Council Work Session Summary

Meeting Date **September 12, 2016**____

TITLE: SAFE APPLICATIONS OF PESTICIDES AND HERBICIDES UPDATE

PURPOSE(S) OF DISCUSSION:

☒ Inform/Update

☐ Direction/Guidance

☐ Legislative Development/Policy

BACKGROUND / KEY ISSUES / CONTRIBUTING FACTORS:

A report of the current usage of pesticides and Integrated Pest Management "IPM" as an alternative.

1. Review of key pesticides currently used by the City of Las Cruces -
   1.1. Health effects of pesticide exposure:
   Glyphosate/Parkinson's Disease, Lewy Body Disease; 2,4-D/Cancer, Disease; permethrin/induces apoptosis (cell death).
2. The development of "resistance" by pests to current chemical formulations -
   2.1. Pesticide formulations are increasingly using a mix of chemicals for enhanced synergistic effects.
3. Introduction to Integrated Pest Management program
   3.1. Basic characteristics with focus on precautionary principle philosophy:
   - Pests need to be identified;
   - Least toxic to be used;
   - Pesticide must be proven safe; and
   - Treat only in presence of problem.
4. Review the IMP policy for Santa Fe
   4.1. Request counsel and advice from professionals about the developmen4t and implementation of IPM.

By: John Hamilton

SUPPORT INFORMATION:

1. Attachment "A", Letter to City Council
2. Attachment "B", The Mosquito Doorknob Hanger

(Continue on additional sheets as required)

3. Attachment “C”, Next Up:2, 4-D, Weed and Insect Resistance Caused by Genetically Engineered Crop Failure Treadmill
4. Attachment “D”, Pyrethroid Pesticide-Induced Alterations in Dopamine Transporter Function
5. Attachment “E”, Pesticides and Non-Hodgkin’s Lymphoma
6. Attachment “F”, Pediatrics Official Journal of the American Academy of Pediatrics
7. Attachment “G”, Beyond Pesticides

(Continue on additional sheets as required)

August 30, 2016

Mayor Miyagishima and Council Members,

The City of Las Cruces is engaged in a discussion regarding the use of pesticides on City property: parks and recs, streets, and facilities. As has been true for quite some time, the City administration has chosen to use these toxic chemicals as the singular tool in controlling pests in our community. Consequently, the contractor hired to reduce or eliminate pests is judged solely on the basis of competance in their usage.

However, there are some serious unintended consequences for even the most successful programs of pest eradication. The chief of which is that the pest population is seldom "eradicated" in total. There is typically a residual population that has then developed a "resistance" to the pesticide being used. Thus a new chemical must be developed and applied in a never ending cycle of application and resistance.

The second problem is that all too often there are negative health effects - i.e. cancer, Parkinson's Disease, etc. - that come with exposure to the pesticide. For example, the herbicide 2,4-D has been linked to Non-Hodgkins Lymphoma as well as Parkinson's Disease (PD). The third pesticide that we encounter locally is permethrin which ironically is deemed suitable for use in mosquito control when clothing is impregnated with this chemical. However, it's clear from an Emory University study (2006) that exposure to permethrin "induces apoptosis (cell death)."

Peck's Bad Boy of current pesticide usage - Glyphosate - has attracted interest on the part of a wide spectrum of investigators seeking to parse out the health risks of this active ingredient of Roundup. Sanisel and Seneff of MIT has conducted the most

wide ranging review in: "Glyphosate to modern diseases III: Manganese, neurological diseases, and associated pathologies (2015)." The key here is that glyphosate interacts with manganese to create multiple pathways to damage both GABAergic and dopaminergic neurons linked to Parkinson's Disease. And this represents the tip of the iceberg in that there are at least six formulations registered in the State of New Mexico for glyphosate.

That brings us to the point of what to do?

It appears to me that the answer lies in the form of an Integrated Pest Management (IPM) program comparable to the IPM program operating in Santa Fe, our state capitol. Each council member and the mayor have received copies of the City of Santa Fe IPM Policy (Ord. #2001) for review. The key to understanding the IPM program as a successful alternative to the practice of relying on toxic chemicals alone lies in the shift in focus.

This shift is expressed in the simple premise that pesticides are "hazardous" to human health; that pest problems should be prevented more than cured; and that pesticides should be used only as a last resort. That being the case, it is critically important for the staff who implement the program be well trained in the Pesticide Precautionary Principles (PPP) philosophy.

To that end, I suggest that the City of Las Cruces contact individuals who have expertise in the development and implementation of an IPM program. There are several professionals who have been recommended including Victor Lucero, IPM program manager in Santa Fe, and Drs. Carol Sutherland and Ashley Bennett, both of NMSU.

What do you think?

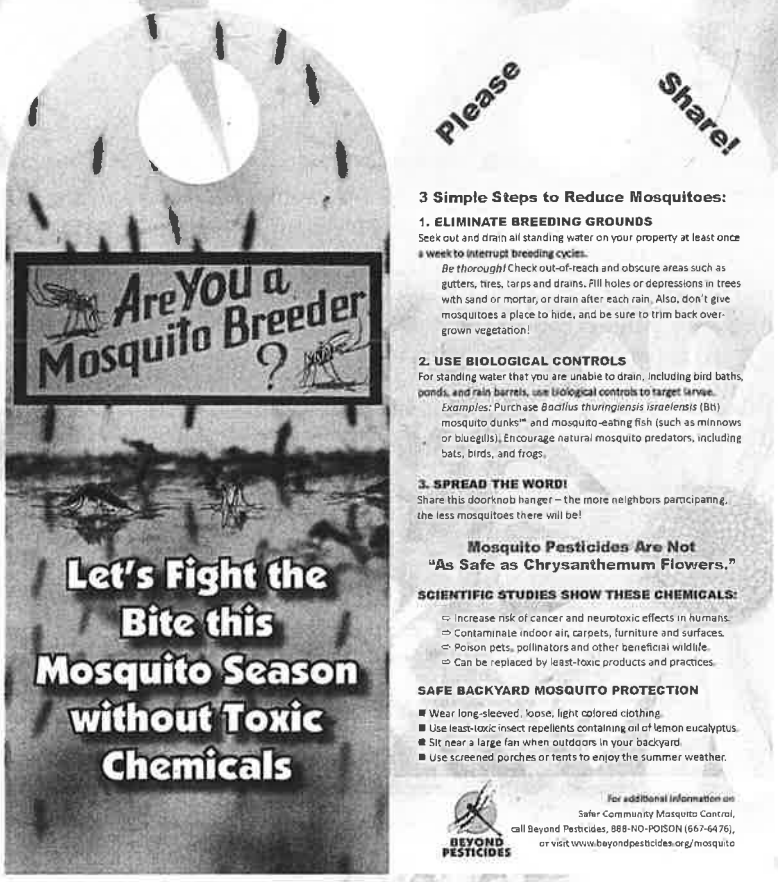
John Hamilton, PRC-NM

Introducing: The Mosquito Doorknob Hanger

Tips on speaking with neighbors on backyard and community mosquito control

A truck pulls up to your neighbor's house and out comes two people with backpack sprayers and face masks. They begin to drench your neighbor's yard with an unknown chemical as you hunker down in your house. You're very concerned, but still trying to muster the confidence needed to speak with your neighbor. Beyond Pesticides' new mosquito doorknob hanger may help.

With the mosquito doorknob hanger, you can simply hang it on your neighbor's door to encourage best practices. While communication is encouraged, the doorknob hanger is a great, effective way to begin a discussion about alternative methods for controlling mosquito populations in your community. The simple, basic information that the mosquito doorknob hanger provides can go a long way toward eliminating mosquitoes at the source, and controlling those that persist with least-toxic means. The hanger also refers back to Beyond Pesticides' least-toxic mosquito management website, where hazard information and more detailed steps on individual and community mosquito management techniques can be found.



Ideas on how to use the hanger

Start Small.

Most urban and suburban mosquitoes are weak fliers and will not travel far from where they breed. In order to see effective results, start small with your immediate, adjacent neighbors. Expand outwards, using your house as a central location. As the hanger says, "The more neighbors participating, the fewer mosquitoes there will be!"

Offer to help!

Maybe your neighbors are elderly or disabled and can't get out and eliminate breeding and habitat as often as needed. Offer your assistance by coming by at least once a week to dump out standing water on their property, or take turns with other neighbors participating in least-toxic mosquito control.

Take it to the halls of power.

Does your town spend money to spray toxic chemicals from trucks throughout neighborhoods in your community? After your neighbors start seeing the benefits of the simple mosquito reduction steps, get your group together and attend your community's next local council or mosquito control board meeting. Raise your collective voice against toxic pesticides that can harm people, pets, and wildlife in favor of least-toxic methods that focus on prevention and community education.

What about the nay-sayers?

More likely than not, you will encounter those who view pesticide use as a personal right. Many also fear the impacts of Zika, West Nile virus, and other mosquito borne diseases. Things could get heated. Don't let them. Stay calm and positive, and remain balanced and logical about the prospects for mosquito reduction without toxic chemicals. Emphasize to unsure neighbors that mosquito chemicals do more harm than good, especially for children and pets, and in the end are not worth the cost, given simple, inexpensive steps outlined on the doorknob hanger. Let them know that former renown professor Dr. David Pimentel (Cornell University) conducted a study on mosquito pesticide spraying which found that 99.999% of insecticides do not reach target mosquitoes, and instead spread into our environment, where they cause harm to public health, pets, and wildlife. Let your neighbors know that these simple steps become more and more effective as the community gets more involved.

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Always encourage them to visit Beyond Pesticides information rich website on mosquito control at www.beyondpesticides.org/mosquito, where we go into more detail on the safe and effective strategies individuals and the community at large can take to prevent mosquitoes and the diseases they may carry.

Request a free pack of 25 doorknob hangers to distribute in your community today! Send an email to info@beyondpesticides.org with "Mosquito Doorknob Hangers" in the subject line, and include your name and mailing address, or call 202-543-5450.

Next Up: 2,4-D

Weed and insect resistance caused by genetically engineered crop failure treadmill

By Nichelle Harriott

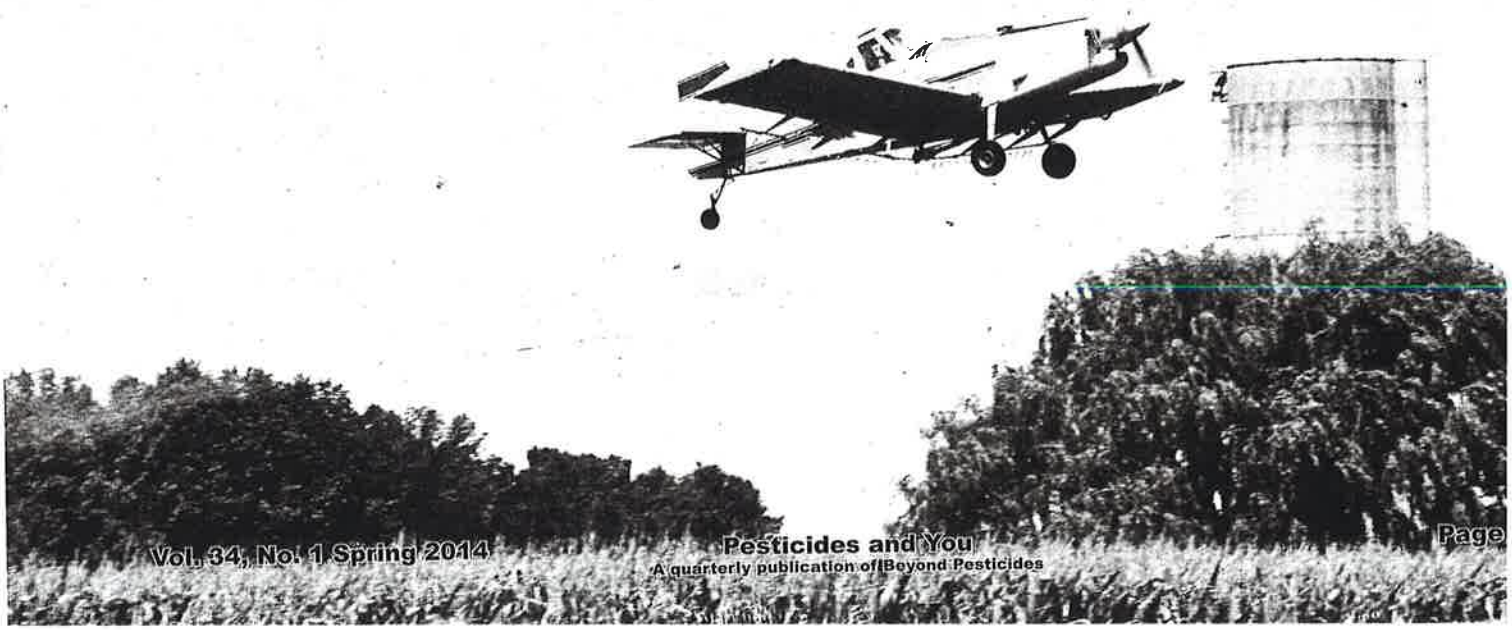
2,4-D Corn and Soybeans: Bad for Agriculture, Bad for the Environment, Bad for Health

The U.S. Department of Agriculture (USDA) is on the verge of allowing into cultivation the latest round of genetically engineered (GE) crops –corn and soybeans engineered to be resistant to the highly toxic herbicide 2,4-D. The agency released its draft Environmental Impact Statement (DEIS) last December for public comment, announcing its plan to deregulate these crops. This is a devastating decision for farmers, the environment, and public health. 2,4-D, one ingredient in the deadly Agent Orange that was used to defoliate forests during the Vietnam war and the cause of severe illness in exposed veterans, will now enter the environment at elevated rates as integral to a cropping system that uses 2,4-D-tolerant engineered crops. This, despite decades of science showing that this chemical is highly toxic, linked to numerous short- and long-term health and environmental impacts.

Behind this development is a story that has been unfolding in the science literature and on farmland across the country. Genetically engineered, herbicide-tolerant, Roundup Ready crops (created by Monsanto) are failing. The GE crops, originally designed to be cultivated with and tolerant of the use of the herbicide Roundup (glyphosate), have spawned a new generation of resistant "superweeds." These superweeds are no longer being killed by Roundup, whose use on these crops has increased dramatically since their introduction in 1996. In fact, one 2012 report shows that GE crop: have been responsible for an increase of 404 million pounds of pes ticide, or about 7%, in the U.S. over the first 16 years of commercia use of GE crops (1996-2011). The prolific presence of Roundup i the environment means that wild plant/weed species gradually de veloped an immunity to the chemical. Not surprisingly, industry' solution to the growing GE-induced weed resistance, given that it business model requires increasing pesticide sales, is to develo new engineered crops tolerant to more toxic pesticides. Those fo lowing the history of chemical-intensive agriculture, which deve oped with World War II chemicals and an orientation to killing ur wanted organisms rather than preventing them with managemer practices, are watching history repeat itself –from the pesticid treadmill to the herbicide and insecticide-tolerant GE crop trea mill. What makes this point in history different, however, is th burgeoning organic agriculture and food industry that has prove the commercial and economic value of soil-building practices ar systems respectful of beneficial organisms.

A Solution for Weed Resistance?

2,4-D tolerant corn and soybeans, and their accompanying use 2,4-D (a new choline salt of 2,4-D, Enlist™), are being market by the petitioner Dow AgroSciences as a solution to combat tl surge in Roundup-resistant weeds brought on by Roundup Rea GE crops and the accompanying increase in herbicide use. In th ory, 2,4-D, with its different mode of action, would now cont these resistant weeds.



However, experts say these new 2,4-D-tolerant crops and the associated increased 2,4-D use will not provide the solution to escalating weed resistance. Instead, they threaten to introduce more damage to plants through the selection of yet another strain of resistant weeds –2,4-D resistance. It is therefore counterintuitive and futile to treat the impacts of GE use with more GE crops and increased herbicide use.

USDA estimates 2,4-D use to increase 1.75-3 times current use, with the new GE corn and soybean crops. Independent estimates are much higher. Additionally, USDA notes in its DEIS that, given the prevalence of Roundup-resistant weeds, it is "very likely" that 2,4-D resistant weeds will occur, and that the adoption of 2,4-D corn and soybean can have a "potentially significant environmental impact" on the proliferation of resistant weeds, due to an increased reliance on 2,4-D for weed control. Further, the agency acknowledges that possible onset of 2,4-D resistant weeds will mean that farmers relying on 2,4-D will likely experience "increased socioeconomic impacts from more costly and restrictive weed control alternatives" to combat these weeds. Already, 28 species across 16 plant families have evolved resistance to the synthetic auxin herbicides, of which 2,4-D is one. They mimic plant growth hormones (also known as plant growth regulators). Sixteen species of plants are known to be resistant specifically to 2,4-D. As 2,4-D resistance grows, chemical-intensive farmers will look to even more toxic chemicals to control these weeds at great economic and environmental costs.

