

Pesticide assessment: Protecting public health on the home turf

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Pesticide regulation is examined in the context of Health Canada's Pest Management Regulatory Agency's assessment of the chlorophenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) for turf. 2,4-D is the most common herbicide used to kill weeds in grass.

The medical literature does not uniformly indicate harms from herbicides. However, the balance of epidemiological research suggests that 2,4-D can be persuasively linked to cancers, neurological impairment and reproductive problems. These may arise from 2,4-D itself, from breakdown products or dioxin contamination, or from a combination of chemicals.

Regulators rely largely on toxicology, but experiments may not replicate exposures from 2,4-D application to lawns because environmental breakdown products (eg, 2,4-dichlorophenol) may not accumulate and selected herbicides are possibly less contaminated. Dioxins are bioaccumulative chemicals that may cause cancer, harm neurological development, impair reproduction, disrupt the endocrine system and alter immune function. No dioxin analyses were submitted to the Pest Management Regulatory Agency, and the principal contaminants of 2,4-D are not among the 17 congeners covered in pesticide regulation. Independent assessment of all dioxins is needed, in tissues and in the environment.

The 2,4-D assessment does not approach standards for ethics, rigour or transparency in medical research. Canada needs a stronger regulator for pesticides. Potentially toxic chemicals should not be registered when more benign solutions exist, risks are not clearly quantifiable or potential risks outweigh benefits. Until landscaping pesticides are curtailed nationally, local bylaws and Quebec's Pesticide Code are prudent measures to protect public health. Physicians have a role in public education regarding pesticides.

Key Words: 2,4-dichlorophenoxyacetic acid; Dioxin; Herbicide; Legislation; Pesticide; Toxicity

Pesticides (herbicides, insecticides, fungicides and other '-cides') are spread in the environment for their toxic effects, but does regulation of these high-volume chemicals protect human and ecosystem health? In the present paper, we examine Canada's pesticide regulation in the context of the chlorophenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), the most common herbicide used to kill weeds in grass.

L'évaluation des produits antiparasitaires : La protection de la santé publique appliquée aux pelouses

La réglementation des produits antiparasitaires est examinée dans le cadre de l'évaluation, par l'Agence de réglementation de la lutte antiparasitaire de Santé Canada, des utilisations, sur les pelouses, de l'acide 2,4-dichlorophénoxyacétique (2,4-D), un herbicide chlorophénoxy. Le 2,4-D est l'herbicide le plus utilisé pour tuer les mauvaises herbes sur les pelouses. Les publications médicales ne font pas uniformément état des dommages causés par les herbicides. Cependant, selon la majorité des recherches épidémiologiques, le 2,4-D aurait une corrélation étroite avec les cancers, les atteintes neurologiques et les troubles de la reproduction. Cette corrélation peut être attribuable au 2,4-D même, à des produits de dégradation, à la contamination par dioxine ou à une association de produits chimiques.

Les organismes de réglementation se fient largement à la toxicologie, mais les expériences ne répliquent pas nécessairement les expositions à l'application de 2,4-D sur les pelouses, car les produits de dégradation environnementaux (p. ex., 2,4-dichlorophénol) ne s'accumulent peut-être pas et que certains herbicides sont peut-être moins contaminés. Les dioxines sont des produits chimiques bioaccumulatifs qui peuvent être responsables du cancer, porter préjudice au développement neurologique, nuire à la reproduction, perturber le système endocrinien et altérer la fonction immunitaire. Aucune analyse de dioxine n'a été soumise à l'Agence de réglementation de la lutte antiparasitaire, et les principaux contaminants du 2,4-D ne font pas partie des 17 congénères examinés dans la réglementation sur les produits parasitaires. Une évaluation indépendante de toutes les dioxines s'impose, dans les tissus et dans l'environnement.

