An examination of the 2,4-D issue

Is there fire where there is smoke?

by Christopher Sann

2,4-D, or 2,4-dichlorophenoxyacetic acid, first registered 45 years ago in the U.S., may be the most widely produced and widely-used pesticide in history. 2,4-D is a simple organic acid that is used as a selective, broad leaf, weed and plant control agent. 2,4-D is used in agriculture and forestry, for weed control on rights-of-way, on range lands, in parks, on golf courses, in water for aquatic weed control, and for commercial and residential turf management.

When 2,4-D is applied to plants it is absorbed through both the leaves and the roots. Once absorbed, it is sent throughout the plant by the vascular system, where it stimulates growth by simulating the action of naturally-occurring plant hormones. Older cells are rejuvenated and young cells are overstimulated causing abnormal growth and plant death. The internal plant functions that are affected by 2,4-D are cell production, enzymatic activity, and the carbon dioxide-oxygen respiration cycle. In addition it affects nucleic acid and protein synthesis, and the flow of water and nutrients through the vascular system. 2,4-D affects all plants to some extent, but it develops its selectivity because broad leaf plants have a larger surface areas than grasses and they absorb more of the material.

It was estimated that almost 70 million pounds of the active ingredient of 2,4-D was produced and used in as many as 1,500 different products and formulations in 1990. With this wide use has come a substantial amount of scientific testing. It was estimated that more than 40,000 scientific articles had been written about 2,4-D by 1978. Many more studies have been conducted in the 15 years since. None of these more than 40,000 studies have raised any significant concerns about the safety of 2,4-D.

A recent history of concerns about safety

Speculation about the safety of the phenoxy herbicide 2,4-D began in the late 1970's with the controversy surrounding the use of 10 million gallons of Agent Orange, a phenoxy-based herbicide mixture that contained 2,4-D. It was sprayed by the U.S. military to defoliate the jungles during the Vietnam war. In that uproar 2,4-D was not suspected as the controversial compound in the mixture but rather a dioxin-contaminated, ester formulated herbicide, 2,4,5-T or Silvex, was believed to have caused a variety of long term symptoms to American soldiers who had direct exposure to the material years before. The 2,4,5-T was itself not suspected of causing the observed problems so much as the dioxin. This dioxin contamination was a by-product of

Notes on 2,4-D studies

by Christopher Sann

As I researched the information for and wrote about the safety of 2,4-D in the preceding article, I became frustrated and bewildered. Frustrated enough that I felt the need to comment on my feelings.

Questionable techniques in control studies

I am frustrated about the use of such questionable survey techniques in the scientific community. Specifically, I don't understand why the researchers associated with the National Cancer Institute continued to release the questionable conclusions of their case control studies on the safety of 2,4-D over a period of five years, when the use of the study technique to establish a direct link between a cause — exposure to 2,4-D — and an effect — elevated levels of three cancers — was highly controversial.

The Institute continued to release its conclusions of successive studies even though the conclusions from its earlier studies had received a universally negative reaction to the design and the execution of those studies when they were examined by peer review panels.

New scientific theories generated by good science

The nature of the scientific process is rife with controversy, and has been for hundreds of years. Controversy may stimulate advances in scientific knowledge because of efforts by scientists to defend their theories in the face of established dogma. But, in order for new theories to displace existing theories, they must have been generated from good science. Good science is a process by which an established set of procedures and protocols are followed to test hypotheses. Without the acceptance and practice of good scientific procedures, all scientific inquiry becomes a complicated version of Abbott and Costello's classic piece "Who's on first?".

Case control studies are a part of good science

Case control studies are a part of good science: they are an established survey technique designed to develop an hypothesis concerning the possible cause of an occurrence. This is done by using an established format with well-designed procedures to try to establish a possible cause or hypothesis. Once the hypothesis has been developed, then a series of specific, controlled follow-up studies are performed to test the hypothesis. It is the results of these follow-up studies that must support the hypothesis in order for the hypothesis to become accepted as fact.

A well-designed case control study should meet certain criteria. First, it should have an appropriate control group to eliminate as many confounding factors as possible. Second, it should survey a large enough group of individuals so that the results can have statistical significance.