Given that USDA is aware of the problems associated with GE crops, herbicide use, and the onset of resistant weeds, it is remarkable to those tracking the technology that the agency is effectively encouraging successive generations of GE crops. Critics say that the agency should be encouraging farmers to move to sustainable farming practices that protect the economic and environmental future of U.S. agriculture.

2,4-D ChemWatch Profile

CAS Registry Number: 94-75-7

Use: 2,4-Dichlorophenoxyacetic acid, commonly known as 2,4-D, is a widely used herbicide in the phenoxy class of chemicals. 2,4-D is a selective herbicide used to kill broadleaf weeds, and is the most commonly used pesticide in the non-agricultural sector, and in the top 10 most common in the agricultural sector, with 25-29 million pounds being used in the U.S. annually.

Mode of Action: 2,4-D is a plant growth regulator, and mimics the natural plant growth hormone, auxin. It causes rapid cell growth leading to plant death. While 2,4-D is normally applied to a plant's leaves, it can be absorbed through the roots and stems. 2,4-D is produced in several forms, including acids, salts, amines and esters, and its toxicity varies between the different forms.

Environmental Fate & Toxicity: 2,4-D is said to have low persistence in both soil and water. However, 2,4-D has a high potential to leach from soils, and therefore a potential for contaminating groundwater. 2,4-D has been shown to have negative impacts on a number of animals. 2,4-D is slightly toxic to wildfowl and slightly to moderately toxic to birds. In frogs, 2,4-D interferes with a sex hormone and stops frog eggs from maturing. 2,4-D is linked with both cancer and testicular problems in dogs. Exposure of certain dogs to lawns treated with phenoxy herbicides is associated with an increased risk of bladder cancer. The herbicide also has negative effects on a range of beneficial insects. It reduces offspring numbers in honey bees, kills predatory beetles and ladybug larvae.

Ignoring the Science: 2,4-D Drift, Dioxin Contamination, Threats to Human and Environmental Health

Compounding the costs of weed resistance is the inherently toxic nature of 2,4-D and the environmental damage that can occur. 2,4-D drift has long been a known problem to off-site locations, endangered species, and non-target crops. Many forms of 2,4-D volatilize above 85°F and 2,4-D drift has been known to damage specialty crops, like tomatoes and grapes, half a mile or more from the application site, even at concentrations 100 times below the recommended label rate. In addition to non-target plants, 2,4-D can impact species listed under the jurisdiction of the *Endangered Species Act* (ESA). In fact, in 2011, the National Marine Fisheries Service (NMFS) identified 2,4-D as likely to jeopardize all listed salmonid, based on current registration and label directions. No surprise that 2,4-D is also commonly detected in surface and ground water in regions of heavy use.

Dow AgroSciences maintains that the new 2,4-D choline salt formulation (Enlist™), which will be exclusively used with the new 2,4-D-tolerant corn and soybeans, is anticipated to have lower volatility (50 times lower) and, as a result, decreased drift compared to other forms of 2,4-D. However, the technical information supporting this has not been made available for public or peer review. Moreover, the surfactants and adjuvants added to commercial mixtures that can substantially alter volatility are, at present, unknown. There is no publicly available data to verify Dow's claims. The U.S. Environmental Protection Agency (EPA) is currently reviewing the registration of 2,4-D, including this new choline salt, but will not have a decision before 2017.

In addition to the environmental consequences 2,4-D use brings, the pesticide's contamination with dioxins remains a part of 2,4-D's chemistry. While recent manufacturing advancements have reduced dioxin levels in 2,4-D, the threat of dioxin contamination is still very much a consequence of 2,4-D use. The science is very clear that dioxins are a class of chemicals that cause cancer, reproductive and developmental problems, damage the immune system, and interfere with hormones. They have left a toxic legacy for human and environmental health across the U.S. due to their persistence and toxicity. The issue of 2,4-D contaminants, such as dioxins that are present in formulations, has been ignored and is probably much more serious in terms of degradation issues than the "active ingredient." Dioxins have notoriously long half-lives, are bioaccumulative, and present broadly significant health risks developmentally and postnatally, including increased risk of heart disease and diabetes.

In regard to human toxicity, the scientific literature demonstrates that 2,4-D as an active ingredient is neurotoxic, mutagenic and genotoxic, and poses serious risks to human health. 2,4-D is also an endocrine disruptor and is known to interfere with the thyroid hormone. According to EPA, current data "demonstrate effects on the thyroid and gonads following exposure to 2,4-D, [and] there is concern regarding its endocrine disruption potential." EPA researchers found that persons with urinary 2,4-D presence have low levels of thyroid hormone. Their results also indicate that exposure to 2,4-D is associated with changes in biomarkers that have been linked to risk factors for acute myocardial infarction and type-2 diabetes. Other studies find that those exposed to 2,4-D have poor semen quality. Higher rates of birth defects are also observed in farmers with long-term exposure to 2,4-D.

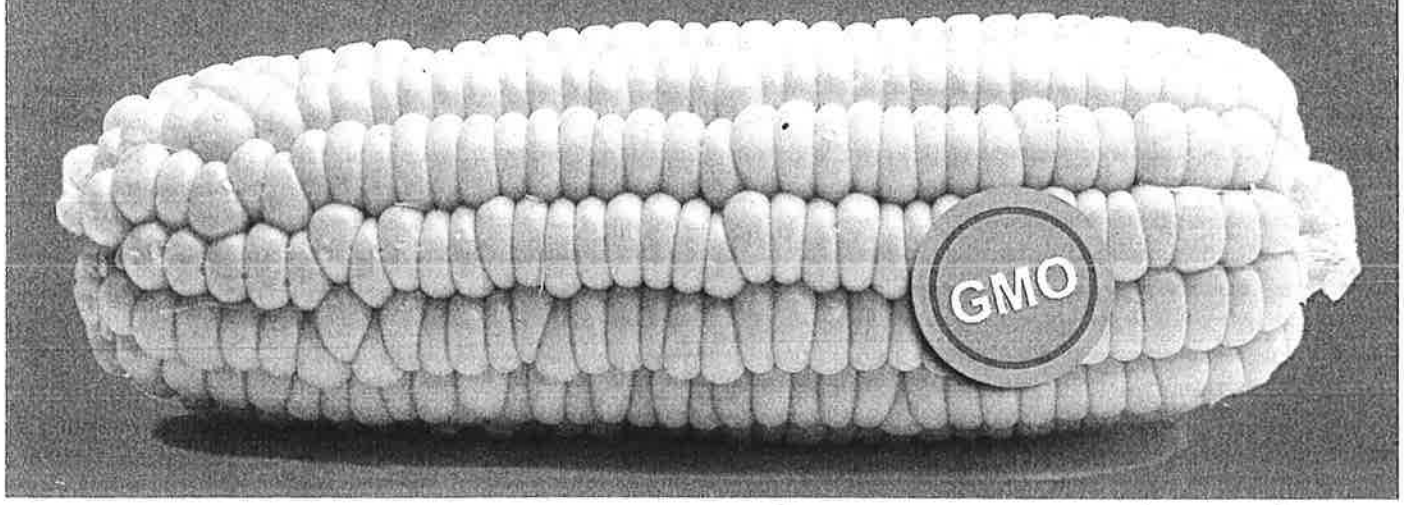
Occupational exposure to 2,4-D has also been observed to increase the risk of Parkinson's disease. Studies have reported that 2,4-D has effects on dopaminergic neurons in experimental settings and is associated with more than a three-fold increased risk of the disease. 2,4-D is also associated with non-Hodgkin lymphoma (NHL) and a high incidence of NHL has been reported among farmers and other

Right to Know How Food Is Produced

People nationwide want the right to know whether or not their food is grown with or contains GE ingredients. A recent *New York Times* poll shows national support for GE labeling reaching 93%, a number consistent with past polls showing broad support that cuts across race, gender, socio-economic class, and political party affiliation. Consumers are concerned with the environmental and human health impacts that are associated with the cultivation of GE crops. They care about the food they eat.

In the absence of a federal labeling requirement, it is up to the states to give consumers the information they need to make informed choices for their families. States passing legislation are putting consumers first and give them the power of choice. People want to be able to make choices in the marketplace that they believe are protective of their family's health and the larger environment in which food is grown. Because we have a regulatory system at the federal level that has deregulated major GE crops in agriculture without complete health and safety reviews associated with their cropping systems, consumers want the ability to make independent judgments. This is especially true in light of increased pesticide use in GE crops, elevated pesticide exposure, and residues of modified toxins found in human blood samples.

Politico reported early in 2014 that, "The Grocery Manufacturers Association, on behalf of the food industry, is pitching to Capitol Hill lawmakers a bill that would preempt any state mandatory GMO labeling requirement by creating a voluntary labeling standard..." The discussion draft of the legislation would prohibit states from requiring GE food labeling legislation.

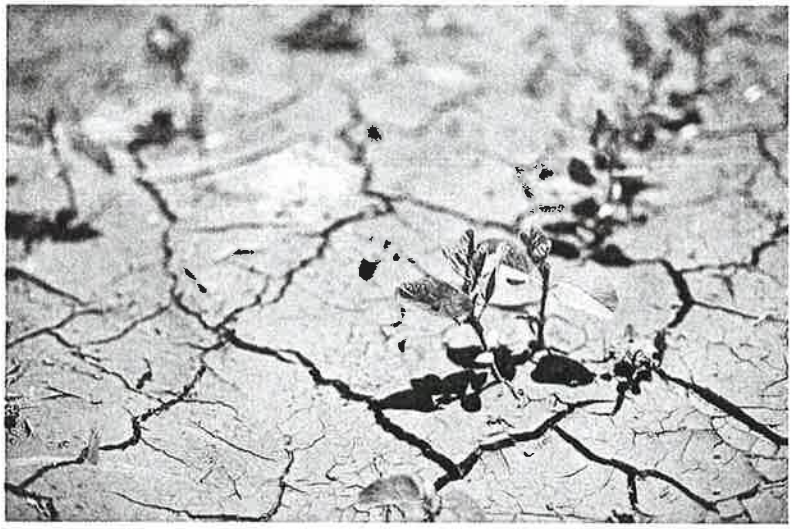


occupational groups working with 2,4-D. According to the National Cancer Institute, frequent use of 2,4-D has been associated with two- to eight-fold increases of NHL in studies conducted in Sweden, Kansas, Nebraska, Canada, and elsewhere. Farmers using 2,4-D are associated with an increased risk of NHL in 131 lymphohematopoietic cancers (LHC) in a case-control study embedded in a cohort of 139,000 members of United Farm Workers of America (UFW) diagnosed in California between 1988 and 2001.

Advocates have argued that the science has shown for decades that 2,4-D is a chemical whose use should be decreasing, not increasing with new chemical-reliant crops. With environmental damage to non-target plants, possible dioxin contamination and human health concerns, 2,4-D has proven that it is harmful for the environment and human health.

Non-GE and Organic Farmers Left to Fend for Themselves

It is inevitable that genetic drift from GE fields can contaminate non-GE and organic crops. For instance, corn, a wind pollinated crop, has the potential to have its genetic material (pollen) transfer across neighboring plants and crops. Evidence suggests that GE corn plants can cross-pollinate non-GE corn plants up to and beyond a distance of 200 meters. Unfortunately, many farmers have been sued by Monsanto after GE genetic material was detected on their farms. Industry giants like Monsanto claim that farmers are responsible and liable for its genetic property being found on land farmed by farmers who did not pay to cultivate the company's genetically engineered crop. Organic farmers have continued to fight for their rights against GE contamination, but it has been an uphill battle. A 2011 lawsuit, *Organic Seed Growers and Trade Association (OSGATA) et al., v. Monsanto*, sought to protect farmers from GE trespass. A District Court dismissal (2012), followed by a U.S. Court of Appeals decision (2013) upholding the lower court, entered under the rules of evidence an assurance from Monsanto that it would not sue farmers with "trace amounts" (less than 1%) of GE crop contamination for patent infringement. According to *Reuters*, between 1997 and 2010 the agrichemical giant filed 144 patent-infringement lawsuits against farmers that it said made use of its seed without paying royalties. The U.S. Supreme Court refused to hear the case. Organic and non-GE farmers remain seriously concerned that their farms and livelihoods will be adversely affected by GE contamination.



USDA, in deregulating GE crops, continues to put non-GE and organic farmers at risk from economic losses and legal retaliation from industry. The agency believes that these farmers should take steps to defend themselves by erecting barriers and buffer zones, or delaying planting to minimize contamination. With this scenario, the burden lies solely on the farmer, who is afforded little to no redress for lost value of the contaminated crop and still unprotected from GE drift. Even though Dow claims that the new formulation of 2,4-D is less volatile than other forms, 2,4-D drift remains a serious concern.

Failed Promises, New Way Forward

The proposed deregulation of GE crops is being met with criticism from farmers, environmentalists, and other concerned groups. A decision to deregulate 2,4-D-tolerant crops and allow its unrestrained marketing will exacerbate the treadmill of U.S. chemical-intensive farmers becoming more dependent on toxic inputs to grow food. Thus far, after billions of dollars in research and public relations campaigns, the promises made by the biotechnology sector have not come to pass. GE crops have ushered in increased pesticide use, increased weed resistance, and a regression to more toxic chemicals. Additionally, GE yields are not significantly higher than non-GE.

Similar to previous decisions to deregulate other varieties of GE soybeans, alfalfa, and sugar beets, safety advocates charge that USDA continues to fail at taking into account several scientifically-validated environmental and human health concerns, especially in light of documented problems created by these herbicide-tolerant GE crops.

2,4-D and its resistant crops, as well as other herbicide-tolerant strains, are not the solution for weed resistance created by increased herbicide use on GE crops deregulated by USDA. Had proper precaution and thorough environmental assessment been conducted for previous GE decisions, the economic and environmental fallout of resistant weeds could have been avoided. It is time for the agency to focus on organic practices and other sustainable, integrated methods for long-term weed management, which allow the nation's farmers to get off the toxic GE treadmill.

A fully cited version of this article is available online at www.beyondpesticides.org.

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Toxicology and Applied Pharmacology 211 (2006) 188 – 197

Toxicology and Applied Pharmacology

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Pyrethroid pesticide-induced alterations in dopamine transporter function

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Received 7 January 2005; revised 31 May 2005; accepted 2 June 2005
Available online 11 July 2005

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease affecting the nigrostriatal dopaminergic pathway. Several epidemiological studies have demonstrated an association between pesticide exposure and the incidence of PD. Studies from our laboratory and others have demonstrated that certain pesticides increase levels of the dopamine transporter (DAT), an integral component of dopaminergic neurotransmission and a gateway for dopaminergic neurotoxins. Here, we report that repeated exposure (3 injections over 2 weeks) of mice to two commonly used pyrethroid pesticides, deltamethrin (3 mg/kg) and permethrin (0.8 mg/kg), increases DAT-mediated dopamine uptake by 31 and 28%, respectively. Using cells stably expressing DAT, we determined that exposure (10 min) to deltamethrin and permethrin (1 nM–100 μM) had no effect on DAT-mediated dopamine uptake. Extending exposures to both pesticides for 30 min (10 μM) or 24 h (1, 5, and 10 μM) resulted in significant decrease in dopamine uptake. This reduction was not the result of competitive inhibition, loss of DAT protein, or cytotoxicity. However, there was an increase in DNA fragmentation, an index of apoptosis, in cells exhibiting reduced uptake at 30 min and 24 h. These data suggest that up-regulation of DAT by in vivo pyrethroid exposure is an indirect effect and that longer-term exposure of cells results in apoptosis. Since DAT can greatly affect the vulnerability of dopamine neurons to neurotoxicants, up-regulation of DAT by deltamethrin and permethrin may increase the susceptibility of dopamine neurons to toxic insult, which may provide insight into the association between pesticide exposure and PD.
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Keywords: Deltamethrin; Permethrin; Pyrethroid; Dopamine transporter; Parkinson's disease

Parkinson's disease (PD) is a disabling neurodegenerative disorder characterized by the loss of nigrostriatal dopamine neurons and the formation of intraneuronal inclusions termed Lewy bodies (Olanow and Tatton, 1999). Although the exact etiology of PD is unknown, both genetic and environmental factors are thought to contribute to the pathogenesis of PD. While there are rare instances of genetically-linked PD, data from a recent comprehensive twin study found no significant contribution of genetics to late-onset PD (Tanner et al., 1999). This finding suggests that environmental factors or gene–environment interactions play a pivotal role in the development of sporadic PD.

