UPDATE ON 2,4-D AND HUMAN HEALTH CONCERNS

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2,4-Dichlorophenoxyacetic acid is one of the phenoxy herbicides. It is a synthesis of halogenated phenol and sodium chloroacetic acid. Its chemical structure is similar to indole acetic acid, which is the natural plant hormone known as auxin. 2,4-D's similarity to this hormone is the basis for its herbicidal action. Unlike 2,4,5-T or 2,4,5-trichlorophenoxyacetic acid, 2,4-D is not contaminated with TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) during manufacture.

2,4-D was developed as a plant growth stimulator. Its primary agricultural use is to control weeds in grain crops and sugar cane. It is sprayed on forests, pastureland, rangeland, turf, lawns, and along roadsides, railways, and power lines to kill undesirable plants. It also is utilized to control the ripening of citrus fruits and bananas. 2,4-D is one of the most widely utilized herbicides in the United States. In the 1950s, annual use of 2,4-D was about 24 million pounds; in the 1960s, it ranged from 30 million to 60 million pounds; and in the 1970s, use averaged about 45 million pounds. Unlike other halogenated aromatic hydrocarbons, 2,4-D is excreted rapidly from the body because it is water soluble. This property also results in more rapid degradation of 2,4-D in the environment.

Historically, the herbicidal effects of synthetic auxins were first noted in the 1930s. By 1942, 2,4-D was synthesized in England and it was tested in the United States in 1945. The most common uses of 2,4-D in recent times are shown in Table 1. Applications to lawn and turf account for only 5% of 2,4-D utilization.

Concerns about the human health effects of 2,4-D were raised primarily as a result of the interest in health effects related to the use of Agent Orange in Viet Nam. Agent Orange is a 50-50 mixture of 2,4-D and 2,4,5-T. 2,4,5-T and its contaminant, TCDD, have been associated with a wide range of adverse human health effects. As a result, its utilization is much more limited than is that of 2,4-D. Both 2,4-D and 2,4,5-T are regulated water pollutants.

Major studies of the human health effects of 2,4-D have been conducted to assess its relationship to immune dysfunction, adverse reproductive outcomes, liver toxicity, and cancer. In humans, only the liver and kidney have been found to have high levels of 2,4-D after exposure. About 95% of 2,4-D is excreted through the urine within 4 days after exposure.

A large number of studies have been conducted on the reproductive effects of 2,4-D. None of these have shown an excess of birth defects or stillbirths. Likewise, studies of immune dysfunction and liver toxicity resulting from 2,4-D did not reveal any excess of these health effects.

Investigations of the human carcinogenecity of 2,4-D have evaluated excess risks of soft tissue sarcomas, liver cancer, and non-Hodgkin's lymphoma in relationship to the use of 2,4-D. As described in the discussion that follows, the only substantiated health effect associated with the use of 2,4-D as an herbicide is an elevated risk of non-Hodgkin's lymphoma. The term non-Hodgkin's lymphoma is used to refer to a group of cancers that occur primarily in the lymph nodes. Non-Hodgkin's lymphoma is a relatively rare form of cancer, occurring at a rate of about 11 per 100,000 among women and 17 per 100,000 among men. The five-year survival among persons with non-Hodgkin's lymphoma averages 68%.

Studies of the cancer risk of 2,4-D have ranged from general investigations of herbicides, with no specific measures of 2,4-D, to studies assessing direct exposure to 2,4-D or to herbicides containing 2,4-D. Some of these studies also have looked at whether the excess in non-Hodgkin's lymphoma was associated with herbicides containiing 2,4-D or whether it could be attributed to other types of herbicides, pesticides, or agricultural chemicals. These studies are world-wide, having been conducted in the United States, Canada, Sweden, Finland, and New Zealand. They have included various occupational groups: farmers, herbicide applicators (forestry workers, railroad workers, agricultural workers) and chemical plant workers who manufacture these herbicides. The consistency of the association between 2,4-D and non-Hodgkin's lymphoma across geographic areas, in different work groups, and utilizing various methods of assessing exposure strengthens the conclusion that 2,4-D is probably a human carcinogen.

