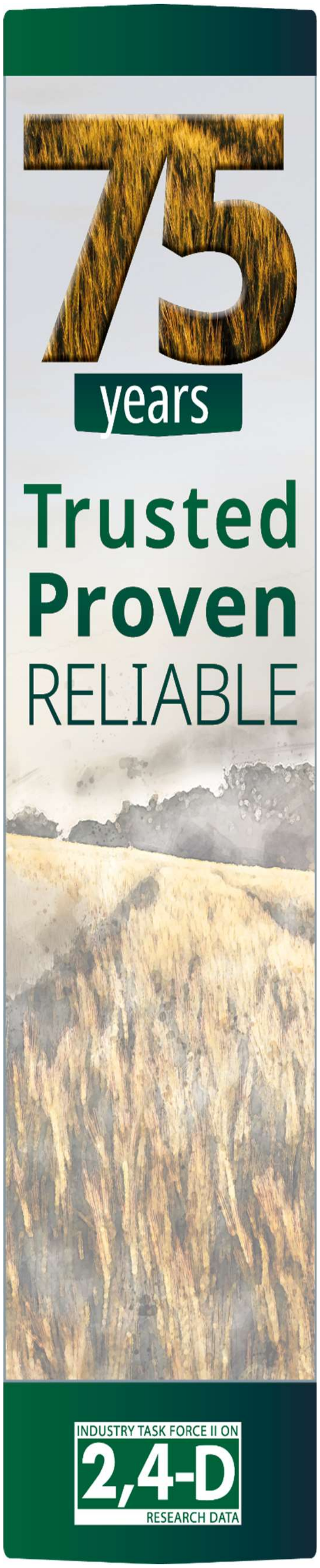


Epidemiology of 2,4-D

Epidemiology studies address relationships of exposures and diseases in populations. The science of epidemiology provides important information about patterns of diseases in groups of people, such as pesticide applicators, farmers and farm workers. The process of identifying causes of disease within pesticide exposed populations is complex, mainly because pesticides are just one of many environmental exposures that people may encounter. Other exposures may include: fertilizers, nitrates, fuels, engine exhausts, solvents, organic and inorganic dusts, ultraviolet radiation, plant pathogens and animal pathogens. Behavioral, dietary and genetic factors may affect their risk of disease as well.

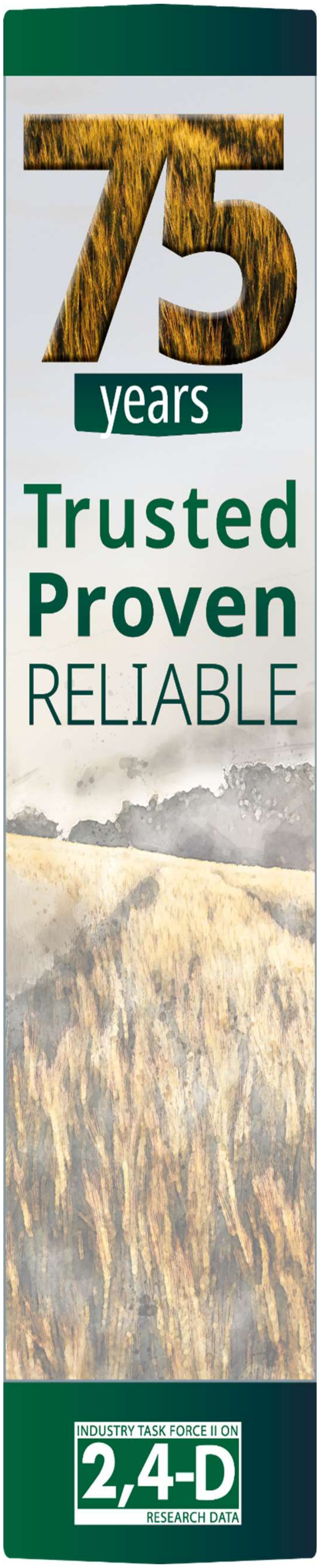
It is difficult to estimate exposure to humans since unlike controlled studies of laboratory animals, epidemiology studies can only approximate *potential* exposures. A common approach is to determine how many applications are made per year and the number of years applied. This approach can identify frequent and long-term applicators from those who rarely apply 2,4-D. However, actual internal exposure may vary with acres applied, method of application and use of protective equipment; i.e., gloves, when mixing/loading. Detection levels in farmers' urine immediately after a 2,4-D application have demonstrated that exposure varies by individual and can be reduced with personal practices (Alexander, 2007; Arbuckle, 2002).

Exposure studies detect little more than trace levels of 2,4-D in urine of the general population, even though 2,4-D is one of the most commonly used herbicides in both the home and garden market and the commercial market (CDC, 2005; Health Canada, 2013) and children of applicators (Alexander et al., 2007). Evaluations of these and other exposure studies have concluded that actual exposures are well below the conservative assumptions made by policy makers for the registration process (Hays 2012; Burns and Swaen 2012).