Several epidemiological studies have identified pesticide exposure as a significant risk factor for Parkinson's disease (Tanner and Langston, 1990; Gorell et al., 1998; Le Couteur et al., 1999; Priyadarshi et al., 2001). Other studies have demonstrated that drinking well-water and living in a rural setting, both of which may increase exposure to agricultural pesticides, increase the risk of developing PD (Rajput et al., 1986; Barbeau et al., 1987; Rajput et al., 1987; Golbe et al., 1990; Semchuk et al., 1991). In addition, exposure to pesticides used in the home has been linked to PD (Stephenson, 2000). However, the majority of studies have not identified specific pesticides or the mechanism by which pesticides damage the dopaminergic system and increase the risk of PD.

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doi:10.1016/j.taap.2005.06.003

Studies by our laboratory and others have demonstrated that exposure of mice to the organochlorine insecticide heptachlor increases the expression of the plasma membrane dopamine transporter (DAT; Miller et al., 1999a; Kirby et al., 2001) at dosage levels that elicit no overt toxicity. DAT is an integral component of normal dopamine function and is responsible for terminating dopamine neurotransmission by rapid reuptake of dopamine into the presynaptic terminal (Shimada et al., 1991; Giros and Caron, 1993; Miller et al., 1999b). Several studies have demonstrated that alterations in the expression of DAT can greatly affect the vulnerability of the dopamine neuron to neurotoxins such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Gainetdinov and colleagues demonstrated the requirement of DAT for the toxicity of MPTP (Gainetdinov et al., 1997), while Donovan et al. (1999) have shown that overexpression of DAT in transgenic mice results in greater loss of dopamine neurons following MPTP exposure. Therefore, exposure to pesticides that increase DAT may increase the susceptibility of dopamine neurons to endogenous neurotoxic dopamine metabolites or exogenous neurotoxicants by increasing their uptake by DAT.

In addition to heptachlor, exposure of mice to the pyrethroid pesticides deltamethrin and permethrin has been demonstrated to increase DAT-mediated dopamine uptake (Kirby et al., 1999; Karen et al., 2001; Gillette and Bloomquist, 2003). Pesticides in the pyrethroid class are widely used in household and agricultural applications and are popular because of their low mammalian toxicity. Although pyrethroids are often considered environmentally labile, they readily cross the blood–brain barrier and can achieve considerable concentrations in the brain (Anadon et al., 1996). Acute toxicity of pyrethroids is primarily mediated through interaction with sodium channels, leading to prolonged depolarization and hyperexcitation of the nervous system (Narahashi, 1982; Tabarean and Narahashi, 2001). Pyrethroids have also been shown to be potent releasers of neurotransmitters, including dopamine (Eells and Dubocovich, 1988; Kirby et al., 1999). However, the mechanism by which pyrethroids are capable of increasing DAT-mediated dopamine uptake is not clear.

Here, we report that in vivo exposure to deltamethrin and permethrin not only causes functional up-regulation of dopamine uptake, but increased levels of DAT protein as well. In addition, acute exposure of SK-N-MC cells stably expressing DAT to these pyrethroids has no effect on dopamine uptake, indicating that deltamethrin and permethrin do not directly interact with DAT. Finally, we found that longer-term exposure to deltamethrin and permethrin reduces dopamine uptake in these cells, and that this effect is most likely the result of an ongoing apoptotic process. Taken together, our results suggest that the effects of pyrethroids on DAT are indirect and that longer-term exposures may be capable of damaging cells through an apoptotic mechanism.

Materials and methods

Materials. Analytical grade (purity ≥98%) deltamethrin and permethrin were obtained from ChemService Inc. (West Chester, PA). ^{3}H-dopamine (58 Ci/mmol) and ^{3}H-WIN 35,428 (85 Ci/mmol) were purchased from Perkin-Elmer Life Sciences (Boston, MA). The rat monoclonal antibody to DAT was purchased from Chemicon (Temecula, CA) and the monoclonal anti-mouse α-tubulin was purchased from Sigma (St. Louis, MO). The goat anti-rat secondary antibody was purchased from ICN (Costa Mesa, CA) and the goat anti-mouse secondary antibody was from Bio-Rad (Hercules, CA). Super Signal West substrate and stripping buffer were obtained from Pierce (Rockford, IL). Cell culture media and supplements were obtained from Meditech (Herndon, VA). All other reagents were obtained from Sigma or Fisher Scientific (Pittsburgh, PA).

Animals and treatments. Male C57BL/6j mice (8 weeks of age) were obtained from Jackson Laboratories (Bar Harbor, ME). Animals were group housed (6 per cage) under a 12:12 light–dark cycle and acclimatized for 1 week prior to initiation of experiments. Standard rodent chow and tap water was available ad libitum. All procedures were conducted in accordance with the *Guide for Care and Use of Laboratory Animals* (National Institutes of Health) and previously approved by the Institutional Animal Care and Use Committee at Emory University.

A total of 24 mice were used for these experiments. Control mice were injected intraperitoneally with vehicle (methoxytriglycol; $n = 12$) and treated mice were injected with deltamethrin (3 mg/kg; $n = 6$) or permethrin (0.8 mg/kg; $n = 6$) three times over a 2-week period (Days 1, 8, and 15) as described previously (Kirby et al., 1999; Miller et al., 1999b; Gillette and Bloomquist, 2003). One day following the last treatment, striatal tissue was dissected out and prepared for assay as described below.

Synaptosomal dopamine uptake, ^{3}H-WIN 35,428 binding, and Western blot analysis. Dopamine uptake studies were performed as described previously (Miller et al., 1999a). Briefly, crude synaptosomes were prepared from fresh striatal tissue and incubated in assay buffer (4 mM Tris, 6.25 HEPES, 120 mM NaCl, 5 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 0.6 mM ascorbic acid, 5.5 mM glucose, 10 μM pargyline; pH 7.4) containing a saturating concentration of dopamine (1 μM final concentration) and a tracer amount of ^{3}H-dopamine (20 nM). A single saturating concentration of dopamine was chosen to assess effects of pyrethroids on the V_{max} of DAT, since previous studies using the same dosing paradigm have demonstrated no significant effect on K_m (Kirby et al., 1999; Karen et al., 2001). Uptake was allowed to proceed for 3 min at 37 °C, and then terminated by the addition of ice-cold buffer and rapid vacuum filtration over GF/B filter paper using a Brandel harvester. Filters were washed twice more with buffer, allowed to air

dry, and placed in scintillation vials containing 8 ml of Econoscint (Fisher Scientific, Pittsburgh, PA) for scintillation counting. Uptake rates were calculated as specific uptake (total uptake−non-specific uptake), with non-specific uptake defined by the inclusion of 10 μM nomifensine. Following determination of synaptosomal protein concentration (Bradford, 1976), uptake rates were calculated as pmol/min-mg protein and expressed as percentage of control values.

Determination of ^{3}H-WIN 35,428 binding to DAT was performed essentially as described by Coffey and Reith (1994) with modifications to reduce the total volume to 200 μl, for assay in 96-well microtiter plates. Preliminary kinetic studies indicated that the binding of ^{3}H-WIN 35,428 to striatal synaptosomes was best fit to a one-site model determined by non-linear curve fitting techniques (GraphPad Prism 3.0) with a K_d of 6.58 nM and a B_{max} of 1.08 pmol/mg protein. Therefore, binding studies with crude synaptosomes were conducted with a single concentration (10 nM) of ^{3}H-WIN 35,428 in 25 mM sodium phosphate buffer (125 mM NaCl, 5 mM KCl; pH 7.4) for 1 h at 4 °C in 96-well plates. Incubations were terminated by rapid vacuum filtration onto GF/B filter plates and radioactivity was determined by liquid scintillation counting. Non-specific binding was determined by the inclusion of 10 μM nomifensine and specific binding was calculated as the total binding (incubated without 10 μM nomifensine) minus non-specific binding (incubated with nomifensine). Data were calculated as pmol/mg protein and expressed as percentage of control values.

Western blots were performed as previously described (Richardson and Miller, 2004). Briefly, samples (20 μg) were subjected to SDS PAGE on 10% precast NuPage gels (InVitrogen, Carlsbad, CA). Samples were electrophoretically transferred to a polyvinylidene difluoride membrane, and non-specific sites were blocked in 7.5% nonfat dry milk in Tris-buffered saline (135 mM NaCl, 2.5 mM KCl, 50 mM Tris, and 0.1% Tween 20, pH 7.4). Membranes were then incubated in a monoclonal antibody (Chemicon, Temecula, CA) to the N-terminus of DAT (Miller et al., 1997). Antibody binding was detected using a goat anti-rat horseradish peroxidase secondary antibody (ICN, Costa Mesa, CA) and enhanced chemiluminescence. The chemiluminescent signal was captured on an Alpha Innotech Fluorchem 8800 (San Leandro, CA) imaging system and stored as a digital image. Densitometric analysis was performed and calibrated to co-blotted dilutional standards of pooled cells from all control samples. Membranes were then stripped for 15 min at 25 °C with Pierce Stripping Buffer and reprobed with a monoclonal α-tubulin antibody to ensure equal protein loading across samples.

Cell culture. SK-N-MC (human neuroblastoma) cells stably expressing human DAT (SK-DAT; Stephans et al., 2002) were maintained in minimum essential medium (MEM) supplemented with Earle's salts, 10% heat-inactivated fetal bovine serum, 50 U/ml penicillin, 50 μg/ml streptomycin, 2 mM L-glutamine, 1 mM sodium pyruvate, and 1 mM non-essential amino acids (Mediatech, Herndon, VA), and incubated under a humidified atmosphere of 5% CO_2 in air at 37 °C. For pyrethroid exposure, deltamethrin and permethrin were dissolved in dimethylsulfoxide (DMSO) at a concentration of 10 mM. Further dilutions were made in uptake buffer for experiments with dopamine uptake and in serum-free media for experiments to determine cytotoxicity and DNA fragmentation. The final concentration of DMSO was ≤0.1% for all experiments and had no effect on any of the parameters studied. Control experiments were performed in the presence of DMSO in a concentration similar to that used in the pyrethroid-treated cells.

^{3}H-Dopamine uptake and Western blot studies in cells. Dopamine uptake by SK-DAT cells was performed as described elsewhere (Pifl et al., 1996). Briefly, cells were plated in 24-well plates and incubated for 48 h in the above MEM medium. Cells were washed once with the uptake buffer (4 mM Tris, 6.25 HEPES, 120 mM NaCl, 5 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 0.6 mM ascorbic acid, 5.5 mM glucose; pH 7.4). For acute studies (10 and 30 min), cells were incubated with various concentrations of either deltamethrin or permethrin (1 nM–10 μM). For longer-term studies (24 h), cells were exposed to the pyrethroids in serum-free media for 24 h and then washed once in uptake buffer. Following the wash step, cells were incubated for 5 min at 37 °C with uptake buffer containing unlabeled DA (2.5 μM) and a tracer amount (20 nM) of ^{3}H-dopamine. Pargyline (10 μM) was included during all the uptake periods to inhibit monoamine oxidase and non-specific uptake was defined in the presence of 10 μM GBR-12935. After the incubation period, the buffer was quickly aspirated off and cells were washed twice with ice-cold buffer. Cells were then dissolved in 0.5 ml of 0.1 M NaOH and the solubilized cellular contents were transferred to liquid scintillation vials containing 8 ml of liquid scintillation cocktail. The radioactivity was measured by scintillation counting and an aliquot of the solubilized cells was used for protein determination using bovine serum albumin as standard (Lowry et al., 1951). Uptake rates were calculated as specific uptake (total uptake−non-specific uptake) and expressed as percentage of control values.

To determine the effects of pyrethroids on the K_m and V_{max} of dopamine uptake in SK-DAT cells, cells were incubated with pyrethroids for 10 min or 24 h and dopamine uptake was determined as described above using increasing concentrations (0.5–40 μM) of dopamine. K_m and V_{max} were determined by non-linear regression using GraphPad Prism 3.0 (GraphPad Software, San Diego, CA).

Western blots were performed as previously described (Miller et al., 1997). Briefly, cells were scraped from culture plates and sonicated at 4 °C in a buffer containing 300 mM sucrose, 10 mM HEPES, and 1 μg/ml of leupeptin,

aprotinin, and pepstatin. Samples (20 μg) were subjected to SDS PAGE on 10% precast NuPage gels (InVitrogen, Carlsbad, CA). Samples were electrophoretically transferred to a polyvinylidene difluoride membrane, and non-specific sites were blocked in 7.5% nonfat dry milk in Tris-buffered saline (135 mM NaCl, 2.5 mM KCl, 50 mM Tris, and 0.1% Tween 20, pH 7.4). Membranes were then incubated in a monoclonal antibody (Chemicon, Temecula, CA) to the N-terminus of DAT (Miller et al., 1997). Antibody binding was detected using a goat anti-rat horseradish peroxidase secondary antibody (ICN, Costa Mesa, CA) and enhanced chemiluminescence. The chemiluminescent signal was captured on an Alpha Innotech Fluorchem 8800 (San Leandro, CA) imaging system and stored as a digital image. Densitometric analysis was performed and calibrated to co-blotted dilutional standards of pooled cells from all control samples. Membranes were then stripped for 15 min at 25 °C with Pierce Stripping Buffer and reprobed with a monoclonal α-tubulin antibody to ensure equal protein loading across samples.

Cytotoxicity and DNA fragmentation assays. The possible cytotoxic effects of pyrethroid exposure on SK-DAT cells was evaluated by measuring lactate dehydrogenase (LDH) leakage into the extracellular fluid using a cytotoxicity detection kit (Roche Applied Science, Indianapolis, IN). Briefly, cells (1×10^4 cells/well) were incubated with different concentrations of pyrethroids (1, 5, or 10 μM) for 24 h in serum-free MEM and the incubation medium was collected and centrifuged. The cell-free supernatant (100 μl) was then mixed with 100 μl of the catalyst-dye mix (included in kit) in a 96-well microtiter plate. LDH activity in the media was determined spectrophotometrically at 490 nm by monitoring the increase in absorbance over a 30-min period. To determine the total amount of LDH in each sample, the original cells and media were lysed in 1% Triton X-100 for 30 min and LDH activity was determined as described above. The LDH release for each sample was defined as the LDH activity in the incubation media divided by the total amount of LDH activity following Triton-lysis and data expressed presented as percentage LDH leakage.

To determine whether pyrethroid exposure resulted in apoptosis in SK-DAT cells, we used the Cell Death Detection ELISA Plus Assay kit (Roche Applied Science, Indianapolis, IN), which provides an index of DNA fragmentation. This kit measures amount of histone-associated low molecular weight DNA, which is indicative of histone-associated DNA fragments which have been cleaved by endonuclease, in the cytoplasm of cells and has been used as a measure of apoptosis in cells exposed to other toxicants (Anantharam et al., 2002; Kitazawa et al., 2002). Briefly, cells were seeded in microplate wells (1×10^4 cells/well) and treated for 24 h in serum-free MEM with either deltamethrin or permethrin. After treatment, cells were pelleted and washed once with phosphate-buffered saline. Cells were then incubated with lysis buffer (supplied with the kit) at room temperature for 30 min and centrifuged. Aliquots of supernatant (20 μl) were dispensed into a streptavidin-coated 96-well microtiter plate (supplied with the kit) and incubated with 80 μl of antibody cocktail for 2 h at room temperature with shaking. The antibody cocktail consisted of a mixture of anti-histone biotin and anti-DNA-HRP, which binds to both single-stranded DNA and double-stranded DNA, which are major constituents of nucleosomes. After incubation, plates were washed with incubation buffer and determination of the amount of nucleosomes retained by anti-DNA-HRP was determined spectrophotometrically with 2,2′-azino-di[3-ethoxybenzyl thiazoline sulfonate] as an HRP substrate (supplied with the kit). Measurements were made at 405 nm using a Spectramax Plus microplate reader (Molecular Devices). Non-specific signal was determined by subtraction of a reagent blank and data were expressed as mU (defined as absorbance $\times 10^{-3}$) cytoplasmic oligonucleosomes.

Statistical analysis. Results were expressed as the mean ± SEM. In instances where data were presented as percentage of control, all statistical procedures were performed on the raw numbers. Data were analyzed by Student's t test or one-way analysis of variance (ANOVA). If a significant F was determined by ANOVA, post hoc analysis was performed with Dunnett's test. Statistical significance is reported at the $P \leq 0.05$ level.