L'évaluation du 2,4-D ne s'approche pas des normes d'éthique, de rigueur et de transparence imposées par la recherche médicale. Le Canada a besoin d'une réglementation plus ferme à l'égard des produits parasitaires. Les produits chimiques au potentiel toxique ne devraient pas être recensés lorsque des solutions plus inoffensives existent, que les risques ne peuvent être clairement quantifiés ou que les risques potentiels sont supérieurs aux bienfaits. En attendant que les produits parasitaires utilisés pour l'aménagement paysager soient restreints sur la scène nationale, la réglementation locale et le Code de gestion des pesticides du Québec constituent des mesures prudentes pour protéger la santé publique. Les médecins ont une responsabilité dans l'éducation du public à l'égard des produits antiparasitaires.

2,4-D, often mixed with other chlorophenoxy herbicides, has been used to kill broadleaf weeds since the 1940s. In 2002 and 2003, commercial lawn care companies in Ottawa applied three metric tons annually of chlorophenoxy herbicide active ingredients (1). 2,4-D is the most common chlorophenoxy herbicide. The United States Environmental Protection Agency (EPA) reports that 66% of 2,4-D is used for agriculture, while 25% of 2,4-D is used for landscaping

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(7% by turf maintenance contractors, 6% by private citizens and 12% in combination products with fertilizers) (2).

Canada's Pest Management Regulatory Agency (PMRA), within Health Canada, registers pesticides for import and sale in Canada. Registration is based on an assessment of risks to human health and the environment, and of efficacy. Importantly, within the legal framework of the Pest Control Products Act (PCPA [3]), benefit is not weighted against risk. The *Proposed Acceptability for Continuing Registration* (PACR) for 2,4-D on turf was published by the PMRA in 2005 (4).

HEALTH ASSESSMENT

The PMRA assesses human health risk chiefly on the basis of animal toxicity studies and human exposure estimates. Many of these studies are proprietary or not peer-reviewed. Moreover, extrapolation from studies of rats may be inappropriate because rats have genes that do not exist in people for the detoxification of chemicals (5), making the setting of 'safety factors' to account for inter- and intraspecies differences somewhat subjective. For instance, in the PACR, a 10-fold safety factor for children's vulnerabilities was frequently reduced to threefold in the modelling of various scenarios.

Exposure estimates are also inexact, especially because 2,4-D is mobile and pervasive. It is washed from lawns into Canadian waterways (6,7) and falls in the rain in the Canadian Prairies (8). It is tracked indoors and, in the absence of degradation by soil microbes and sunlight, it lingers (9). House dust can contribute up to 30% of children's total exposure before application to lawns and up to 76% of the exposure postapplication. The PACR indicates that elimination of 2,4-D from residential landscaping could substantially reduce children's exposure.

In the context of the Declaration of Helsinki (10), epidemiological studies are the chief ethical and publicly available evidence of effects of toxic chemicals on human health. Although many would believe that human trials of pesticide exposure should not be considered by regulators, availability of human test data allows applicants to avoid interspecies 'safety factors' and thereby increase allowable exposures (11). The EPA is proposing to consider intentional human dosing studies for pesticide assessments (12). The PACR cites a report of intentional human dosing with 2,4-D in a slurry with milk (13).

Epidemiology seldom provides absolute proof of harm and cannot discriminate among toxic components in a mixture (2,4-D may be mixed with other herbicides and proprietary 'formulants' to increase tissue penetration and spray performance) or among a variety of exposures (other pesticides, and other occupational or household chemicals). Odds ratios of the harm (eg, cancer) occurring may be decreased to insignificance by many factors (including the 'healthy worker effect'), covariables (such as an active outdoor lifestyle) and reporting mortality rather than incidence while treatments are improving.

The PMRA does not consider many epidemiological studies because it is bound by the PCPA to consider one

chemical at a time, and observed epidemiological effects cannot be linked unequivocally to a single chemical. Thus, two separate bodies of evidence are considered by the regulators (animal toxicity and exposure estimates) and the medical community (epidemiology). It may not be a surprise that they reach divergent conclusions regarding the advisability of using 2,4-D on lawns where children play.

With the foregoing caveats, evidence that chlorophenoxy herbicides, including 2,4-D, likely have multiple adverse effects on human health is summarized briefly.

