxyacetic Acid in Rodents. *Fund. Appl. Toxicol.* 33: 166172.
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- ⁵ Kaneene, JB and R. Miller. 1999. Reanalysis of 2,4-D Use and the Occurrence of Canine Malignant Lymphoma. *Veterinary and Human Toxicology*, Vol. 41, No. 2:164170.
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- ⁸ European Commission Health & Consumer Protection Directorate-General. 2001. Commission Working document. Review Report for the Active Substance 2,4-D Re-evaluation. 7599/VI/97final. 1 October 2001
- ⁹ PMRA. (2005). Proposed Acceptability for Continuing Registration; Re-evaluation of the Lawn and Turf Uses of (2,4-Dichlorophenoxy) acetic Acid [2,4-D]. www.pmrarla.gc.ca/english/consum/2,4-De.html
- ¹⁰ Glickman L.T., Raghavan M, Knapp DW, Bonney PL, Dawson MH. 2004. Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers. *J Am Vet Med Assoc.* 24:12901297.
- ¹¹ Hansen WH, Quaife ML, Habermann RT. Chronic toxicity of 2,4-Dichlorophenoxyacetic acid in rats and dogs. *Toxicol Appl Pharmacol* 1971;20:122129.

¹² Charles JM, Dalgard DW, Cunny HC, Wilson RD, Bus JS. Comparative subchronic and chronic dietary toxicity studies on 2,4-Dichlorophenoxyacetic acid, amine, and ester in the dog. *Fund Appl Toxicol* 1996;29:7885.

¹³ Knapp DW, Peer WA, Conteh A, Diggs AR, Cooper BR, Glickman NW, Bonney PL, Stewart JC, Glickman LT, Murphy AS. Detection of herbicides in the urine of pet dogs following home lawn chemical application. *Science of the Total Environment* 2013, 456, 24-41

¹⁴ European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance 2,4-D. *EFSA Journal* 2014;12(9):3812 (Scientific output, published on 11 March 2015, replaces the earlier version published on 7 August 2014)



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