2,4-D Epidemiology Studies

There are numerous published epidemiology studies pertinent to 2,4-D. As highlighted by some non-government organizations, some of these studies looked at the links between 2,4-D and non-Hodgkin lymphoma (NHL) and soft-tissue sarcoma, both forms of cancer. These reports fail to clarify that early investigations – with weak methodology reported an association, but later independent investigations with more robust methods – did not validate these findings (Garabrant and Philbert, 2001).

For example, two of these early studies are the National Cancer Institute's (NCI) studies in Kansas (Hoar 1986) and Nebraska (Zahm 1990), both of which received considerable media attention. A later NCI study in Iowa and Minnesota (Cantor 1992) showed no association between 2,4-D and NHL. The studies were critically



weakened by differential exposure perceptions among study respondents. All three studies relied heavily on information provided by proxy respondents.

That is, in many cases, the person chosen to participate in the study was not available, so next-of-kin or neighbors were asked about the unavailable person's pesticide use over a previous period of more than forty years.

Subsequent studies have shown that information on pesticide use provided by proxies is often invalid. In the NCI Nebraska study, for example, when the information provided by the self-respondents (i.e., the farmers themselves) is analyzed separately from the information provided by the neighbors or next-of-kin, there is no association between 2,4-D and cancer (Olsen 1996). The NCI combined the data from all three studies and reported, *"This analysis of the pooled data found no association with having ever used 2,4-D."* The weight of evidence from these NCI studies is that 2,4-D is not a carcinogen.

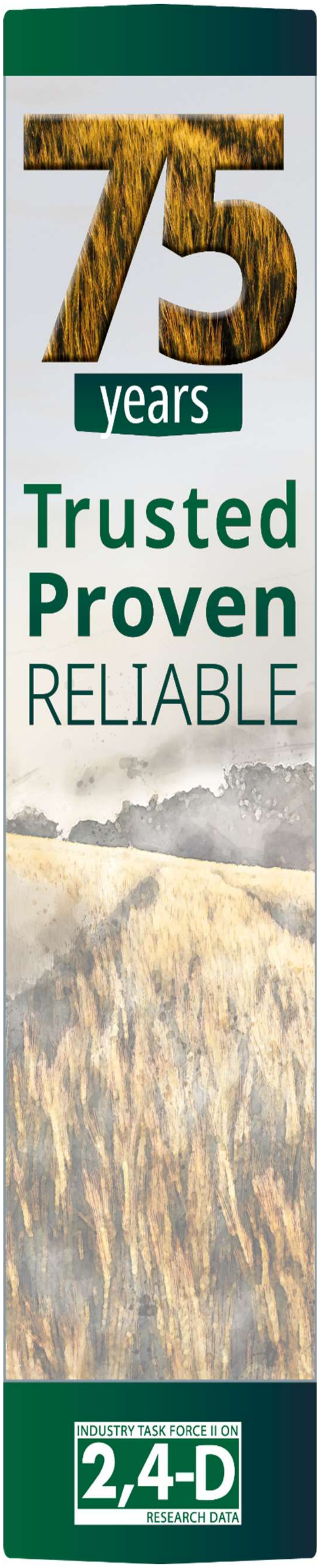
The extensive toxicology of 2,4-D (i.e., animal feeding studies done under controlled laboratory conditions in accordance with EPA GLP standards) does not support the hypothesis that 2,4-D is a carcinogen (WHO 1996; USEPA 2007), and the most robust studies in epidemiology consistently agree with the toxicology and biomonitoring studies. The review of the extensive toxicology and epidemiology of 2,4-D completed in 2001 by Garabrant and Philbert of the University of Michigan School of Public Health concluded:

> ***"Despite several thorough in vitro and in vivo animal studies, no experimental evidence exists supporting the theory that 2,4-D or any of its salts or esters damages DNA under physiologic conditions. Studies in rodents demonstrate a lack of oncogenic or carcinogenic effects following lifetime dietary administration of 2,4-D. Epidemiologic studies provide scant evidence that exposure to 2,4-D is associated with soft tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease or any other cancer. Overall, the available evidence from epidemiologic studies is not adequate to conclude that any form of cancer is causally associated with 2,4-D exposure."***

Recent published reviews and governmental regulatory decisions support the views of Garabrant and Philbert (von Stackelberg, 2013; Burns and Swaen, 2012; USEPA, 2012; Health Canada PMRA, 2008; USEPA, 2005).

An excellent reference guide for further information on epidemiology studies is the Purdue University report titled, "Pesticides and Epidemiology: Unraveling Disease Patterns" (Purdue 1998).