Cancer

The PMRA determined that 2,4-D was not classifiable regarding carcinogenicity, although the International Agency for Research on Cancer classifies 2,4-D as "possibly carcinogenic to humans" (14). The PMRA's independent Science Advisory Panel advised that childhood cancer merited further study, but this was not done because single-agent epidemiological studies are not available. Non-Hodgkin lymphoma, leukemia and sarcoma are frequently noted in association with chlorophenoxy herbicides (15), and the incidence of the intractable childhood cancer neuroblastoma doubles when landscaping pesticides are used around the home (16). These malignancies are increasing in North America and are linked to pesticide exposure (17). The PACR did not reference a 2004 report of a fourfold increase in canine bladder cancer with exposure to chlorophenoxy herbicides (18). The EPA has since revised its guidelines for carcinogenic risk assessment for children, recognizing that children are much more susceptible to carcinogens than adults (19).

Reproductive effects

2,4-D has been found in urine and semen (20), and chlorophenoxy herbicides have been linked to sperm abnormalities (21), increased miscarriage rates (22), difficulties conceiving and bearing children, and birth defects (23). An animal study (24) using an 'off-the-shelf' chlorophenoxy herbicide mixture demonstrated failure of pregnancy. The PACR was published before a reproductive study (required by the PMRA) was received from the Industry Task Force II on 2,4-D Research Data ('industry'). The State of California is now proposing to list 2,4-D products as developmental toxicants under California's Safe Drinking Water and Toxic Enforcement Act (25) based on studies not commonly available (26) and the EPA's recent Reregistration Eligibility Decision for 2,4-D (27).

Neurological impairment

Lawn pesticides are implicated in neurological disorders, such as Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, autism and attention deficit hyperactivity disorder (15). Mechanisms of neurological harm from pesticides were recently reviewed, including developmental neurotoxicity mechanisms and effects of 2,4-D (28). Possible neurological impairment (dizziness, muscle weakness, loss of coordination and fatigue) is noted on the pesticide label for professional applicators but not for

homeowners. The PACR was published before a developmental neurotoxicity study had been received from industry, although myelin deficiencies were noted in exposed animals in other included studies.

ASSESSMENT DEFICIENCIES

In addition to the required reproductive and neurotoxicity studies noted above that were not in hand at the time of publication of the PACR, contaminants (eg, dioxins), breakdown products (eg, 2,4-dichlorophenol) and product ingredients were not assessed. The quality of evidence and scrutiny required for pesticide registration is much lower than that for a pharmaceutical product, and there is no ongoing surveillance of the extent or effects of cumulative exposures.

Dioxins

Polychlorodibenzodioxins (PCDDs) are formed during chlorophenoxy herbicide manufacturing, with higher-chlorinated congeners and furans being produced at increased temperatures. Normally, dioxins with two or three chlorine atoms are formed in the manufacture of 2,4-D, although higher-chlorinated congeners have been measured in Canadian products (26,29,30). Higher reactor temperatures also favour more rapid and complete conversion of reactants to herbicide during manufacture, so there is a concern that in the absence of enforced regulatory limits, the economic incentive to improve efficiency may foster the production of contaminated herbicides.

PCDDs, furans and polychlorinated biphenyls with four or more chlorine atoms bind with the aryl hydrocarbon receptor (AhR), and thereby trigger a number of toxic effects in mammals (31-33). Outcomes include cancers; endocrine effects, such as diabetes (34); and reproductive problems, such as endometriosis (35), failure to conceive, changed sex ratio of offspring and birth defects. The strength of AhR binding is the basis of dioxin regulation, by which 17 of 76 dibenzo-p-dioxins are regulated (36). It is now recognized, however, that toxic effects of dioxins are also initiated by many other mechanisms (37-41). This throws into question the AhR basis of regulation, particularly because aromatic conjugated ring structures are generally known to possess biological activity and polynuclear aromatic hydrocarbons are known carcinogens (42).

PCDDs with more than two chlorine atoms are 'Track 1 substances', and are targeted for virtual elimination under the Canadian Environmental Protection Act (CEPA) (43). Environment Canada reported that 2,4-D is the second largest chemical source of lower-chlorinated dioxins in Canada (44). Not only was the PACR published before dioxin analyses had been supplied by the industry, the PMRA asked only for analyses of dioxins with four or more chlorine atoms. By focusing on higher-chlorinated congeners, the PMRA is ignoring the bulk of dioxin contamination, as well as the CEPA targets. Prudence calls for independent measurement of all dioxin contaminants – in 'off-the-shelf' products, in areas of highly maintained turf and in biological samples.