Results

No overt signs of toxicity, defined as tremor, choreoathetosis, and salivation, were observed following administration of either deltamethrin or permethrin. There were also no significant changes in weight in any of the treated animals (data not shown).

Based upon previous studies demonstrating increased dopamine uptake following deltamethrin or permethrin exposure (Kirby et al., 1999; Gillette and Bloomquist, 2003), we administered deltamethrin (3 mg/kg) or permethrin (0.8 mg/kg) three times over 2 weeks to determine the effects of these compounds on DAT-mediated dopamine uptake and the number of DAT-binding sites. Deltamethrin exposure increased DAT-mediated dopamine uptake in striatal synaptosomes by 31% ($P < 0.01$) 1 day following the last treatment (Fig. 1A). At this same time, permethrin exposure increased dopamine uptake by 28% ($P < 0.01$). The increases in dopamine uptake observed were accompanied by increases in DAT-binding sites as determined by ^{3}H-WIN 35,428 binding in striatal synaptosomes (Fig. 1B). Deltamethrin resulted in a 32% increase ($P < 0.01$), while permethrin exposure increased DAT-binding sites by 24% ($P < 0.01$). The increase in DAT-binding sites and uptake by exposure to deltamethrin and permethrin were accompanied by similar increases (31.2% and 29.3%, $P < 0.01$) in total DAT protein as measured by Western immunoblotting (Fig. 1C).

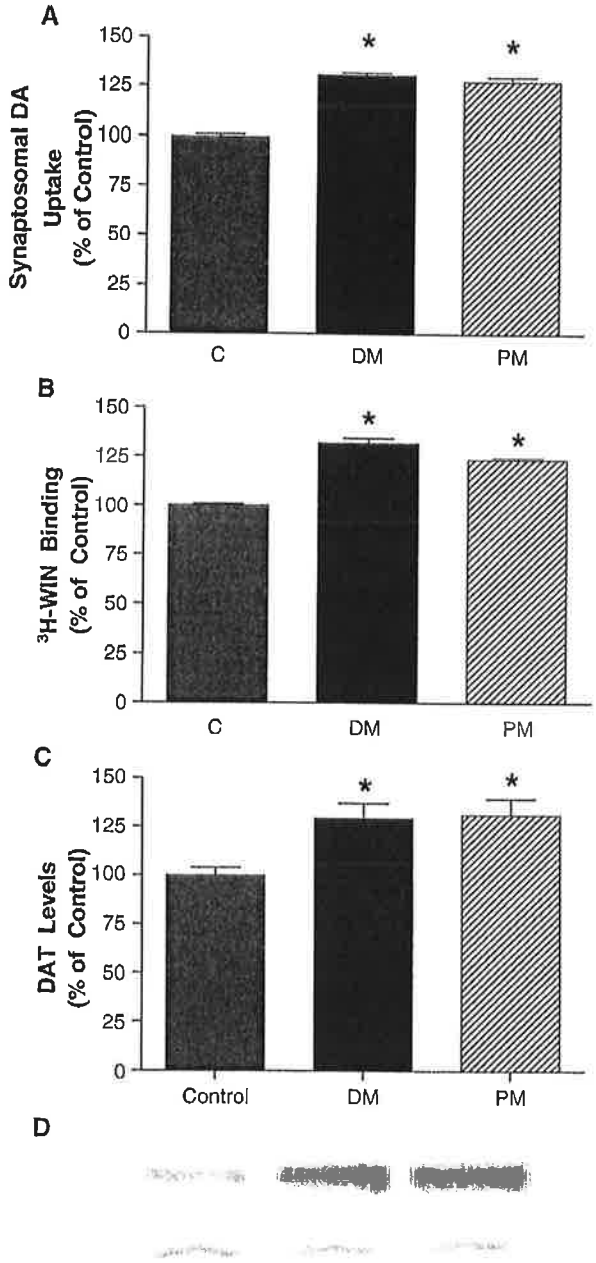

Fig. 1. Repeated administration of deltamethrin (DM; 3 mg/kg) or permethrin (PM; 0.8 mg/kg) to C57 mice increases (A) ^{3}H-dopamine uptake in striatal synaptosomes, (B) DAT levels in striatal synaptosomes as determined by ^{3}H-WIN 35,428 binding, and (C) DAT levels in striatal synaptosomes as determined by Western immunoblotting. Data are presented as percentage of control values and represent mean ± SEM (n = 5–6 animals per treatment for pyrethroids and 12 animals for control). *Groups are significantly different from control values ($P \leq 0.01$) using the untransformed data as determined by ANOVA followed by Dunnett's test. (D) Representative Western blots of DAT (top) and α-tubulin (bottom) from control, deltamethrin-, and permethrin-treated animals.

Since we observed significant up-regulation of DAT following in vivo exposure to deltamethrin and permethrin, we sought to determine whether these effects were the result of direct action of the pyrethroids on DAT. To accomplish this, we exposed SK-N-MC neuroblastoma cells stably expressing DAT (SK-DAT) to various concentrations of pyrethroids for 10 min, 30 min, or 24 h. Exposure of SK-DAT cells for 10 min with either deltamethrin or permethrin (1 μM to 10 μM) had no significant effect on DAT-mediated dopamine uptake (Fig. 2A). Extending the incubation time to 30 min resulted in a significant decrease in dopamine uptake by both deltamethrin (20%; $P < 0.01$) and

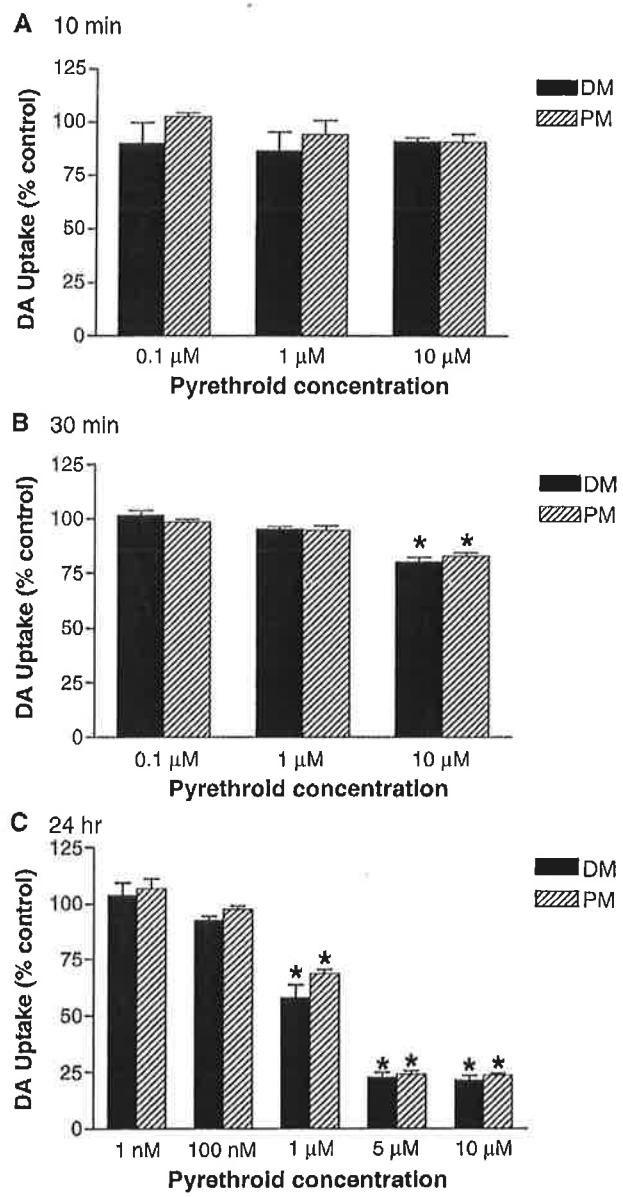

Fig. 2. Effects of deltamethrin (DM) and permethrin (PM) on dopamine uptake in SK-N-MC neuroblastoma cells stably expressing the human DAT. Cells were incubated with various concentrations of DM or PM for 10 min (A), 30 min (B), or 24 h (C) and dopamine uptake was determined as described in Materials and methods. Data are presented as percentage of control values and represent mean ± SEM (n = 3). *Groups are significantly different from control values ($P \leq 0.01$) using the untransformed data as determined by ANOVA followed by Dunnett's test.

permethrin (18%; $P < 0.01$) only at a concentration of 10 μM (Fig. 2B). Further extending the incubation time to 24 h resulted in a greater decrease of dopamine uptake, as both permethrin ($P < 0.01$) and deltamethrin ($P < 0.01$) decreased dopamine uptake by 32 to 42% at 1 μM and 75% at concentrations of 5 and 10 μM (Fig. 2C). To determine the nature of the inhibition of DAT-mediated uptake by deltamethrin and permethrin, we performed kinetic analysis of dopamine uptake in SK-DAT cells exposed to 10 μM of either compound for 24 h. Both pyrethroids showed significant alterations in V_{max}, with variable effects on K_m, suggesting that the decreased uptake may be the result of non-competitive inhibition (Figs. 3A and B). Similar results were observed following 30-min incubations with both compounds (data not shown).

Based upon the time and concentrations required for deltamethrin and permethrin to cause decreased dopamine uptake, we considered that the decreased uptake may be the result of loss of DAT protein. Exposure of cells to 10 μM of deltamethrin or permethrin was without effect on the total levels of DAT as determined by Western immunoblotting (Fig. 3C). We next examined whether exposure to

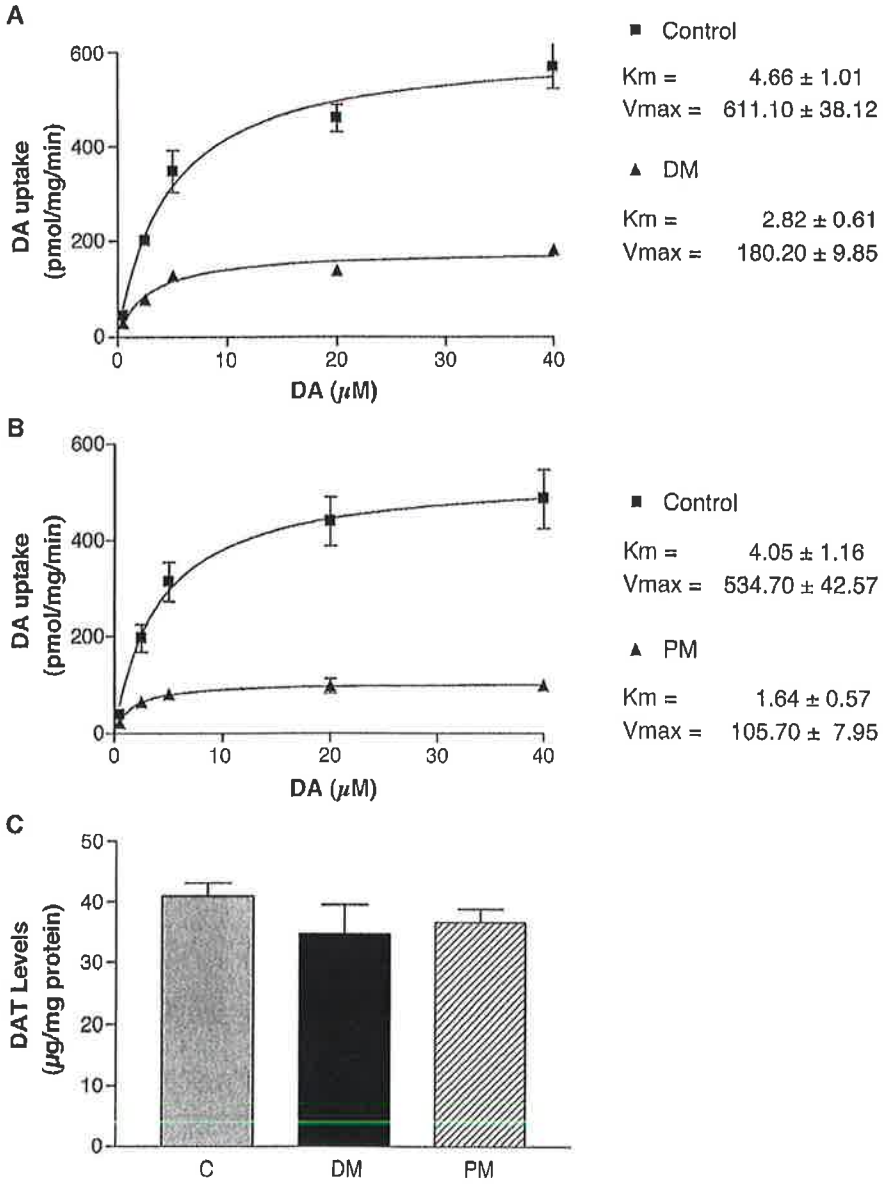

Fig. 3. Effects of (A) deltamethrin (DM; 10 μM) or (B) permethrin (PM; 10 μM) treatment for 24 h on the kinetics of dopamine uptake in SK-N-MC neuroblastoma cells stably expressing the human DAT. Cells were incubated with DM or PM for 24 h and the kinetics of dopamine uptake were determined by using varying concentrations of dopamine as described in Materials and methods. Data represent mean ± SEM ($n = 3$) and absence of error bars indicates that the standard error resides within the size of the symbol. (C) Total DAT levels in cells treated with DM or PM for 24 h as determined by Western immunoblotting. Data represent mean ± SEM ($n = 3$).

deltamethrin or permethrin resulted in cytotoxicity by assessing LDH leakage from the cells into the incubation medium. Treatment of SK-DAT cells with 1 to 10 μM of deltamethrin or permethrin for 24 h did not produce any significant change in LDH leakage (Fig. 4A), effectively ruling out overt cytotoxicity as a mechanism for the decreased dopamine uptake. However, exposure of SK-DAT cells to 5 or 10 μM of permethrin or 10 μM deltamethrin for 24 h significantly increased DNA fragmentation, an indication of an active apoptotic process (Fig. 4B). Exposure to 5 μM permethrin increased the amount of fragmentation by 191% ($P < 0.05$) and exposure to 10 μM increased fragmentation by 422% ($P < 0.01$). Deltamethrin increased fragmentation by 223% ($P < 0.05$) only at 10 μM. Similarly, increased DNA fragmentation was observed following 30 min of exposure to 10 μM of deltamethrin (35%; $P < 0.05$) or permethrin (65%; $P < 0.05$). No significant effects were observed with lower concentrations (data not shown).

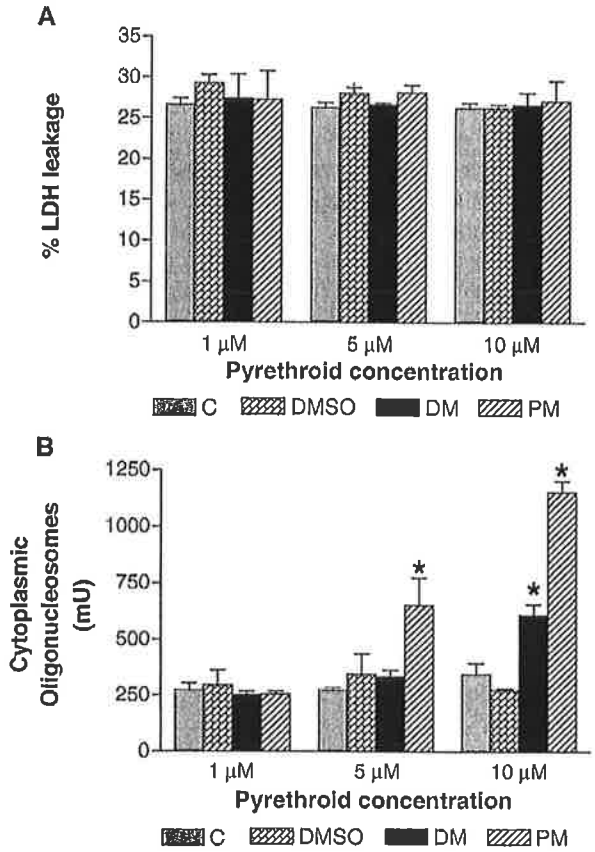

Fig. 4. Effects of deltamethrin or permethrin on (A) LDH leakage and (B) DNA fragmentation. SK-N-MC cells stably expressing the human DAT were treated with media (C), vehicle (DMSO), deltamethrin (DM; 1–10 μM), or permethrin (PM; 1–10 μM) for 24 h. After exposure, cell-free media samples were collected and assayed for LDH levels by spectrophotometry. DNA fragmentation in cells following 24 h of exposure was determined as described in Materials and methods. Data for LDH are presented as percentage of LDH leakage and represent mean ± SEM ($n = 3$). *Groups are significantly different from control values ($P \leq 0.05$) using the untransformed data as determined by ANOVA followed by Dunnett's test.