Toxicology and epidemiology studies often referenced by those opposed to pesticides do not sufficiently document exposures and are inadequate to make cause and effect conclusions. In contrast, the extensive modern regulatory toxicology profile



available for 2,4-D provides a robust and reassuring characterization of the compound. In conclusion, "*EPA has determined that this use is safe for humans and the environment when used according to the label.*" (USEPA 2014)

On October 14, 2014, the U.S. EPA published a memorandum in response to Public Comments received regarding an expanded use pattern in corn and soybeans. The agency concluded that:

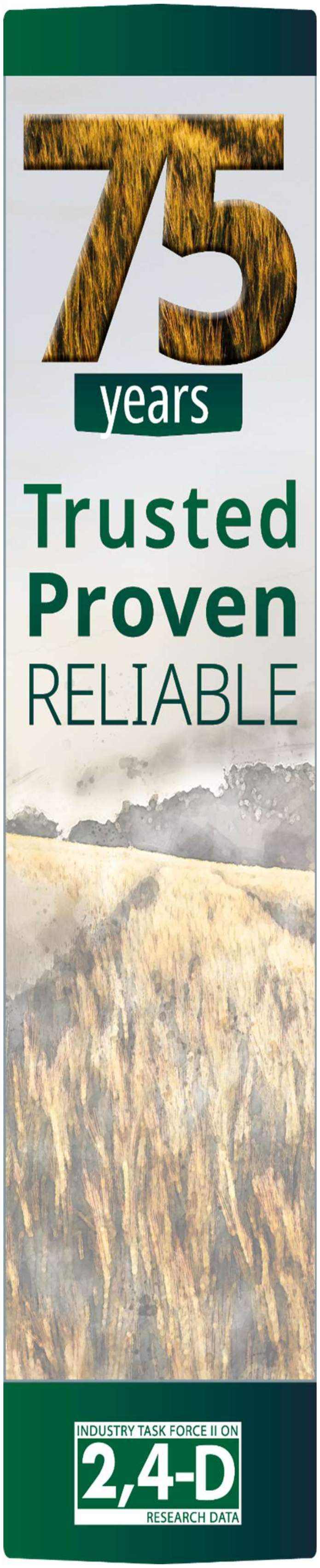
> ***"EPA thoroughly examined all of the significant environmental and health risks of 2,4-D including inhalation and aggregate exposure. EPA's inhalation assessment evaluated risks using the most sensitive toxic effect – effects in the respiratory tract. Exposure to both residential pesticide users and professional applicators who would be applying the new 2,4-D formulation to herbicide resistant corn and soybeans were well below levels of risk concern."***

The agency goes on to state:

> ***"EPA's aggregate exposure assessment included contributions from food, drinking water, and non-occupational exposure, and was done for both adults and children. High-end, unrefined screening level inputs were used which resulted in exposure estimates well below levels of risk concern. Adult aggregate exposure included contributions from food, drinking water, and incidental oral exposure from swimming in a 2,4-D treated water body; the aggregate MOE was 1,800. Children's aggregate exposure included contributions from food, drinking water, and incidental oral exposure hand to mouth from turf; the aggregate MOE was 340."***

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 Industry Task Force II on 2,4-D Research Data is made up of companies holding technical registrations on the active ingredient in 2,4-D herbicides. They are Corteva Agriscience (U.S.), Nufarm, Ltd. (Australia) and Agro-Gor Corp (U.S.).



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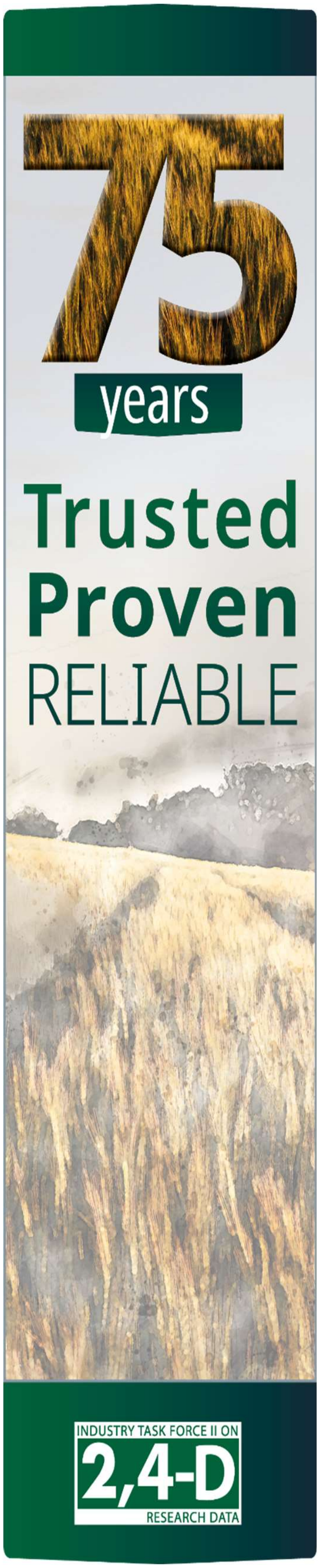

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