Breakdown product – 2,4-dichlorophenol

'Environmental fate' data in the PACR describe the first step in chemical breakdown – disappearance of the parent compound – rather than complete breakdown into basic compounds, such as carbon dioxide and water. The spring-time stench in stores and communities without pesticide restrictions is largely the smell of chlorinated phenols. Half-lives reported in the PACR for esters refer to breakdown into the 2,4-D acid, and half-lives for the 2,4-D acid refer to breakdown into 2,4-dichlorophenol. Half-lives for individual parent compounds and breakdown products range up to a month or longer, but exposures resulting from landscaping are considered to be short term (one week) rather than chronic.

Toxicities of breakdown products were not addressed in the PACR. In animals, 2,4-D is excreted largely unchanged; thus, 2,4-dichlorophenol exposures under controlled experimental conditions would be relatively low. However, the United States Centers for Disease Control and Prevention report that 2,4-D degradation is a significant population-wide exposure source for 2,4-dichlorophenol (45). Monitoring indicates that the population is much more heavily contaminated with 2,4-dichlorophenol than with 2,4-D, with urine levels more than one order of magnitude higher. 2,4-dichlorophenol is considered a possible human carcinogen by the International Agency for Research on Cancer (46).

Real products not considered

2,4-D is formulated as a mixture of salts and esters. The diethanolamine salt is particularly toxic and was explicitly excluded from the PACR. However, searches of label information (47), PMRA information requests and fertilizer information provided by the Canadian Food Inspection Agency confirm that 'mixed amines', generally containing diethanolamine salt, are in most herbicide and 'weed and feed'-type products.

2,4-D for lawn care is usually mixed with other pesticides and always with other ingredients. Toxicities of mixtures were not considered, although the aggregate toxicity of all chlorophenoxy herbicides in a mixture should be assessed under the new (2002) PCPA (48). As well, many products containing 2,4-D also contain racemic mecoprop. This chlorophenoxy herbicide is being withdrawn from the market by the manufacturers, who have declined to submit up-to-date data, but it may be sold to homeowners until 2009 (49).

Scientific process

The method for obtaining the highest quality of medical evidence, the randomized controlled trial, is unethical for pesticide testing. However, serious inadequacies in evidence stem from study and review procedures. Pesticide assessment falls short of current best practices by relying on industry-supplied proprietary studies that are not open to independent review and on reviews by interested parties rather than independent systematic reviews of primary literature.

The evidence supporting pesticide registrations is poor compared with that for pharmaceutical trials and federal drug approvals (50), and the drug approval system itself has been found to be lacking. The medical community, through medical journals, has been improving accountability and transparency in pharmaceutical studies by instituting trial registration (51) and standards for trial design, reporting (52) and systematic review (53). Ironically, the PMRA criticized the Ontario College of Family Physicians pesticides report (15) for their lack of inclusion of data (some of which was only available to the PMRA) and for using the well-accepted process of systematic literature review (53).

In response to drug data falsification and withholding of unfavourable information on the part of corporations, the *Journal of the American Medical Association* (JAMA) recently took further steps, requiring independent scrutiny of raw data from trials, with independent researchers accepting scientific responsibility for studies (54). Despite protests (55,56), the JAMA editors insisted, "By virtue of these serious scientific and ethical problems, and the associated lack of trust and lack of confidence they have engendered among physicians and the public, device and drug manufacturers have brought an unprecedented level of 'special scrutiny' on themselves and on the studies they sponsor" (57).

There is considerable corporate overlap between drug and pesticide manufacturers, but no comparable measures of scrutiny are being implemented for pesticides. Furthermore, epidemiological studies are hampered because Canada does not track pesticide sales or use, does not gather information on biological levels of pesticides and other toxic contaminants (58), and has no reporting system for adverse effects (although regulations for a system are under development).