Discussion

Previous studies have demonstrated that repeated exposure of mice to the pyrethroid pesticides, deltamethrin and permethrin, results in increased synaptosomal dopamine uptake (Kirby et al., 1999; Karen et al., 2001; Gillette and Bloomquist, 2003). In this study, we confirm these observations and extend them by demonstrating that the functional up-regulation is accompanied by increases in DAT-binding sites. In addition, we demonstrate that permethrin and deltamethrin have no direct effect on DAT and that longer-term in vitro exposure of cells stably expressing DAT results in decreased DAT-mediated dopamine uptake and DNA fragmentation.

Deltamethrin and permethrin are members of the pyrethroid class of pesticides which are synthetic derivatives of the naturally occurring pyrethrum from chrysanthemum flowers. These compounds exert their toxicity primarily through binding to sodium channels and prolonging the opening of the channel (Narahashi, 1996; Soderlund et al., 2002). However, recent data suggest that these compounds may specifically target the dopaminergic system. It has been demonstrated that exposure of mice to deltamethrin or permethrin results in an increase in dopamine uptake in striatal synaptosomes, possibly indicative of an up-regulation of DAT (Karen et al., 2001; Kirby et al., 1999). In addition, up-regulation of dopamine uptake following deltamethrin exposure was accompanied by increased binding of ^{3}H-GBR 12935 (Gillette and Bloomquist, 2003). In this study, we found significant increases in DAT-binding sites as measured with ^{3}H-WIN 35,428 that mirrored the increase in DAT-mediated dopamine uptake. While no specific mechanism has been identified for the increase of DAT by these compounds, chemicals known to cause dopamine release, like amantidine and the organochlorine pesticide heptachlor, can increase DAT expression (Gordon et al., 1996; Miller et al., 1999a, 1999b; Page et al., 2000; Kirby et al., 2002). If this were to be sustained over time, one would expect that the elevated extracellular dopamine would increase the expression of the dopamine transporter in an attempt to clear and recycle dopamine. Indeed, deltamethrin has been demonstrated to cause dopamine release from pre-loaded synaptosomes (Kirby et al., 1999; Bloomquist et al., 2002). Another possibility is up-regulation of DAT at the transcriptional level. The transcription factor Nurr1 is critical for the development of the dopaminergic phenotype and has been shown to directly enhance transcription of DAT (Sacchetti et al., 2001; Hermanson et al., 2003). Since Nurr1 transcription is enhanced by neuronal activity and membrane depolarization (Brosenitsch and Katz, 2001), dopamine release and/or blockade of sodium channels by pyrethroids may cause up-

regulation of Nurr1, ultimately leading to increased expression of DAT.

In contrast to the in vivo data, our in vitro results show that short-term (10 min) incubation of SK-DAT cells with deltamethrin or permethrin had no effect on DAT-mediated dopamine uptake. However, if the incubation time was extended to 30 min or 24 h, significant decreases in dopamine uptake were observed. Thus, the reduction of dopamine uptake in SK-DAT cells by deltamethrin and permethrin, is both time and concentration dependent. The lack of a significant effect on dopamine uptake after the 10-min incubation time suggests that both compounds are devoid of any direct effect on dopamine uptake. In addition, the decreases we observed with the longer exposure times were associated with significant changes in V_{max} and little effect on K_m, providing further evidence that pyrethroids do not directly interact with DAT. We also found that these effects were not the result of loss of DAT protein. Since a direct (cocaine-like) action on DAT is excluded by our results, other mechanism(s) appear to be involved in the reduction of dopamine uptake observed here. One possibility is that long-term higher-level exposure to pyrethroids leads to prolonged depolarization (Narahashi, 1982; Tabarean and Narahashi, 2001). Indeed, in vitro exposure of rat striatal synaptosomes to high concentrations (10–50 μM) of veratridine, a sodium channel activator, resulted in decreased dopamine uptake (Holz and Coyle, 1974). In addition, pyrethroids have been demonstrated to inhibit respiratory chain function in isolated mitochondria at submicromolar levels, which could lead to down-regulation of DAT function (Gassner et al., 1997; Maragos et al., 2002; Braguini et al., 2004). Although there are few studies reporting pyrethroid concentrations in the brain following systemic administration, Sheets et al. (1994) reported that brain levels of deltamethrin were 0.023 μg/g and 0.145 μg/g following a single oral exposure to 4 or 80 mg/kg in adult rats. These brain concentrations are roughly equivalent to 45 and 287 nM, which are in the range of the concentrations used in our in vitro studies that were without effect on the DAT, but lower than those demonstrated to effect mitochondrial function (EC_{50} 793 nM for permethrin and >200 nM for deltamethrin; Gassner et al., 1997; Braguini et al., 2004). Thus, it is likely that the concentrations employed in our in vitro studies are similar to the higher doses of permethrin (25–200 mg/kg) demonstrated to decrease mitochondrial function, dopamine uptake, and DAT immunoreactivity in mice (Karen et al., 2001; Bloomquist et al., 2002; Gillette and Bloomquist, 2003; Pittman et al., 2003).

Since we found that neither deltamethrin nor permethrin has a direct effect on DAT and we estimated that the concentrations employed were similar to those that decrease mitochondrial function, we sought to determine whether the reduction in dopamine uptake was the result of pyrethroid-induced cytotoxicity. Following 30 min or 24 h exposure to 10 μM of deltamethrin or permethrin, there was no significant cytotoxic effect as determined by LDH assay. This is in agreement with the observation that exposure to pyrethroids for 24 h did not produce any significant effect on LDH release from mouse cerebellar granule cells (Imamura et al., 2000), and indicates that the decreased dopamine uptake we observed is not due to cytotoxicity. Since we observed no overt cytotoxicity at any of the concentrations or times tested, we tested the possibility that deltamethrin and permethrin were causing apoptosis. Our findings reveal that both deltamethrin and permethrin induce apoptosis, as indicated by increased DNA fragmentation, following 30-min and 24-h incubations at the highest concentration used (10 μM), whereas at lower concentrations (5 μM), only permethrin induced apoptosis. These data suggest that apoptosis may explain, in part, some of the observed decrease in dopamine uptake in these cells at the higher concentrations used. There is evidence indicating that apoptosis might play a crucial role in the toxic actions of pyrethroids by induction of apoptosis and altering the expression of p53, Bax, and Bcl-2 genes (Wu and Liu, 2000a, 2000b), although the doses used were greater than 4-fold higher than we used in our in vivo studies. Taken together with our results, these studies suggest that higher-level exposure to pyrethroids may result in apoptosis, similar to that seen with our in vitro studies.

The alteration of DAT function and expression by pyrethroid exposure is of particular interest when taken in context of the role of DAT in Parkinson's disease (PD). Several studies have identified pesticide exposure as a risk factor for PD (Priyadarshi et al., 2001). However, the mechanism by which pesticides enhance the risk of PD is not known. Previously, we and others have demonstrated that alterations of DAT expression can greatly affect the vulnerability of the dopamine neuron to neurotoxins such as MPTP or methamphetamine (Gainetdinov et al., 1997; Donovan et al., 1999; Fumagalli et al., 1998). In addition, the brain regions most vulnerable to parkinsonism-inducing toxin MPTP and those most affected by PD display the highest levels of DAT expression (Miller et al., 1999b; Uhl, 1998). Supporting the observation in humans, animals overexpressing DAT (Donovan et al., 1999) are more susceptible to MPTP toxicity. Therefore, enhanced DAT levels and function by pesticides may increase the susceptibility of dopamine neurons to endogenous neurotoxic dopamine metabolites or exogenous toxicants by increasing uptake through DAT. Additionally, the decreased dopamine uptake and increased DNA fragmentation, suggestive of an ongoing apoptotic process, following in vitro pyrethroid exposure may be relevant to PD as well. Positron emission topographic imaging with ^{11}C-WIN 35,428 has revealed early reductions in DAT levels in mild cases of PD (Frost et al., 1993), suggesting that reductions in DAT levels may be an early indicator of clinical PD in humans. Additionally, activated caspase-3, a primary apoptotic effector, has been demonstrated to precede apoptotic death in human PD brain (Hartmann et al., 2000). Therefore, lower level exposure to

pyrethroids may contribute to PD through up-regulation of DAT and increased uptake of endogenous and exogenous neurotoxicants while increased levels result in apoptotic cell death. However, the exact mechanism of pesticides, including pyrethroids, in the etiology of PD remains to be established.

In conclusion, the present study clearly demonstrates that deltamethrin and permethrin increase DAT and DAT-mediated dopamine uptake in striatal synaptosomes following in vivo exposure. However, in vitro experiments revealed that the in vivo effects are likely indirect as acute in vitro exposure of cells stably expressing DAT had no effect on dopamine uptake. We also found that prolonged higher-level exposure decreases dopamine uptake in SK-DAT cells, which may be due in part to induction of apoptosis. These results may shed light on the mechanisms underlying pyrethroids-induced neurotoxicity and might implicate pyrethroids as environmental risk factors leading to the development of PD.

Acknowledgments

This work was supported by the US Army Medical Research and Materiel Command under Award No. 00267036 (GWM), and in part by NIH U54 ES012068 (GWM) and F32 ES013457 (JRR), and an EPA STAR Fellowship (TSG). Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army, NIH, or EPA.

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[CANCER RESEARCH (SUPPL.) 52, 5485s–5488s, October 1, 1992]

Cancer

Pesticides and Non-Hodgkin's Lymphoma[1]

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Abstract

The incidence of non-Hodgkin's lymphoma (NHL) has increased over 50% in the last 15 years. This paper reviews the possible role of pesticides in this increase. While small increases in risk of NHL among farmers have been observed in general occupational surveys, recent studies focusing on specific pesticides have observed much larger risks. Frequent use of phenoxyacetic acid herbicides, in particular, 2,4-dichlorophenoxyacetic acid, has been associated with 2- to 8-fold increases of NHL in studies conducted in Sweden, Kansas, Nebraska, Canada, and elsewhere. Canine malignant lymphoma has also been associated with dog owner use of 2,4-dichlorophenoxyacetic acid and commercial lawn pesticide treatments. There are much fewer data linking NHL to other types of pesticides, but triazine herbicides, organophosphate insecticides, fungicides, and fumigants have also been associated with increased risk of NHL. Pesticide exposures are not limited to agricultural populations but are widespread in the general population through use on lawns, golf courses, rights-of-way, and elsewhere. Since the use of pesticides, particularly phenoxy herbicides, has increased dramatically preceding and during the time period in which the incidence of NHL has increased, they could have contributed to the rising incidence of NHL.

Introduction

The incidence of NHL[2] has increased over 50% in the last 15 years (1). The United States cancer mortality time trends map for NHL during 1950–1980 shows a significant increase in the central part of the United States, a predominantly agricultural area (2). This report focuses on one group of agricultural exposures, pesticides, that might be contributing to this increase. Pesticides include herbicides (weed killers), insecticides, fungicides, and other agents. Other exposures common to agriculture that may also play a role in NHL etiology are mentioned in other reports in this volume (3, 4).

Non-Hodgkin's Lymphoma and Farming

In a recent review of the descriptive and analytical studies concerning agriculture and cancer (5), we found 21 cohort studies of farmers or broad occupational surveys of cancer that presented descriptive data on NHL and farming (Table 1). In these 21 studies, the risk ratios for NHL ranged from 0.6 to 2.6. Eleven reported excesses among farmers, but only three were statistically significant. One survey had a significantly depressed risk ratio for NHL. The range of risk ratios was not large and the excess risks were generally small. The analytical studies reviewed included both case-control studies and cross-sectional studies of NHL that evaluated the farming occupation. Of 19 such studies, 12 reported excess NHL among farmers with 8 statistically significant associations. Six studies had less than expected NHL among farmers with one significant deficit observed. The range in the risk estimates was again small, 0.6–1.9.

Both the descriptive and analytical data tend to show excesses, but are not impressive overall. This may be because they are based on the broad occupational category "farmers." Farming is a highly variable occupation with exposures that differ considerably depending upon the commodity produced. Combining farmers with different exposures would tend to dilute the effects of relevant exposures and bias risk estimates toward the null value. For example, among the population-based controls from a National Cancer Institute study in Iowa/Minnesota, 16% of those who had lived on farms had never used insecticides and 49% had never used herbicides (6). Only 40% had used phenoxyacetic acid herbicides and 20% had used organophosphate insecticides, the two most frequently used pesticide classes. If the subgroup of farmers who had used phenoxy herbicides had twice the risk of NHL as nonusers, an analysis of all farmers combined would yield a relative risk of only 1.4. Thus, it is not surprising that risks among farmers as a group are small.

Non-Hodgkin's Lymphoma and Pesticides

There have been some, but not many, studies that have tried to go beyond the job title farmer and examine the associations between specific agricultural exposures and NHL. These studies have identified the following types of pesticides as possible risk factors for NHL: phenoxyacetic acid herbicides, triazine herbicides, organophosphate insecticides, and fungicides and fumigants.

Phenoxy Herbicides. Phenoxy herbicides include 2,4-D, 2,4,5-T (banned for all uses in the United States in 1978), 2-methyl-4-chlorophenoxyacetic acid, and other related compounds. 2,4-D is one of the most commonly used broadleaf herbicides in North America (7). It is widely used in agriculture on crops such as wheat, corn, oats, rye, barley, sugar cane, and sorghum. It is also used on range and pastureland, in forestry, on rights-of-way, and on lawns and other turf, such as golf courses. The Environmental Protection Agency estimates that 40–65 million pounds of 2,4-D and related compounds are applied yearly in the United States (8).

Some death certificate-based studies have shown an association between NHL mortality and county per capita use of herbicides (9, 10), but stronger evidence linking herbicides and, in particular, phenoxy herbicides to NHL comes from interview-based case-control studies. In 1981, Hardell *et al.* from Sweden [11] reported a 6-fold risk of malignant lymphoma among persons exposed to phenoxyacetic acids or chlorophenols. Although no site-specific relative risks were presented, the authors said that the association existed for both NHL and Hodgkin's disease. We conducted a population-based case-control study of NHL in Kansas that showed a 2-fold excess (odds ratio, 2.2) of NHL among farmers who used phenoxy herbicides (12). Risk rose with days per year of use of herbicides to over 7-fold among those reporting use for 21 or more days per year and who specifically reported use of 2,4-D, a trend that was highly significant (Table 2). The risk was higher among farmers who did not regularly use protective equipment when applying pesticides. The association could not be explained by exposure to other herbicides, insecticides, or other risk factors for NHL.

We obtained similar findings from a study in Nebraska (13). An overall risk of 1.5 for NHL was found among farmers who

[1] Presented at the National Cancer Institute Workshop, "The Emerging Epidemic of Non-Hodgkin's Lymphoma: Current Knowledge Regarding Etiological Factors," October 22–23, 1991, Bethesda, MD.

[2] The abbreviations used are: NHL, non-Hodgkin's lymphoma; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

Table 1 *Review of epidemiologic studies concerning farming and non-Hodgkin's lymphoma*[a]

Study type	No. of studies	RR[b] range	RR> 1.0	RR> 1.0[c]	RR< 1.0	RR< 1.0[c]
General occupational surveys or farmer cohorts	21	0.6–2.6	11	3	7	1
Case-control or cross-sectional	19	0.6–1.9	12	8	6	1

[a] Source: Blair and Zahm, 1991 (5).
[b] RR, risk ratio.
[c] Statistically significant.

mixed or applied 2,4-D. Risk rose to 3.3 for farmers who handled 2,4-D 21 or more days per year (Table 2). Risk also rose the longer farmers wore their application work clothes before changing to clean work garments. This finding is consistent with investigations that show the dermal route is the most important for 2,4-D and most other pesticide exposures (14). Although the risks were lower than in Kansas, the patterns were similar.

A New Zealand case-control study of NHL, using other cancers as controls, found no excess risk associated with potential exposure to phenoxy herbicides (15, 16). In a later report, Pearce (17) examined NHL risk by days per year of phenoxy herbicide use in these New Zealand data (Table 2). The trend was not significant, but risk did increase to a 2-fold level in the 10–19 days per year category and then decreased to 1.1. Considering all three studies, it is hard to dismiss these risks as due to chance. It should be noted that, in contrast to the United States where the phenoxy herbicide evaluated was 2,4-D, the predominant phenoxy herbicide in use in New Zealand was 2,4,5-T.