Because of the many unique aspects involved in designing case control studies, there are few if any off-the-shelf design directions to follow. It is left to the individual scientist to account for variables in his design. If the study is not well designed, or if it contains a significant number of sampling errors or confounding variables, then it is imperative that the examining scientist take these weaknesses into account and use caution when formulating his conclusions. If, as is the case with many human case-control studies, the scientist's concern for the specific health implications of the study override these cautions, then it is of utmost importance that the scientist make a major effort to see that his conclusions are rendered in the light of concerns for accuracy.

2,4-D case control studies were flawed

Unfortunately, it does not appear that these cautions or concerns for accuracy were the overriding considerations in the design, execution and conclusions of many of the case control studies on the safety of 2,4-D. All of this would not be of such concern if it weren't for the fact that the concerns for the safety of 2,4-D raised from these studies came at a time when questions about the use of pesticides in general and specifically by turfgrass managers were already at an all-time high. Whether they manage large facilities or home lawns, turfgrass managers are highly visible and are often the public's first and only direct contact with pesticide use or its users. The National Cancer Institute studies have made turfgrass managers' lives considerably more difficult and for no apparent reason.

There is an old saying in the data processing industry that seems appropriate in this context: garbage in, garbage out. ■

manufacturing the 2,4,5-T and it was considered to be difficult to eliminate from the manufacturing process. The contamination of 2,4,5-T by dioxins was known to the members of the chemical manufacturing community in late 1950's and was ignored by the military in their specifications for the manufacture of Agent Orange.

This concern over the phenoxy herbicides in general, coupled with a speculative study published by a Swedish scientist about the potential carcinogenicity of 2,4-D, 2,4,5-T, and their contaminants' connection to several unusual cancers — Hodgkin's disease, soft tissue sarcoma, and non-Hodgkin's lymphoma — led the EPA to issue the following statement in 1980.

"...EPA believes that available information on potential adverse health effects of 2,4-D does not warrant a regulatory action to remove its products from the market. The agency also does not see imminent hazard or unreasonable health effects when 2,4-D products are used according to label instructions and precautions."

This statement was issued despite the fact that the EPA had already suspended the registration and all uses of the suspect herbicide, Silvex.

Six years later, the National Cancer Institute published the results of a study of Kansas farmers. The study stated that a connection existed between the use of phenoxy herbicides for more than 21 days per year and a small increase in non-Hodgkins lymphoma. That study did not single out 2,4-D but covered herbicides in general. In response to some questions about this study, four independent reviews of the methodology employed and the conclusions reached in this Kansas study were initiated. All four of the reviews concluded that the study's conclusion of a cancer risk from exposure to 2,4-D was not supported by the data.

Undaunted, the Institute published a report in 1990 that said the same cancer link existed in a study of Nebraska farmers. A blue-ribbon panel conducted by the Harvard School of Public Health concluded that the link between the herbicide and the cancer that the new Nebraska farmer study had alluded to had not been established.

In 1991 the Institute published the results of yet another study that claimed to establish a link between the use of four applications of phenoxy herbicides per year on home lawns and the development of malignant lymphoma in dogs. Another review of this third Institute study concluded that because of poor design of the study, the conclusions about cancer in dogs was not shown.

Finally, the Institute published a fourth study concluding that there was a slight increase in the occurrence of cancer in Nebraska farmers. This conclusion was made despite the fact that there did not appear to be an increase in the occurrence of the cancer in the surveyed population with the passage of time nor was there a reduction in its occurrence when the farmer/applicator used protective clothing during the handling of the herbicide.

Studies show human exposure is low

The three possible human exposure routes to 2,4-D are the same as any pesticide:

- dermal: through the skin,
- ingestion: through the stomach and intestines,
- inhalation: through the lungs.

Because of the manner in which 2,4-D is applied, the predominant routes of exposure are through inhalation and dermal exposures. Ingestion of significant quantities of 2,4-D would be by a deliberate act or by accidental poisoning.

Human exposures are in five groups — farm workers, forestry workers, commercial applicators, homeowners, and bystanders. In the studies of farm workers, the potential for exposures averaged from 0 to 40 hours per year. Homeowner exposures depend on the frequency of use by the homeowner, but it can be assumed to range between 0 to 4 hours per year. Bystander exposures would be either accidental or by proximity to an area of application and would range from 0 to 2 hours per year. Forestry workers averaged 0 to 160 hours per year while commercial applicators have the highest potential exposures at 0 to 300 hours per year.

