NEW PERSPECTIVES ON AN ESSENTIAL PRODUCT: 2,4-D

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SUMMARY

The herbicide 2,4-D has been shown to be relatively inexpensive and extremely effective in controlling broadleaf weeds in a wide variety of applications. State-of- the-art and new technologies indicate that 2,4-D offers these benefits at low risk to humans and the environment. This article discusses the findings of recent scientific activities regarding the toxicology of 2,4-D and examines the benefits of this long-used product.

INTRODUCTION

For the past 45 years, the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) has been widely used for broadleaf weed control in farming, forestry, power line maintenance, roadside brush control, aquatics, on home lawns, and for other end uses (15). During this time, the compound has been shown to be both relatively inexpensive and extremely effective. The compound has also been thoroughly evaluated in terms of health and safety, with over four decades of laboratory testing and extensive user experience documenting its requirements for safe use and environmental protection.

Because research in support of product safety is an ongoing commitment, many new studies are currently underway on 2,4-D to update previous work. Much of this research has been sponsored by Industry Task Force II on 2,4-D Research Data[2], which was formed to address a 1988 U.S. Environmental Protection Agency reregistration data call-in requiring over 200 new studies to support continued registration.

Today, few products on the market have been as thoroughly researched and evaluated as 2,4-D. Task Force II expects to spend about $25 million in meeting current reregistration expectations. An additional $5 million is expected to be spent by individual companies to address research needs of proprietary forms of the compound. A previous task force has spent yet another $4 million pursuing research requirements under an earlier data call-in.

These new 2,4-D research studies required by the most recent EPA guidelines have incorporated both state-of-the-art and previously unavailable technologies. These methods of analysis are significantly more sophisticated than earlier testing techniques, and thus permit development of an improved understanding of the fate of 2,4-D and its breakdown

2,4-Dichlorophenoxyacetic acid (2,4-D) is widely used to control broadleaf weeds on pastures and rangeland.

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products in animals, crops, and the environment.

The extensive amounts of new research on 2,4-D provide valuable new perspectives affirming the minimal potential for the use of 2,4-D to adversely affect the environment or human health (9). The findings of the recent scientific activities supporting this conclusion are briefly summarized in this paper.

TOXICOLOGY

Carcinogenicity

The carcinogenicity of 2,4-D has been reviewed by numerous scientific and regulatory groups including the Environmental Protection Agency, Agricultural Canada, the Ontario Ministry of the Environment, the Council on Agricultural Science and Technology, and the Harvard School of Public Health (1,4,6,7,10, 12,15,21) (Table 1). The EPA has placed 2,4-D in carcinogenicity category "D," pending the submission and assessment of the repeat studies (8,10).[1] The consensus opinion is that the weight of the evidence does not show a cause and effect relationship between 2,4-D and cancer.

Animal Studies: Lifetime studies in laboratory animals completed in 1986 found no evidence of cancer in female rats or in male and female mice fed high doses of 2,4-D (16). Importantly, a finding of a weak association between 2,4-D treatment and brain tumors (astrocytomas) in male rats has been judged by a third-party cancer expert to be unrelated to herbicide treatment (20). Thus, the weight-of-evidence conclusion from the 1986 studies was that 2,4-D cannot be viewed as causing cancer in animals.

EPA testing guidelines require that animal cancer tests must be conducted at the maximum tolerated dose (MTD), i.e., the largest daily exposure that causes evidence of toxicity to the animals but does not cause excessive deaths over the life span of the animals. After an evaluation of the 1986 study, the EPA questioned whether the top dose had attained an MTD dose level. To ensure that the potential carcinogenicity of 2,4-D had been assessed under conditions of MTD dosing, the EPA requested that lifetime studies in rats and mice be repeated at top dose levels from three to six times higher than those used in the previous research. These new 2-year lifetime tests were conducted at significantly higher doses and were completed in 1995. The results showed no evidence of brain cancer or other types of cancer (16,17).

Epidemiology: Retrospective studies of exposed populations have yielded inconsistent results, with some studies suggesting a risk of non-Hodgkin's lymphoma (2,14,35) and others questioning it (5,18,23,28,33). More recently, however, an EPA-convened panel of toxicology and epidemiology experts concluded in 1994 (12), after evaluating both the animal and human evidence, that specific associations reported between use of 2,4-D in agriculture and appearance of cancer were at most weak and inconsistent. Significantly, the EPA panel further noted that possible cancer risks in farm workers could not be attributed specifically to the use of 2,4-D when compared to other potential hazards associated with farming as an occupation. Given the levels of exposure for users, the report concludes that if 2,4-D were to cause cancer, it would have to be an extremely potent carcinogen affecting humans but not animals and acting by a unique mechanism which has yet to be understood. Additional studies were suggested by the EPA panel as a means of distinguishing these inconsistencies.