There have been three other case-control studies, conducted in Washington State, Sweden, and Italy, that examined the association between herbicides and NHL (18–20). None had information on days per year. In Italy, a significant trend with duration of exposure to herbicides was observed (20). In a Swedish study, Persson *et al.* (19) reported an odds ratio of 4.9 (95% confidence interval, 1.3–18) for NHL for occupations exposed to phenoxy acids. A study in Washington State reported significant odds ratios of 1.3 for farmers and 4.8 for persons who sprayed forests with herbicides. Most other exposed occupations had nonsignificantly elevated risks (16). In a second report, the Washington farmers who used 2,4-D had no elevation in NHL risk, but, again, no days per year data were available (21).

Another Swedish report, by Olsson and Brandt (22), is interesting and unusual in that the authors examined the risk for patients with cutaneous NHL. Phenoxy herbicides were associated with an odds ratio of 1.3 for NHL overall, but with an odds ratio of 10.0 for NHL localized to the skin.

In a cohort mortality study of male farmers in Saskatchewan, Canada, NHL was associated with use of herbicides, as recorded in the 1971 Census of Agriculture (23). Among farmers with operations of less than 1000 acres, risk ratios rose significantly with the number of acres sprayed with herbicides from 1.3 for less than 100 acres, 1.9 for 100–249 acres, to 2.2 for 250 or more acres (Table 3). No other cause of death showed this pattern. Although the association is with herbicides in general, the authors noted that 90% of the herbicides used by weight in Saskatchewan in the 1960s and 75% in the 1970s was 2,4-D. It seems unlikely, therefore, that the association could be due to some herbicide other than 2,4-D.

Three manufacturing cohorts exposed to phenoxy herbicides have demonstrated slight excesses of NHL, based on small numbers of cases (Table 4) (24–26). A cohort study of cancer incidence among Swedish licensed pesticide applicators did not show an excess of NHL, but the predominant phenoxy herbicide was 2-methyl-4-chlorophenoxyacetic acid, with much less 2,4-D and 2,4,5-T used (27). An international cohort study of both manufacturing production workers and applicators exposed to a variety of phenoxy herbicides in 10 countries showed a small, nonsignificant excess in mortality from NHL among production workers, but not applicators (28).

The most recent study, to our knowledge, to be published on herbicides and lymphoma was a hospital-based case-control study of lymphoma in dogs (29). Excess risk was associated with the dog owners' use of 2,4-D on their lawns and/or treatment of yards by commercial lawn care companies (Table 5). The risk of canine lymphoma rose significantly to a 2-fold excess with 4 or more yearly owner applications of 2,4-D.

Other Pesticides. There are much fewer data linking NHL to pesticides other than phenoxy herbicides. Triazine herbicides were associated in the Kansas case-control study (12). For atrazine, a member of the triazine family, an odds ratio of 2.7 (95% confidence interval, 1.2, 5.9) was observed. In Nebraska, farmers who used atrazine for more than 15 years had a 2-fold risk of NHL (13). The Nebraska study also demonstrated a more

Table 2 *Number of white male NHL cases and controls and odds ratios by days per year of exposure to herbicides in Kansas, Nebraska, and New Zealand*[a]

State	Type of herbicide	Days/yr	No. of NHL cases	No. of controls	Odds ratio[b]
Kansas	2,4-D users:	0	37	286	1.0
	Days/yr exposed to herbicides[c]	1–2	6	17	2.7
		3–5	4	16	1.6
		6–10	4	16	1.9
		11–20	4	9	3.0
		21+	5	6	7.6
Nebraska	Days/yr handled 2,4-D[d]	0	54	184	1.0
		1–5	16	44	1.2
		6–20	12	25	1.6
		21+	3	4	3.3
New Zealand	Use of phenoxy herbicides (primarily 2,4,5-T)[e]	0	139	266	1.0
		1–4	20	40	0.9
		5–9	8	11	1.2
		10–19	4	3	2.2
		20+	5	7	1.1

[a] Source: Hoar et al., 1986 (12), Zahm *et al.*, 1990 (13), Pearce, 1989 (17).
[b] Statistically significant.
[c] Kansas: *P*-value for trend, 0.0001.
[d] Nebraska: *P*-value for trend, 0.051.
[e] New Zealand: *P*-value for trend, 0.290.

Table 3 *Number of NHL deaths and relative risks (RR) for acres sprayed with herbicides in 1970, restricted to farms less than 1000 acres, in Saskatchewan farmers, 1971–1985*[a]

Acres sprayed	No. of NHL deaths	RR (95% CI)[b]
0	35	1.0
1–99	14	1.3 (0.7, 2.4)
100–249	28	1.9 (1.2, 3.3)
250+	10	2.2 (1.0, 4.6)

[a] Source: Wigle *et al.*, 1990 (23).
[b] RR (95% CI), relative risk (95 % confidence interval), multivariate Poisson regression analysis.

Table 4 *Number of observed and expected number of NHL deaths and standardized mortality ratios (SMR) for manufacturing and pesticide applicator cohorts exposed to phenoxyacetic acid herbicides*

Cohort type	Study	Ref. no.	No. of NHL deaths	No. of expected deaths	SMR
Manufacturing	Bond (1988)	24	2	0.5	391
	Coggon (1991)	25	2	0.7	272
	Fingerhut (1991)	26	10	7.3	137
	Saracci (1991)[a]	28	8	5.4	149
Applicators	Wiklund (1987)[b]	27	21	20.8	101
	Saracci (1991)	28	3	6.3	49

[a] Saracci *et al.* (28) is an international study with data from 10 countries and includes both manufacturing production workers and pesticide applicators.
[b] Wiklund *et al.* (27) studied cancer incidence, so the data represent numbers of cases and standardized morbidity (or incidence) ratios.

Table 5 *Number of canine malignant lymphoma cases and controls and odds ratios (OR) by dog owners' use of 2,4-D and/or commercial lawn treatment*[a]

Owner application of 2,4-D and/or commercial lawn treatment	No. of cases	No. of controls	OR
None or dog never allowed in yard	300	641	1.0
Yes	191	304	1.3[b]
Commercial treatment only	115	189	1.3
Owner applied 2,4-D only	60	99	1.3
Both	16	16	1.9
No. of dog owner applications of 2,4-D/yr[c]			
1	20	34	1.3
2	28	47	1.3
3	11	17	1.3
4+	17	17	2.0

[a] Source: Hayes *et al.*, 1991 (29).
[b] Statistically significant.
[c] *P*-value for trend < 0.02.

than 2-fold risk of NHL associated with use of organophosphate insecticides (odds ratio, 2.4), adjusted for 2,4-D use. Chlorophenols have been linked to NHL in case-control studies from New Zealand (16, 17) and Sweden (11), although the New Zealand findings were not statistically significant. Fungicides in general were associated with NHL in Kansas (12). Grain millers, exposed to fungicides and fumigant pesticides, have been reported to have excess NHL (30). A nested case-control study within a cohort mortality study of 22,938 grain millers reported a 4-fold excess of NHL among flour mill employees. Risk rose to 9-fold after 25 years of follow-up. Garry *et al.* (31) reported that fumigant applicators previously exposed, 6 weeks to 3 months earlier, to phosphine or to phosphine plus other pesticides, had significantly increased stable chromosome rearrangements, primarily translocations in G-banded lymphocytes.

Evaluation of the Role of Pesticides in the Increasing Incidence of Non-Hodgkin's Lymphoma

Studies from a number of countries and a variety of exposure situations suggest that pesticides may contribute to the development of NHL. To determine the proportion of the recent increases in NHL incidence that may be caused by pesticides, we need better information on the risks associated with specific pesticide exposures, information on the prevalence of pesticide exposures, and, in particular, information on the changes of exposure over time.

To refine risk estimates, future research on pesticides and NHL needs to incorporate improved exposure assessment techniques. Considering farmers or other pesticide applicators as a group, without detailed exposure data, introduces misclassification and dilutes risk estimates (32, 33). Two approaches should be used. First, etiologic studies may need to be preceded by methodological research to assess the reliability and validity of current techniques used to estimate agricultural exposures and to develop new approaches. This would provide a better basis for exposure assessment in retrospective studies. Another approach would be to conduct a prospective study of an agricultural population (men, women, and farm dependents), which would provide the opportunity for repeated exposure assessment. The need for better exposure data extends beyond occupational situations to general population contacts that may arise from lawn care treatments and other pesticide uses in urban areas. Research on biomarkers of exposure and intermediate outcomes are needed to shed light on the mechanisms of action of pesticides. Possible areas of research include the role of phenoxy herbicides in immunosuppression, peroxisome proliferation, and other epigenetic mechanisms.

The prevalence of use of phenoxy herbicides has changed over the last 45 years, going from essentially zero in 1945 to one of the most commonly used pesticide classes in the United States in 1989 (8). The phenoxy herbicides were discovered in 1942 and were first field tested during World War II by the United States government with the goal of destroying the Japanese rice crop (34). Since 1965, the amount of herbicides used per year in the United States has quadrupled while insecticide use has declined slightly (35).

It is important to remember that pesticide exposures are not limited to agricultural workers. Approximately 70 million pounds of pesticides are applied on lawns each year (36) and the use of lawn care pesticides is increasing 5 to 8% annually (37). The Environmental Protection Agency has estimated that in 1988 as many as 11% of single family households used a commercial lawn care service (36), with about twice as many householders applying pesticides to their lawns themselves (37). The amount of pesticides per treated acre of household lands is almost five times the application rate for treated agricultural lands (38).

Conclusion

In conclusion, NHL is associated with pesticide use, particularly phenoxy herbicides. Exposure to phenoxy herbicides is widespread in the agricultural and general populations. The use has increased dramatically preceding and during the time period in which the incidence of NHL has increased, which could explain at least part of the rising incidence of NHL.

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Pesticide Exposure in Children

COUNCIL ON ENVIRONMENTAL HEALTH

Pediatrics 2012;130;e1757; originally published online November 26, 2012;
DOI: 10.1542/peds.2012-2757

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

POLICY STATEMENT

Pesticide Exposure in Children

COUNCIL ON ENVIRONMENTAL HEALTH

KEY WORDS
pesticides, toxicity, children, pest control, integrated pest management

ABBREVIATIONS
EPA—Environmental Protection Agency
IPM—integrated pest management

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www.pediatrics.org/cgi/doi/10.1542/peds.2012-2757
doi:10.1542/peds.2012-2757
PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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abstract

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This statement presents the position of the American Academy of Pediatrics on pesticides. Pesticides are a collective term for chemicals intended to kill unwanted insects, plants, molds, and rodents. Children encounter pesticides daily and have unique susceptibilities to their potential toxicity. Acute poisoning risks are clear, and understanding of chronic health implications from both acute and chronic exposure are emerging. Epidemiologic evidence demonstrates associations between early life exposure to pesticides and pediatric cancers, decreased cognitive function, and behavioral problems. Related animal toxicology studies provide supportive biological plausibility for these findings. Recognizing and reducing problematic exposures will require attention to current inadequacies in medical training, public health tracking, and regulatory action on pesticides. Ongoing research describing toxicologic vulnerabilities and exposure factors across the life span are needed to inform regulatory needs and appropriate interventions. Policies that promote integrated pest management, comprehensive pesticide labeling, and marketing practices that incorporate child health considerations will enhance safe use. *Pediatrics* 2012;130:e1757–e1763

INTRODUCTION

Pesticides represent a large group of products designed to kill or harm living organisms from insects to rodents to unwanted plants or animals (eg, rodents), making them inherently toxic (Table 1). Beyond acute poisoning, the influences of low-level exposures on child health are of increasing concern. This policy statement presents the position of the American Academy of Pediatrics on exposure to these products. It was developed in conjunction with a technical report that provides a thorough review of topics presented here: steps that pediatricians should take to identify pesticide poisoning, evaluate patients for pesticide-related illness, provide appropriate treatment, and prevent unnecessary exposure and poisoning.[1] Recommendations for a regulatory agenda are provided as well, recognizing the role of federal agencies in ensuring the safety of children while balancing the positive attributes of pesticides. Repellents reviewed previously (eg, N,N-diethyl-meta-toluamide, commonly known as DEET; picaridin) are not discussed.[2]

SOURCES AND MECHANISMS OF EXPOSURE

Children encounter pesticides daily in air, food, dust, and soil and on surfaces through home and public lawn or garden application, household insecticide use, application to pets, and agricultural product

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TABLE 1 Categories of Pesticides and Major Classes

Pesticide category	Major Classes	Examples
Insecticides	Organophosphates	Malathion, methyl parathion, acephate
	Carbamates	Aldicarb, carbaryl, methomyl, propoxur
	Pyrethroids/pyrethrins	Cypermethrin, fenvalerate, permethrin
	Organochlorines	Lindane
	Neonicotinoids	Imidacloprid
	N-phenylpyrazoles	Fipronil
Herbicides	Phosphonates	Glyphosate
	Chlorophenoxy herbicides	2,4-D, mecoprop
	Dipyridyl herbicides	Diquat, paraquat
	Nonselective	Sodium chlorate
Rodenticides	Anticoagulants	Warfarin, brodifacoum
	Convulsants	Strychnine
	Metabolic poison	Sodium fluoroacetate
	Inorganic compounds	Aluminum phosphide
Fungicides	Thiocarbamates	Metam-sodium
	Triazoles	Fluconazole, myclobutanil, triadimefon
	Strobilurins	Pyraclostrobin, picoxystrobin
Fumigants	Halogenated organic	Methyl bromide, Chloropicrin
	Organic	Carbon disulfide, Hydrogen cyanide, Naphthalene
	Inorganic	Phosphine
Miscellaneous	Arsenicals	Lead arsenate, chromated copper arsenate, arsenic trioxide
	Pyridine	4-aminopyridine

residues.[3–9] For many children, diet may be the most influential source, as illustrated by an intervention study that placed children on an organic diet (produced without pesticide) and observed drastic and immediate decrease in urinary excretion of pesticide metabolites.[10] In agricultural settings, pesticide spray drift is important for residences near treated crops or by take-home exposure on clothing and footwear of agricultural workers.[9,11,12] Teen workers may have occupational exposures on the farm or in lawn care.[13–15] Heavy use of pesticides may also occur in urban pest control.[16]

Most serious acute poisoning occurs after unintentional ingestion, although poisoning may also follow inhalational exposure (particularly from fumigants) or significant dermal exposure.[17]

ACUTE PESTICIDE TOXICITY

Clinical Signs and Symptoms

High-dose pesticide exposure may result in immediate, devastating, even lethal consequences. Table 2 summarizes features of clinical toxicity for the major pesticides classes. It highlights the similarities of common classes of pesticides (eg, organophosphates, carbamates, and pyrethroids) and underscores the importance of discriminating among them because treatment modalities differ. Having an index of suspicion based on familiarity with toxic mechanisms and taking an environmental history provides the opportunity for discerning a pesticide's role in clinical decision-making.[18] Pediatric care providers have a poor track record for recognition of acute pesticide poisoning.[19–21] This reflects their self-reported lack of medical education and self-efficacy on the topic.[22–26] More in-depth review of acute toxicity and management can be found in the accompanying technical report or recommended resources in Table 3.

The local or regional poison control center plays an important role as a resource for any suspected pesticide poisoning.

There is no current reliable way to determine the incidence of pesticide exposure and illness in US children. Existing data systems, such as the American Association of Poison Control Centers' National Poison Data System or the National Institute for Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks,[27,28] capture limited information about acute poisoning and trends over time.

There is also no national systematic reporting on the use of pesticides by consumers or licensed professionals. The last national survey of consumer pesticide use in homes and gardens was in 1993 (Research Triangle Institute study).[29]

Improved physician education, accessible and reliable biomarkers, and better diagnostic testing methods to readily identify suspected pesticide illness would significantly improve reporting and surveillance. Such tools would be equally important in improving clinical decision-making and reassuring families if pesticides can be eliminated from the differential diagnosis.

The Pesticide Label

The pesticide label contains information for understanding and preventing acute health consequences: the active ingredient; signal words identifying acute toxicity potential; US Environmental Protection Agency (EPA) registration number; directions for use, including protective equipment recommendations, storage, and disposal; and manufacturer's contact information.[30] Basic first aid advice is provided, and some labels contain a "note for physicians" with specific relevant medical information. The label does not specify the pesticide class or "other"/"inert" ingredients that may have significant toxicity and can account for up to 99% of the product.