There is an interesting paradox that human studies demonstrate excess risk of cancer among those who use 2,4-D, while laboratory studies have not been able to demonstrate carcinogenicity of this chemical. In this regard, it is like arsenic, which is a classic case in which human studies clearly indicate the carcinogencity of arsenic in a variety of occupational settings, yet laboratory experiments have not been able to demonstrate any carcinogenic effects upon animals.

Two recent studies of the relationship between use of 2,4-D and its association with non-Hodgkin's lymphoma will illustrate the excess risk of this cancer among persons directly involved in the application of this herbicide. Both studies involved farmers. One was conducted in Canada, the other in the United States. These studies are not only the most recent to report elevated levels of non-Hodgkin's lymphoma among persons using 2,4-D, they provide the strongest evidence of the human carcinogenicity of this herbicide.

The Canadian study was conducted in Saskatchewan. It included a cohort of more than 69,000 farmers and found an increase in non-Hodgkin's lymphoma. This study demonstrated several specific effects: deaths from non-Hodgkin's lymphoma doubled among farmers who sprayed herbicides on larger farms - over 250 acres - and was highest among those using herbicides on farms between 250 and 1,000 acres. On farms of this size, the farmers were more likely to have applied the herbicides themselves. Although a wide variety of causes of death were studied in this investigation, the only association with herbicide use was with non-Hodgkin's lymphoma. Use of other fertilizers or insecticides did not reduce the elevated levels of risk observed in relationship to herbicide use. Although no information was collected on the specific herbicide used by these farmers, it is known that during primary years of herbicide use included in the study, about 75% of the herbicide-active ingredients used in Saskatechewan agriculture was 2,4-D.

The study undertaken in the United States included farmers from 66 counties in eastern Nebraska. This was a study which compared the work histories of men diagnosed with non-Hodgkin's lymphoma with the occupational histories of a group of men from the same geographic area and in the same age group, but who did not have non-Hodgkin's lymphoma. In this study, excess risk ranged from 50% to 300%, depending upon the type of exposure and the number of days per year of exposure. Several important observations are made by this study that add to our knowledge of the relationship between 2,4-D and non-Hodgkin's lymphoma. First, the highest elevation in risk was seen among farmers who used 2,4-D for 21 days or more per year. Second, risk was higher among farmers that had direct skin contact with 2,4-D. Third, this study found no elevated risk among farmers who changed into clean work clothes immediately after handling 2,4-D compared to a five-fold elevated risk of non-Hodgkin's lymphoma among farmers who did not change to clean work clothes until the next day or later.

The evidence from human studies leaves little doubt that exposure to 2,4-D results in elevated risk of non-Hodgkin's lymphoma among persons directly involved in the application of these herbicides. Risk is especially high among those who have direct skin contact, who use 2,4-D for more than 20 days per year, and who fail to change into clean work clothes immediately after application of 2,4-D.

TABLE 1

Herbicide Uses of 2,4-D

Applications	Proportion of All Uses
Wheat and other small grains	31%
Corn and grain sorghum	26%
Pasture and rangeland	25%
Industrial and commercial	9%
Lawn and turf	5%
Aquatic weed control	3%
Rice and fruit	1%

There are several actions that can be taken to reduce the risk of non-Hodgkin's lymphoma among persons who must have direct contact with 2,4-D when applying this herbicide:

1 - limit exposure to 2,4-D,
2 - eliminate skin contact by 1,4-D,
3 - wear protective gear,
4 - change clothing immediately after use of 2,4-D,
5 - wash clothing contaminated with 2,4-D separately from other clothing, and
6 - use tractor application, rather than hand applicators
7 - when possible, avoid use of 2,4-D

SUGGESTED READINGS

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