Mutagenicity: 2,4-D is considered nonmutagenic based on 26 studies of seven derivatives of 2,4-D (technical formulations) conducted under current protocols. Although some prior studies have yielded positive results, the previously noted EPA expert panel concluded that these older studies have significant experimental deficiencies and that "the currently available evidence suggests that 2,4-D is nongenotoxic" (12).

Metabolism: Research in animals and humans has shown that 2,4-D has a very short half-life in the body, estimated at between 10 and 36 hours. The compound is absorbed into the body intact and excreted essentially unchanged (not metabolized), with nearly all of the 2,4-D body burden being cleared within 2 to 4 days in the absence of sustained exposure (19,24,25,29,30). Given its rapid clearance, 2,4-D is not regarded as a pesticide that will accumulate in the body. It is im-

TABLE 1. Toxicological test summary of 2,4-D (acid).

Test	NOEL[a] mg/kg-body weight/day	Results
21-Day dermal	1000 (NOAEL[b])	slightly irritating
Teratology, rat	25	not teratogenic
Teratology, rabbit	30	not teratogenic
2-Generation, rat	5	low reproductive risk
13-Week subchronic, rat	5	NOEL is 18 mg/kg/day for 2,4-D DMA[c] NOEL is 22 mg/kg/day for 2,4-D 2-EHE[d]
13-Week subchronic, mouse	15	—[e]
2-Year chronic, rat	5	no evidence of carcinogenic effects
2-Year chronic, mouse	5	no evidence of carcinogenic effects
1-Year chronic, dog	1	LOEL[f] is 5 mg/kg/day
1-Year chronic neurotoxicity, rat	5	not neurotoxic
Mutagenicity		
Ames	—	not mutagenic
Chromosome aberration	—	not mutagenic
Unscheduled DNA synthesis	—	not mutagenic

[a]*NOEL is the no observed effect level.*
[b]*NOAEL is the no observed adverse effect level.*
[c]*Dimethylamine salt of 2,4-D.*
[d]*Ethylhexyl ester of 2,4-D.*
[e]*Only 2,4-D (acid) was tested in mouse.*
[f]*LOEL is the lowest observed effect level.*

[1]Category D is defined as inadequate data upon which to make an assessment of pesticide oncogenicity.

portant to note that the amine, ester, and sodium formulations of 2,4-D are all also rapidly cleared because of their rapid conversion to 2,4-D acid on absorption into the body. The rapid clearance of unchanged 2,4-D from the body, coupled with its lack of genotoxicity, further supports the conclusion that there is no plausible toxicological evidence whereby 2,4-D can be expected to be a carcinogen (27).

Neurotoxicity

High and repeated dose testing in numerous studies with multiple species have not detected neurological impacts from exposure to 2,4-D (22,27). Subchronic oral studies in rats with 2,4-D acid, ester, and amine salt derivatives found no evidence of histological lesions or clinical signs of toxicity to the nervous system (13,16). In addition, neurological effects have not been reported in a 13-week oral subchronic study of 2,4-D acid in mice, nor in dogs treated with single oral doses up to 125 mg/kg (31), nor in a 1-year chronic feeding study in dogs, nor in several 2-year chronic studies in rodents (16,17).

No neurological effects were indicated in a recent 1-year chronic neurotoxicological study in rats (16). The rats were evaluated by functional observational battery, motor activity assay, and neuropathology assessment. The only effect noted in rats exposed to 75 mg/kg/day was a slight decline (4%) in average body weight.

Reproduction/Teratology

No birth defects have been observed related to 2,4-D or its derivatives in several reproductive and developmental studies conducted in laboratory animals (16). Available studies suggest that exposures high enough to be toxic to the mother may also be toxic to the fetus, with resulting effect on reproduction and development; however, no effects were seen at lower doses. These effects occur only when the dose is so large as to overwhelm the processing capacity of the mother's kidneys. The substantially lower exposures sustained by humans could not plausibly result in these effects.