Chronic toxicity information is not included, and labels are predominantly available in English. There is significant use of illegal pesticides (especially in immigrant communities), off-label use, and overuse, underscoring the importance of education, monitoring, and enforcement.[31]

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TABLE 2 Common Pesticides: Signs, Symptoms, and Management Considerations[a]

Class	Acute Signs and Symptoms	Clinical Considerations
Organophosphate and N-methyl carbamate insecticides	• Headache, nausea, vomiting, abdominal pain, and dizziness	• Obtain red blood cell and plasma cholinesterase levels
	• Hypersecretion: sweating, salivation, lacrimation, rhinorrhea, diarrhea, and bronchorrhea	• Atropine is primary antidote
	• Muscle fasciculation and weakness, and respiratory symptoms (bronchospasm, cough, wheezing, and respiratory depression)	• Pralidoxime is also an antidote for organophosphate and acts as a cholinesterase reactivator
	• Bradycardia, although early on, tachycardia may be present	• Because carbamates generally produce a reversible cholinesterase inhibition, pralidoxime is not indicated in these poisonings
	• Miosis	
	• Central nervous system: respiratory depression, lethargy, coma, and seizures	
Pyrethroid insecticides	• Similar findings found in organophosphates including the hypersecretion, muscle fasciculation, respiratory symptoms, and seizures	• At times have been mistaken for acute organophosphate or carbamate poisoning
	• Headache, fatigue, vomiting, diarrhea, and irritability	• Symptomatic treatment
	• Dermal: skin irritation and paresthesia	• Treatment with high doses of atropine may yield significant adverse results
		• Vitamin E oil for dermal symptoms
Neonicotinoid insecticides	• Disorientation, severe agitation, drowsiness, dizziness, weakness, and in some situations, loss of consciousness	• Supportive care
	• Vomiting, sore throat, abdominal pain	• Consider sedation for severe agitation
	• Ulcerations in upper gastrointestinal tract	• No available antidote
		• No available diagnostic test
Fipronil (N-phenylpyrazole insecticides)	• Nausea and vomiting	• Supportive care
	• Aphthous ulcers	• No available antidote
	• Altered mental status and coma	• No available diagnostic test
	• Seizures	
Lindane (organochlorine insecticide)	• Central nervous system: mental status changes and seizures	• Control acute seizures with lorazepam
	• Paresthesia, tremor, ataxia and hyperreflexia	• Lindane blood level available as send out
Glyphosate (phosphonate herbicides)	• Nausea and vomiting	• Supportive care
	• Aspiration pneumonia type syndrome	• Pulmonary effects may be secondary to organic solvent
	• Hypotension, altered mental status, and oliguria in severe cases	
	• Pulmonary effects may in fact be secondary to organic solvent	
Chlorophenoxy herbicides	• Skin and mucous membrane irritation	• Consider urine alkalinization with sodium bicarbonate in IV fluids
	• Vomiting, diarrhea, headache, confusion	
	• Metabolic acidosis is the hallmark	
	• Renal failure, hyperkalemia, and hypocalcemia	
	• Probable carcinogen	
Rodenticides (long-acting anticoagulants)	• Bleeding: gums, nose, and other mucous membrane sites	• Consider PT (international normalized ratio)
	• Bruising	• Observation may be appropriate for some clinical scenarios in which it is not clear a child even ingested the agent
		• Vitamin K indicated for active bleeding (IV vitamin K) or for elevated PT (oral vitamin K)

IV, intravenous; PT, prothrombin time.

[a] Expanded version of this table is available in the accompanying technical report.[1]

CHRONIC EFFECTS

Dosing experiments in animals clearly demonstrate the acute and chronic toxicity potential of multiple pesticides. Many pesticide chemicals are classified by the US EPA as carcinogens. The past decade has seen an expansion of the epidemiologic evidence base supporting adverse effects after acute and chronic pesticide exposure in children. This includes increasingly sophisticated studies addressing combined exposures and genetic susceptibility.[1]

Chronic toxicity end points identified in epidemiologic studies include adverse birth outcomes including preterm birth, low birth weight, and congenital

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TABLE 3 Pesticide and Child Health Resources for the Pediatrician

Topic/Resource	Additional Information	Contact Information
Management of acute pesticide poisoning		
Recognition and Management of Pesticide Poisonings	Print: fifth (1999) is available in Spanish, English; 6th edition available 2013	http://www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm
Regional Poison Control Centers		1 (800) 222-1222
Chronic exposure information and specialty consultation		
The National Pesticide Medical Monitoring Program (NPMMP)	Cooperative agreement between Oregon State University and the US EPA. NPMMP provides informational assistance by E-mail in the assessment of human exposure to pesticides	npmmp@oregonstate.edu or by fax at (541) 737-9047
Pediatric Environmental Health Specialty Units (PEHSUs)	Coordinated by the Association of Occupational and Environmental Clinics to provide regional academically based free consultation for health care providers	www.aoec.org/PEHSU.htm; toll-free telephone number (888) 347-AOEC (extension 2632)
Resources for safer approaches to pest control		
US EPA	Consumer information documents	www.epa.gov/oppfead1/Publications/Cit_Guide/citguide.pdf
Citizens Guide to Pest Control and Pesticide Safety	• Household pest control • Alternatives to chemical pesticides • How to choose pesticides • How to use, store, and dispose of them safely • How to prevent pesticide poisoning • How to choose a pest-control company	
Controlling pests	Recommended safest approaches and examples of programs	www.epa.gov/pesticides/controlling/index.htm
The University of California Integrative Pest Management Program	Information on IPM approaches for common home and garden pests	www.ipm.ucdavis.edu
Other resources		
National research programs addressing children's health and pesticides	• NIEHS/EPA Centers for Children's Environmental Health & Disease Prevention Research	www.niehs.nih.gov/research/supported/centers/prevention
	• The National Children's Study	www.nationalchildrensstudy.gov/Pages/default.aspx
US EPA	Pesticide product labels	www.epa.gov/pesticides/regulating/labels/product-labels.htm#projects
The National Library of Medicine "Tox Town"	Section on pesticides that includes a comprehensive and well-organized list of web link resources on pesticides	http://toxtown.nlm.nih.gov/text_version/chemicals.php?id=23

anomalies, pediatric cancers, neurobehavioral and cognitive deficits, and asthma. These are reviewed in the accompanying technical report. The evidence base is most robust for associations to pediatric cancer and adverse neurodevelopment. Multiple case-control studies and evidence reviews support a role for insecticides in risk of brain tumors and acute lymphocytic leukemia. Prospective contemporary birth cohort studies in the United States link early-life exposure to organophosphate insecticides with reductions in IQ and abnormal behaviors associated with attention-deficit/hyperactivity disorder and autism. The need to better understand the health implications of ongoing pesticide use practices on child health has benefited from these observational epidemiologic data.[32]

EXPOSURE PREVENTION APPROACHES

The concerning and expanding evidence base of chronic health consequences of pesticide exposure underscores the importance of efforts aimed at decreasing exposure.

Integrated pest management (IPM) is an established but undersupported approach to pest control designed to minimize and, in some cases, replace the use of pesticide chemicals while achieving acceptable control of pest populations.[33] IPM programs and knowledge have been implemented in agriculture and to address weeds and pest control in residential settings and schools, commercial structures, lawn and turf, and community gardens. Reliable resources are available from the US EPA and University of California—Davis (Table 3). Other local policy approaches in use are posting warning signs of pesticide use, restricting spray zone buffers at schools, or restricting specific types of pesticide products in schools. Pediatricians can

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play a role in promotion of development of model programs and practices in the communities and schools of their patients.

RECOMMENDATIONS

Three overarching principles can be identified: (1) pesticide exposures are common and cause both acute and chronic effects; (2) pediatricians need to be knowledgeable in pesticide identification, counseling, and management; and (3) governmental actions to improve pesticide safety are needed. Whenever new public policy is developed or existing policy is revised, the wide range of consequences of pesticide use on children and their families should be considered. The American Academy of Pediatrics, through its chapters, committees, councils, sections, and staff, can provide information and support for public policy advocacy efforts. See http://www.aap.org/advocacy.html for additional information or contact chapter leadership.

Recommendations to Pediatricians

1. Acute exposures: become familiar with the clinical signs and symptoms of acute intoxication from the major types of pesticides. Be able to translate clinical knowledge about pesticide hazards into an appropriate exposure history for pesticide poisoning.
2. Chronic exposures: become familiar with the subclinical effects of chronic exposures and routes of exposures from the major types of pesticides.
3. Resource identification: know locally available resources for acute toxicity management and chronic low-dose exposure (see Table 3).
4. Pesticide labeling knowledge: Understand the usefulness and limitations of pesticide chemical information on pesticide product labels.
5. Counseling: Ask parents about pesticide use in or around the home to help determine the need for providing targeted anticipatory guidance. Recommend use of minimal-risk products, safe storage practices, and application of IPM (least toxic methods), whenever possible.
6. Advocacy: work with schools and governmental agencies to advocate for application of least toxic pesticides by using IPM principles. Promote community right-to-know procedures when pesticide spraying occurs in public areas.

Recommendations to Government

1. Marketing: ensure that pesticide products as marketed are not attractive to children.
2. Labeling: include chemical ingredient identity on the label and/or the manufacturer's Web site for all product constituents, including inert ingredients, carriers, and solvents. Include a label section specific to "Risks to children," which informs users whether there is evidence that the active or inert ingredients have any known chronic or developmental health concerns for children. Enforce labeling practices that ensure users have adequate information on product contents, acute and chronic toxicity potential, and emergency information. Consider printing or making available labels in Spanish in addition to English.
3. Exposure reduction: set goal to reduce exposure overall. Promote application methods and practices that minimize children's exposure, such as using bait stations and gels, advising against overuse of pediculicides. Promote education regarding proper storage of product.
4. Reporting: make pesticide-related suspected poisoning universally reportable and support a systematic central repository of such incidents to optimize national surveillance.
5. Exportation: aid in identification of least toxic alternatives to pesticide use internationally, and unless safer alternatives are not available or are impossible to implement, ban export of products that are banned or restricted for toxicity concerns in the United States.
6. Safety: continue to evaluate pesticide safety. Enforce community right-to-know procedures when pesticide spraying occurs in public areas. Develop, strengthen, and enforce standards of removal of concerning products for home or child product use. Require development of a human biomarker, such as a urinary or blood measure, that can be used to identify exposure and/or early health implications with new pesticide chemical registration or reregistration of existing products. Developmental toxicity, including endocrine disruption, should be a priority when evaluating new chemicals for licensing or reregistration of existing products.
7. Advance less toxic pesticide alternatives: increase economic incentives for growers who adopt IPM, including less toxic pesticides. Support research to expand and improve IPM in agriculture and nonagricultural pest control.
8. Research: support toxicologic and epidemiologic research to better identify and understand health risks associated with children's exposure to pesticides. Consider supporting another national study of pesticide use in the home and garden setting of US households as a targeted initiative or through cooperation with existing research opportunities (eg, National Children's Study, NHANES).
9. Health provider education and support: support educational efforts to increase the capacity of pediatric health care providers to diagnose and manage acute pesticide

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poisoning and reduce pesticide exposure and potential chronic pesticide effects in children. Provide support to systems such as Poison Control Centers to provide timely, expert advice on exposures. Require the development of diagnostic tests to assist providers with diagnosing (and ruling out) pesticide poisoning.

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ERRATA

Spooner. We Are Still Waiting for Fully Supportive Electronic Health Records in Pediatrics. *Pediatrics*. 2012;130(6):e1674–e1676.

An error occurred in this article by Spooner, titled "We Are Still Waiting for Fully Supportive Electronic Health Records in Pediatrics" published in the December 2012 issue of *Pediatrics* (2012;130[6]:e1674–e1676; originally published online November 19, 2012; doi:10.1542/peds.2012-2724). On page e1674, on line 33, this reads: "The alarming result from the survey was that only 3% of AAP Fellows reported that they had a system that provided all of the items listed by Leu and colleagues." This should have read: "The alarming result from the survey was that only 9.6% of AAP Fellows reported that they had or planned to adopt within 12 months a system that provided all of the five "pediatric-supportive" items listed by Leu and colleagues."

doi:10.1542/peds.2013-0134

Auger et al. Medical Home Quality and Readmission Risk for Children Hospitalized With Asthma Exacerbations. *Pediatrics*. 2013;131(1):64–70

An error occurred in this article by Auger et al, titled "Medical Home Quality and Readmission Risk for Children Hospitalized With Asthma Exacerbations" published in the January 2013 issue of *Pediatrics* (2013;131[1]:64–70; doi:10.1542/2012-1055). On page 69, in Table 2 under the heading Adjusted HR, on the line Medicaid, this reads: "0.28 (0.51–1.34)." This should have read: "0.82 (0.51–1.34)."

doi:10.1542/peds.2013-0187

Council on Environmental Health. Policy Statement: Pesticide Exposure in Children. *Pediatrics*. 2012;130(6):e1757–e1763

A couple of errors occurred in this AAP Policy Statement titled "Pesticide Exposure in Children" published in the December 2012 issue of *Pediatrics* (2012;130[6]:e1757–e1763; originally published online November 26, 2012; doi:10.1542/peds.2012-2757). In Table 2, in the second and third columns where glyphosate is discussed, the words "organic solvent" should be replaced with the word "surfactant." On page e1758, in the first paragraph of the left-hand column, immediately beneath Table 1, the first full sentence should be amended to read: "For many children, diet may be the most influential source, as illustrated by an intervention study that placed children on an organic diet (produced without most conventional pesticides) and observed drastic and immediate decrease in urinary excretion of organophosphate pesticide metabolites."

doi:10.1542/peds.2013-0576

Robert JR, Karr CJ; Council on Environmental Health. Technical Report: Pesticide Exposure in Children. *Pediatrics*. 2012;130(6):e1765–e1788

Several inaccuracies occurred in this AAP Technical Report titled "Pesticide Exposure in Children" published in the December 2012 issue of *Pediatrics* (2012;130[6]:e1765–e1788; originally published online November 26, 2012; doi:10.1542/peds.2012-2758). On page e1773 and in Tables 1 and 2 where the phosphonate herbicide glyphosate is discussed, changes should be noted. In the first paragraph of the first column on page e1773 about acute glyphosate poisoning, the word "intentional" should be substituted for the word "unintentional." In this same paragraph as well as in Tables 1 and 2, the word "surfactant" should replace the words "hydrocarbon solvent" and "organic solvent, respectively." The

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Statement of
Beyond Pesticides

August 19, 2016

Thank you for the opportunity to address the local leaders in Las Cruces, NM. Beyond Pesticides is a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to improve protections from pesticides and promote alternative pest management strategies that reduce or eliminate a reliance on toxic pesticides. Our membership spans the 50 states, the District of Columbia, and groups around the world. This statement is being written on behalf of our supporters and advocates in the City of Las Cruces, NM.

We Support Policies that Reduce Toxic Pesticide Use

Beyond Pesticides strongly encourages lawn care practices and the passage of community-based pesticide policies that stop the unnecessary use of hazardous pesticides applied for aesthetic purposes. This approach to pesticide law is critical to the protection of community health, particularly children and elderly, and vulnerable population groups that suffer from compromised immune and neurological systems, cancer, reproductive problems, respiratory illness and asthma, Parkinson's, Alzheimer's, diabetes, and learning disabilities in and around the City of Las Cruces.

Adverse Effects of Chemical Pesticides

Our country's appetite for pesticides raises grave concerns about the effects of chemical-intensive practices, our relationship to nature, chemical effects at the cellular level, and insect and weed resistance to chemical controls. Of the 30 most commonly used lawn pesticides, 16 are linked to cancer, 17 are endocrine disruptors, 21 are reproductive toxicants, 12 are linked to birth defects, 14 are neurotoxic, 25 cause kidney liver effects, and 26 are irritants.[1] The U.S. Geological Survey has linked pesticide use in urban areas to runoff and pesticide contamination of local waterways.[2] Of the 30 most commonly used lawn pesticides, 20 have a high potential to leach into waterways, 19 have been detected seeping into groundwater, 22 are toxic to birds, 14 are toxic to mammals, 29 are toxic to bees, and all 30 of these chemicals present toxicity concerns for fish or other aquatic organisms. [3]

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[1] Health Effects of 30 Commonly Used Pesticides. 2015. Beyond Pesticides. http://www.beyondpesticides.org/lawn/factsheets/30health.pdf (See Appendix A for a fully cited copy of the fact sheet)
[2] United States Geological Survey. 2007. Pesticides in US Streams and Groundwater. *Environmental Science and Technology.* http://water.usgs.gov/nawqa/pnsp/pubs/files/051507.ESTfeature_gilliom.pdf
[3] Environmental Effects of 30 Commonly Used Lawn Pesticides. 2015. Beyond Pesticides. http://www.beyondpesticides.org/lawn/factsheets/30enviro.pdf (See Appendix B for a fully cited copy of the fact sheet.)