Potential exposures are not always realized

Studies show that 90% of homeowners tested were found to have had no detectable residues and 100% of tested bystanders had no detectable residues from any application method other than by airplane. Studies estimating detectable farmer exposures are not available. Testing of forestry workers found that more than 70% of the over 500 aerial application crews tested had no detectable exposures, while the high exposure levels that were found among ground application crews were the results of failures of the workers to wear protective clothing other than gloves and boots. In several cases they lacked clothing such as shirts and or had leaking equipment.

Actual measured exposures of various individuals in the groups varied from no detectable amount, less than 4 parts per billion, to about 1 part in ten million per 2.2 lbs. of body weight. Using information based on records of actual exposures, a hypothetical member of each group with an average body weight of 154 lbs. would have an average estimated daily exposure, see table below.

In general, human exposures and exposure quantities were determined by the type of application equipment used, the way it was used, the safety precautions taken in the application process, and the frequency of application. Applicators were at the greatest risk of exposure, homeowners had a very low potential for exposure and by-standers had the lowest potential of exposure.

98% of 2,4-D is absorbed through the skin

All available data indicate that 98% of 2,4-D absorption is through the skin, but tremendous differences of absorption rates, depending on the formulation and the area of the skin exposed, make it difficult to make a general statement about dermal absorption. But one might say that, if the exposure were by ingestion, as much as 25% would be absorbed within a half hour, and virtually all absorbed within 24 hours.

Once in the blood stream, 2,4-D spreads throughout the body but does not remain. About 90% of it is excreted in the urine within a week of exposure with the majority lost within the first two days. The remaining 10% of the 2,4-D is excreted through perspiration, most within two weeks.

The fact that almost all of the absorbed 2,4-D is excreted is important. It indicates that it does not lodge in tissues that have a potential for chemically-induced change and that any one exposure that occurs will be of a minimal duration, usually less than five days. 2,4-D is excreted chemically intact.

Because of its basic chemical composition, it does not

Average estimated daily exposure

Group	Average Exposure	Equivalent	Actual Product *
Homeowner	< 10 micrograms	< 1/48,000,000 of a lb.	0.0009 of a fl.drop
Bystanders	none	————	————
Farm workers	< 0.5 milligrams	< 1/480,000 of a lb.	0.009 of a fl.drop
Commercial applicators	< 0.5 milligrams	< 1/480,000 of a lb.	0.009 of a fl.drop.
Forestry worker	< 1.0 milligrams	< 1/240,000 of a lb.	0.09 of a fl.drop.

* based on a herbicide with a 25% 2,4-D component

pounds that have caused cellular breakdowns or tissue damage.

Scandinavian, U.S. studies complicate issues

However, the Hardell studies conducted in Scandinavia and NCI studies of human exposures in the Midwestern U.S. indicating that 2,4-D has a low potential to increase Non-Hodgkins lymphoma complicate the issues of whether 2, 4-D causes cancer.

Use of case control studies to determine direct relationships is controversial

There has been considerable scientific controversy about the methodology employed in the original two sets of human studies that indicated increased potential for cancers. The studies conducted in 1978 by Hardell and the National Cancer Institute in the 1980's were based on case-control studies.

Case control studies are general surveys of a specific population of individuals with the intent of determining the potential relationship between abnormal levels of an occurrence and the qualifications for that group. Prior to the Hardell study this study technique had not been used to determine if a particular substance had produced a particular outcome.

This methodology used to identify specific cause and effect relationships has led to acrimony in the scientific community. In the Institute study, survey participants were asked to remember specific information about phenoxy herbicide applications made as many as 30 years before the interviews, information such as days of use per year. Often the information was obtained from the next of kin who may or may not have had any direct information about specific compounds applied or the number of times applications were made.

Peer reviews of the survey methodology employed in the Institute's Kansas study has indicated that because of real-world farming considerations, the majority of the farmers in the survey did not meet the annual exposure data cited in the conclusions of the study, thereby limiting the number of qualified subjects. Also the number of reported cases of non-Hodgkin's lymphoma was so low that the data were not entirely statistically sound.