Environmental Toxicology

Exposures of wildlife to 2,4-D, whether from direct spraying or consumption of treated vegetation, is so low as to have no toxicological significance (26). Indeed, the greatest effect of 2,4-D on wildlife is likely to be the presentation of an enhanced habitat following spraying, which allows the infiltration of lower-growing, fruit-bearing plants. As documented in one long-term study (3), many common game species occupied the habitat created by a sprayed utility right-of-way out of an apparent preference and prospered there over a period of more than two decades.

Current studies show that 2,4-D is practically nontoxic to fish and only slightly toxic to aquatic invertebrates (Table 2). The compound is considered practically nontoxic to the mallard duck and bobwhite quail in 8-day dietary studies, only slightly toxic to birds in acute oral testing, practically nontoxic to honeybees, and slightly toxic to earthworms at high doses (16).

EXPOSURE REDUCTION

In addition to generating new studies, the Task Force has reached an agreement with the EPA to initiate a 2,4-D exposure reduction program (11). The program requires safety procedures in the mixing, handling, and application of 2,4-D; the use of protective clothing; improved personal hygiene practices; and an extensive user education program. All 2,4-D products shipped by registrants in 1995 are being packaged under the new label specified by this program.

Studies show that 2,4-D is practically nontoxic to mallard ducks.

BENEFITS

In response to concern by the EPA about the health effects of farm worker exposure to 2,4-D and the phenoxy class of herbicides, the USDA initiated a benefits assessment in 1993 to determine the economic implications of a complete ban of

TABLE 2. Environmental toxicity summary for 2,4-D (acid).

Species	Test	Dose	Results
Bobwhite quail	acute oral LD_{50}[a]	500 mg/kg (2,4-D DMA[b])	slightly toxic
Mallard duck	8-day dietary LC_{50}[c]	>5620 ppm	practically nontoxic
Bobwhite quail	8-day dietary LC_{50}	>5620 ppm	practically nontoxic
Rainbow trout	96-hour LC_{50}	358 mg/L	practically nontoxic
Bluegill	96-hour LC_{50}	263 mg/L	practically nontoxic
Fathead minnow	96-hour LC_{50}	320 mg/L	practically nontoxic
Daphnia	48-hour LC_{50}	25 mg/L	slightly toxic
Ramshorn snail	48-hour LC_{50}	no effect	practically nontoxic
Honeybee	topical LD_{50}	18 µg/bee	practically nontoxic
Earthworms	14 day NOEC[d]	100 mg/kg	slightly toxic

[a]*The LD_{50} value indicates the lethal dose of an active ingredient which is expected to cause death to 50% of the test animals treated. The higher the LD_{50} the lower the acute toxicity of the compound.*

[b]*Dimethylamine salt of 2,4-D.*

[c]*The LC_{50} value indicates the lethal concentration of an active ingredient which is expected to cause death to 50% of the test animals treated.*

[d]*NOEC is the no observed effect concentration.*

these herbicides in agricultural and non-agricultural uses.[1] Preliminary agricultural use results indicate that the estimated dollar value of yield loss in affected crops and cost of alternative weed control materials and methods combined may reach more than $1.5 billion per year (32). The crops most severely affected include wheat, sugarcane, soybean, and peanuts, while the costs of weed control in pasture and land in fallow would increase markedly. Additional data are being evaluated on the impact of a ban of phenoxies in noncrop applications, where 2,4-D is used extensively as a mixing partner for weed control in turf, forestry, and rights-of-way.

CONCLUSION

This review presents the framework for a weight-of-evidence analysis of the health significance of 2,4-D in comparison with the compound's benefits. Available studies show that 2,4-D is rapidly excreted and not metabolized to reactive intermediates. It does not possess chemical characteristics linked with biological reactivity and does not produce genotoxic or neurological effects in animal systems. Results of animal studies do not suggest that 2,4-D is carcinogenic, and epidemiology studies have yielded inconsistent findings which have not demonstrated a cause-and-effect relationship. Last year an expert EPA panel concluded that there was at most only "weak evidence" for an association between cancer and 2,4-D.

Of equal importance is that actual exposures to 2,4-D today and in the future would be expected to be very limited based on more rigorous protective clothing standards and reduced label application rates. Perhaps the World Health Organization provides the best perspective on the health significance of 2,4-D in its environmental health criteria review, which states that, "as far as the general population is concerned, 2,4-D intake from any source is negligible" (34).

[1]The National Agricultural Pesticide Impact Assessment Program (NAPIAP) Technical Bulletin, The Biologic and Economic Assessment of the Benefits of Phenoxy Herbicides in the United States will be published late in 1995.

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