The PMRA was criticized in 2003 by the Office of the Auditor General for failing to re-evaluate older pesticides according to modern standards and for allowing registrations while lacking pertinent information (59). Problems persist with the 2,4-D PACR released in 2005. The new Pest Control Products Act (2002) is not yet in effect but would not have prevented the shortcomings discussed here.

Weighing risks and benefits

The PMRA made an unprecedented declaration of 'safety' (60) on the release of the PACR and the initiation of the public comment period. It seems both inappropriate and possibly dangerous for a regulator to be prejudging the results of missing studies and to be announcing its conclusion before receiving the independent public comment being sought at the time.

Historically, the PMRA has stated that a pesticide "does not pose an unacceptable risk" (61). While science may delineate some elements of risk, the degree of 'acceptability' is an individual choice.

Canadians are realizing that the cumulative effects of myriad ubiquitous synthetic chemicals on humans (especially children), society and ecosystems can never be thoroughly understood. Invoking the precautionary principle, "Where an activity raises threats of harm to the environment or

human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (62), many residents are choosing safer, effective strategies for pest control in landscaping. Lower-tier governments are restricting pesticides, including 2,4-D, to protect public health. The Supreme Court of Canada approved Hudson, Quebec's landmark pesticide bylaw in 2001 (Canada's first bylaw) and Toronto's pesticide bylaw in 2005. Bylaws in populous areas (63) and Quebec's Pesticide Management Code (64) have been enacted to protect a growing number of Canadians from landscaping pesticides (over one-third of Canadians at the time of writing). Physicians are speaking out: Toronto Public Health took a lead (65), the Ontario College of Family Physicians systematically reviewed the epidemiology of pesticide harms (15), and the Canadian Medical Association advocated banning combination fertilizer and herbicide ('weed and feed') products (66).

CONCLUSIONS AND RECOMMENDATIONS

Although the medical literature does not uniformly indicate that harms arise from phenoxy herbicide exposure, given the strengths and limitations of epidemiological, toxicological and ecological research, it appears that cancer, neurological impairment and reproductive problems are persuasively linked to phenoxy herbicide exposure. It is not possible to distinguish whether these effects arise from 2,4-D itself, from breakdown products or dioxin contamination, or from a combination of ingredients. However, toxicological experiments using selected (possibly less contaminated) herbicides, and during which typical environmental breakdown products (eg, 2,4-dichlorophenol) would not accumulate, may not be representative of exposures from 2,4-D application to lawns.

Potentially toxic chemicals should not be approved for use when more benign solutions exist, when risks are not clearly quantifiable or when the potential risk outweighs the benefit. In light of what is known and knowable, the use of 2,4-D merely to kill broadleaf weeds on turf is unjustified. Physicians should urge caution in the public debate regarding pesticides for landscaping and point to effective, safer alternative landscaping practices. Organic lawn care focuses on growing thick, healthy turf on rich, aerated soil. Natural products, such as compost, are used to feed the soil and enrich microbial populations that break down thatch, and are pathogens for pests, such as grubs. (This is in contrast to synthetic chemical strategies that eliminate important non-target organisms, much as antibiotics damage the flora of the gut.) Weeds may be controlled by hand pulling; by using products with ingredients such as corn gluten meal, beet extract or vinegar; and by cutting grass no shorter than 7 cm to shade seedlings. Many companies offer this service, and franchises are now available for entrepreneurs. Canadians are also moving away from monoculture lawns that require a lot of water and energy to turf with a variety of grasses and other species, such as white Dutch clover, for nitrogen fixation and drought resistance, or thyme. Lawns may also be replaced with hardy alternative landscapes, such as native plants.

Until federal legislation curtails nonessential pesticide use nationally, 'cosmetic' pesticide bylaws and provincial legislation, such as Quebec's Pesticide Management Code, are wise, prudent measures to protect public health.

Dioxins are persistent, bioaccumulative chemicals that may cause cancer, harm neurological development, impair reproduction, disrupt the endocrine system and alter immune function. Only 17 of 76 congeners were addressed in the pesticide regulations, and none were analyzed in 2,4-D samples. Dioxins should be monitored comprehensively in people, food and the environment, and phenoxy herbicides should be screened independently for this contamination.

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