Case control studies often are not designed to eliminate confounding elements, such as exposures to other compounds or cigarette smoke. Even in studies designed to explore the various hypotheses developed by case control studies, it may be very difficult to control for these confounding variables. In a 1981 study designed to confirm the case control survey conclusions on phenoxy herbicides, over 1500 of the participants had been exposed to other pesticides, including individuals that had been exposed to up to three fungicides, nine insecticides, and 14 herbicides, some of which are known carcinogens.

Additionally, if these confounding factors could be controlled, this survey technique had no means of actually measuring direct exposures to the phenoxy herbicides. Using current exposure data from farm workers — 21 days or more of 2,4-D exposure — the standard identified in the Institute studies as the low parameter for exposure, would produce a hypothetical 120 microgram/ 1 kilogram of body weight as the annual exposure of survey participants. This rate of annual exposure would have made 2,4-D the most potent carcinogen known to man. Animal studies using dosage rates of at least 10 times that annual exposure rate and often thousands of times that rate would have expected to produce significant numbers of tumors. This has not been the results of such tests.

Subsequent case control studies are controversial

Since the original National Cancer Institute case control studies, there have been a number of additional so-called cohort studies aimed at confirming the results of the Institute conclusions. There have also been a number of additional case control studies to examine other potential exposures or risks with phenoxy herbicides. Cohort tests are used to try to reproduce the original results either through direct, tightly-controlled testing or, in the instance of human exposures through, examination of other populations of similar subjects.

In 20 recent cohort studies conducted since 1980, a few of the studies have indicated that some elevated results were found to have exceeded expected cancer occurrences, but the types of cancers reported and levels of the elevated responses did not fit any consistent pattern.

A significant number of additional case control studies have been conducted since the initial Swedish studies. Almost all of them suffer from the same problems as the National Cancer Institute studies, primarily a failure to establish consistent results and failure to establish exact exposures.

2,4-D does not appear to cause cancer

It may be said all the studies dealing with the safety of 2,4-D indicate that the conclusions of the Swedish and National Cancer Institute studies are not supported by the evidence. To be specific, 2,4-D is not:

- retained in the body but is rapidly excreted making exposures of short duration,
- metabolized into potent intermediate metabolites associated with other human carcinogens,
- chemically-connected to known human and animal carcinogens,

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- capable of causing cancer in laboratory studies even at very high doses,
- consistently linked with cancer risk in case control studies.

Finally, measured actual human exposures indicate that, if 2,4-D were a carcinogen, it would be the most potent known. Furthermore, the studies that show an increased risk of non-Hodgkins lymphoma were not designed to eliminate viral and genetic confounding factors, factors suspected of contributing to lymphoma occurrences.

The EPA has the final word

In response to the National Cancer Institute studies, the Swedish studies and lingering suspicions regarding Agent Orange, the Environmental Protection Agency (EPA) announced in 1992 its intention to establish a panel to review all of the available scientific data on the safety of 2,4-D. That panel was convened in the fall of 1992. The outcome of that panel's work was the establishment of new labeling standards for the use of 2,4-D products that were introduced in the spring of 1993 for farm, nursery and forestry workers. The new standards go into effect in April of 1994 and will require that workers exposed to the phenoxy herbicides use good protection practices with appropriate protective devices and that reentry periods be established for sprayed areas.

What does this mean for turfgrass workers?

The current worker protection regulations explicitly exempt most turfgrass management uses of 2,4-D from complying with the new standards.

Given the history of the controversy over the safety of 2,4-D and the nature of the environmental politics that surround this issue, turfgrass managers should err on the side of caution and make an effort to comply with the new standards. The EPA is clearly hoping that turfgrass managers will continue with their excellent record of compliance and adopt the new worker protection standards, before the EPA removes the exemption. ■

Leadership *continued from page 14*

Need for a pro-active stance

In summary, I hope that turfgrass managers will take a pro-active stance on promoting the profession by continuing to practice state-of-the-art management strategies, always striving to learn more about the industry and the academic support that goes into the industry. I hope all of you will become even more scientifically and technologically literate so the turfgrass industry will set the example of how plant management can function in harmony with sound environmental stewardship. ■

ASK THE EXPERT

Have a question on any aspect of turf management?

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