Rachel Carson wrote in *Silent Spring*, "By their very nature, chemical controls are self-defeating, for they have been devised and applied without taking into account the complex biological systems against which they have been blindly hurled. The chemicals may have been pretested against a few individual species, but not against living communities." She warned us to protect the diverse organisms that make up a healthy ecosystem, including bees, birds, butterflies and other pollinators.

Pesticide-Induced Diseases

The scientific literature documents elevated rates of chronic diseases among people exposed to pesticides, with increasing numbers of studies associated with both specific illnesses and a range of illnesses. Beyond Pesticides' Pesticide-Induced Diseases Database[4] documents over 750 studies linked to human health effects. Of which, there are 359 studies on cancer; 107 studies on sexual and reproductive dysfunction; 102 studies on Parkinson's disease; 87 studies on learning and developmental disorders; 33 studies on birth defects; 32 studies on asthma; 18 studies on diabetes; and 12 studies on Alzheimer's disease.

The studies in the database show that our current approach to restricting pesticide use through risk assessment-based mitigation measures is not working. This failed human experiment must be ended. The warnings of those who have expressed concerns about risk assessment, such as EPA Administrator under Presidents Nixon and Reagan, William Ruckelshaus, have been borne out by three decades of use and study. Mr. Ruckelshaus in 1984 said, "We should remember that risk assessment data can be like the captured spy: If you torture it long enough, it will tell you anything you want to know." EPA's risk assessment fails to look at chemical mixtures, synergistic effects, certain health endpoints (such as endocrine disruption), disproportionate effects to vulnerable population groups, and regular noncompliance with product label directions. These deficiencies contribute to its severe limitations in defining real world poisoning, as captured by epidemiologic studies in the database.

Key Studies:

Cancer

- In 1999, research published by the American Cancer Society showed an increased risk for Non-Hodgkin's lymphoma (NHL) for people exposed to common herbicides and fungicides, particularly the weedkiller mecoprop (MCPP). Researchers also found that people exposed to glyphosate (found in Roundup®) are 2.7 times more likely to develop NHL. [Hardell, L., et al. 1999. Cancer 85(6):1353-1360]
- A population based, case control study of Long Island, New York breast cancer cases finds an increased risk associated with: (a) lifetime residential pesticide use (OR 1.39); (b) application of lawn insecticides themselves (OR 1.56) and is higher if it is in liquid form (OR 1.77) or a combination of product type for outdoor plants (OR 1.83); (c) professional application of pesticides in a vegetable and fruit garden more than doubled (OR 2.29); and, (d) application of pesticides for insects or diseases on outdoor plants by self (OR 1.58) or by professional (OR 1.79). *[Teitelbaum, S.L., et al. 2007. American Journal of Epidemiology 165(6):643-651.]*

[4] Beyond Pesticides. 2016. Pesticide Induced Diseases Database. http://www.beyondpesticides.org/resources/pesticide-induced-diseases-database/overview

- In an Agricultural Health Study, researchers find that organophosphate (OP) use was associated with an elevated risk of breast cancer. Malathion, the most commonly reported OP, was associated with increased risk of thyroid cancer and decreased risk of non-Hodgkin lymphoma. Diazinon use was associated with ovarian cancer. Authors observed increased risk with OP use for several hormonally-related cancers, including breast, thyroid and ovary, suggesting potential for hormonally-mediated effects. *[Lerro CC, Koutros S, Andreotti G, Friesen MC, et al. 2015. Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. Occup Environ Med. 72(10):736-44]*
- Two studies published in 2013 found that significant associations were observed for parents potentially exposed to pesticides in occupational settings and the occurrence of brain tumor in their offspring. Increased risks are seen for prenatal exposure windows (exposure during pregnancy).
  [Van Maele-Fabry G, Hoet P, Lison D. 2013. Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: a systematic review and meta-analysis. Environ Int. 56:19-31; Greenop KR, Peters S, Bailey HD, Fritschi L, et al. 2013. Exposure to pesticides and the risk of childhood brain tumors. Cancer Causes Control. 24(7):1269-78.]
- One 2013 review reports that epidemiological, molecular biology, and toxicological evidence emerging from recent literature assessing the link between specific pesticides and several cancers including prostate cancer, non-Hodgkin lymphoma, leukemia, multiple myeloma, and breast cancer strongly suggest that the public health problem is real.
  [Alavanja MC, Ross MK, Bonner MR. 2013. Increased cancer burden among pesticide applicators and others due to pesticide exposure. CA Cancer J Clin. 63(2):120-42.]
- A systemic review of published studies on the association between residential expsoure to pesticides and childhood leukemia finds that exposure during and after pregnancy was positively associated with childhood leukaemia, with the strongest risk for exposure during pregnancy.
  [Van Maele-Fabry G, Lantin AC, et al. 2011. Residential exposures to pesticides and childhood leukemia. Environ Int.37(1):280-91]

Parkinson's Disease

- A 2015 study shows that environmental factors, such as neurotoxins, pesticides, insecticides, dopamine itself, and genetic mutations in Parkinson's Disease (PD)-associated proteins contribute to mitochondrial dysfunction which precedes reactive oxygen species formation. PD is a chronic, progressive neurological disease that is associated with a loss of dopaminergic neurons in the brain. The molecular mechanisms underlying the loss of these neurons still remain elusive, however oxidative stress is thought to play an important role in dopaminergic neurotoxicity. *[Blesa J, Trigo-Damas I, Quiroga-Varela A, Jackson-Lewis VR. 2015. Front Neuroanat. 8(9):91]*
- One 2015 study indicates a link between Parkinson's disease and cypermethrin. PD is a motor scarcity disorder characterized by the striatal dopamine deficiency owing to the selective degeneration of the nigrostriatal dopaminergic neurons. While oxidative stress is implicated in PD, prolonged exposure to moderate dose of cypermethrin induces

Parkinsonism. The results demonstrate that cypermethrin alters the status of oxidative stress indicators and impairs antioxidant defence system of the peripheral blood, which could be effectively salvaged by minocycline or syndopa. *[Tripathi P, Singh A, Agrawal S, et al. 2014. J Physiol Biochem. 70(4):915-24.]*

- A 2015 Study shows a significant association of pesticides with tremor dominant PD in men, the most typical PD presentation. High intensity exposure to insecticides was positively associated with PD.
  [Moisan F, Spinosi J, Delabre L, et al. 2015. Association of Parkinson's Disease and Its Subtypes with Agricultural Pesticide Exposures in Men: A Case-Control Study in France. Environ Health Perspec. DOI:10.1289/ehp.1307970]
- One 2013 study's results provide evidence that certain pesticides play a role in the etiology of PD and suggest that genetic variation in certain genes might exacerbate the toxic effects of pesticide exposures.
  [Rhodes SL, Fitzmaurice AG, Cockburn M, et al. 2013. Pesticides that inhibit the ubiquitin-proteasome system: Effect measure modification by genetic variation in SKP1 in Parkinson's disease. Environ Res. pii: S0013-9351(13)00143-6.]
- One meta-analysis of the scientific literature affirms the evidence that exposure to herbicides and insecticides increase the risk of PD.
  [van der Mark, M, Brouwer, M et al. 2012. Is Pesticide Use Related to Parkinson Disease? Some Clues to Heterogeneity in Study Results. Environ Health Perspect. 120(3):340-347]
- Another study finds evidence that genetic susceptibility either in metabolism, elimination and transport of pesticides or in the extent of mitochondrial dysfunction, oxidative stress and neuronal loss may predispose individuals to PD if they have been exposed to pesticides.
  [*Dardiotis E, Xiromerisiou G, et al. 2013. The interplay between environmental and genetic factors in Parkinson's disease susceptibility: the evidence for pesticides. Toxicology. 307:17-23]*

Sexual and Reproductive Dysfunction

- A 2013 systematic review finds evidence that continues to support the hypothesis that exposures to pesticides at environmentally or occupationally relevant levels may be associated with decreased
  sperm health, with significant associations between pesticide exposure and sperm parameters. A decrease in sperm concentration was the most commonly reported finding.
  [Martenies, SE, Perry, MJ. 2013. Environmental and occupational pesticide exposure and human sperm parameters: a systematic review. Toxicology. 307:66-73
- Preliminary evidence exist that atrazine exposure, even at levels below the US EPA water quality standards, is associated with increased menstrual cycle irregularity, longer follicular phases, and decreased levels of menstrual cycle endocrine biomarkers of infertile ovulatory cycles.
  [Cragin LA, Kesner JS, Bachand AM, et al. 2011. Menstrual cycle characteristics and reproductive hormone levels in women exposed to atrazine in drinking water. Environ Res. 111(8):1293-301].

- One study reports pesticides currently used in agriculture contribute to differences in semen quality. Men with high levels of alachlor, atrazine or diazinon in their urine were significantly more likely to have poor sperm quality.
  [Swan, S.H. et al. 2003. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect; 111(12): 1478–1484].

Key Studies: Glyphosate

On March 20, 2014, the International Agency for Research on Cancer (IARC) released its finding that concludes there is sufficient evidence that glyphosate (Roundup™) causes cancer in humans based on laboratory animal studies.[5] By assigning glyphosate a 2A rating, the agency gave this toxic herbicide the highest possible rating for carcinogenicity based on standardized scientific testing methods for identifying cancer effects to prevent human exposure. The only higher cancer rating possible is derived from after-the-fact human data, usually based on occupational exposure test data. Meanwhile, it may be years before EPA considers this finding and takes appropriate regulatory action.

A review of the scientific literature links glyphosate, one of the most popular weed killers in the U.S. and the active ingredient in Roundup, to a wide range of diseases through a mechanism that modifies DNA functioning, adding a new even more troubling dimension to the herbicide's cancer classification by IARC. According to the most recent review, *Glyphosate pathways to modern disease V: Amino acid analogue of glycine in diverse proteins*, conducted by independent scientists Anthony Samsel, Ph.D. and Stephanie Seneff, Ph.D., a scientist at Massachusetts Institute of Technology (MIT), glyphosate acts as a glycine analogue that incorporates into peptides during protein synthesis. In this process, it alters a number of proteins that depend on conserved glycine for proper function. According to the authors, glyphosate substitution for glycine correlates with several diseases, including diabetes, obesity, asthma, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease, among others.

A research study published in the journal Environmental Health links chronic, ultra-low dose exposure to glyphosate in drinking water to adverse impacts on the health of liver and kidneys. The study, *Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure*, is the latest in a string of data showing unacceptable risks resulting from exposure to glyphosate and products formulated with the chemical, like Monsanto's Roundup.[6]

A 2013 study finds that low and environmentally relevant concentrations of glyphosate possess estrogenic activity. In this study, glyphosate exerted proliferative effects in human hormone-dependent breast cancer, T47D cells. Interestingly, the authors of the study found that there was an additive estrogenic effect between glyphosate and genistein, a phytoestrogen in soybeans, which they note warrants further research.[7]

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[5] International Agency for Research on Cancer, World Health Organization. 2015. IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides. http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf.

[6] *Mesnage R, Arno M, Costanzo M, Malatesta M, Seralini GE, Antoniou MN. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. Environ Health. 2015;14:70 http://www.ehjournal.net/content/14/1/70.*

[7] Thongprakaisang S, Thiantanawat A, et al. 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol. pii: S0278-6915(13)00363-3. doi: 10.1016/j.fct.2013.05.057.

Additionally, one study found that people exposed to glyphosate are 2.7 times more likely to contract non-Hodgkin's Lymphoma (NHL).[8] Similarly, in a study of Swedish men showed that glyphosate exposure was *significantly* associated with an increased risk of NHL, and hairy cell leukemia, a rare subtype of NHL.[9]

Key Studies: Neonicotinoids

Since 2006, honey bees and other pollinators in the U.S. and throughout the world have experienced ongoing and rapid population declines. The continuation of this crisis threatens the stability of ecosystems, the economy, and our food supply, as one in three bites of food are dependent on pollinator services. Pollination services are valued at over $125 billion globally. According to a 2014 Presidential Memorandum, pollinators provide $24 billion annually to the economy and honey bees account for $15 billion of that amount.[10] Similarly, native pollinators (such as bumblebees, squash bees, and mason bees) contribute over $3 billion in pollination services to the U.S. agricultural economy, and contribution to pollination of garden plants.

A recently published study by Mogren and Lundgren (2016) confirms that conservation areas set aside for pollinator habitat in agricultural regions do not provide spatial or temporal refuge from harmful bee-toxic pesticides.[11]

Led by the Institute of Bee Health at the University of Bern, researchers have found evidence that two commonly used neonicotinoid insecticides, thiamethoxam and clothianidin, have a significant adverse effect on the reproductive ability of male honey bees (drones) and queen bees in managed and wild colonies. The study, *Neonicotinoid insecticides can serve as inadvertent insect contraceptives*, published in *Royal Society Journal Proceedings* B, focuses on the differences in lifespan and viability of sperm throughout exposed and unexposed drones.[12]

A recent government-sponsored national survey indicates that U.S. beekeepers experienced a 44% annual mortality rate with their hives between April 2015 and April 2016. Winter loss rates during this time period increased from 22.3 percent in the previous winter to 28.1 percent this past winter, while summer loss rates increased from 25.3 percent to 28.1 percent..[13]

Systemic pesticides like the neonicotinoid class of insecticides, have been shown, even at low levels, to impair foraging, navigational, and learning behavior in bees, as well as suppress their immune system to the point of increasing their susceptibility to pathogens and disease.[14] Concentrations of neonicotinoids in soils, waterways, field margin plants, and floral resources overlap substantially with concentrations that control pests in crops, and commonly exceed

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[8] Hardell, L., & Eriksson, M. 1999. A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides. Cancer, 85(6), 1353–1360.

[9] Hardell L, Eriksson M, & Nordstrom M. 2002. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma*, 43(5), 1043-1049.

[10] White House Blog: New Steps to Protect Pollinators, Critical Contributors to Our Nation's Economy http://www.whitehouse.gov/blog/2014/06/20/new-steps-protect-pollinators-critical-contributors-our-nation-s-economy.

[11] Mogren, C and Lundgren J. 2016. Neonicotinoid-contaminated pollinator strips adjacent to cropland reduce honey bee nutritional status. *Scientific Reports* 6, Article number: 29608.

[12] Lars Straub, Laura Villamar-Bouza, Selina Bruckner, Panuwan Chantawannakul, Laurent Gauthier, Kitiphong Khongphinitbunjong, Gina Retschnig, Aline Troxler, Beatriz Vidondo, Peter Neumann, Geoffrey R. Williams Proc. R. Soc. B 2016 283 20160506; DOI: 10.1098/rspb.2016.0506. Published 27 July 2016.

[13] Bee Informed Partnership. Preliminary Results: Honey Bee Colony Losses in the United States, 2015-2016. https://beeinformed.org/2016/05/10/nations-beekeepers-lost-44-percent-of-bees-in-2015-16/.

[14] Harriott, N. 2014, Bees, Birds and Beneficials: How fields of poison adversely affect non-target organisms. Pesticides and You. Vol. 33, No. 4 Winter 2013-14.

levels that are known to kill beneficial organisms.[15] Because these chemicals are broad-spectrum insecticides, beneficial soil dwelling insects, benthic aquatic insects, grain-eating vertebrates, along with pollinators are also victims of these systemic chemicals. Birds are also at risk from neonicotinoids, as one study demonstrates that a single corn kernel coated with a neonicotinoid is toxic enough to kill a songbird.[16] Further, research from the Netherlands has showed that the most severe bird population declines occur in those areas where neonicotinoid pollution is highest.[17] Another study, this time from researchers at the University of Guelph, finds that at very low levels the neonicotinoid pesticide thiamethoxam affects the foraging behavior of bumble bees, changing their floral preferences, hindering their ability to learn and extract nectar and pollen. According to the authors of this Canadian study, "Chronic exposure to a neonicotinoid pesticide alters the interaction between bumblebees and wild plants, "published in the journal Functional Ecology, it is the first to explore how pesticides may impact the ability of bumble bees to forage from common wildflowers that have complex shapes such as white clover and bird's foot trefoil. The researchers found that bumble bees exposed to environmental levels of thiamethoxam (10ppb) took longer to collect pollen than unexposed bees, as well as foraged from different flowers.

To compound these findings, surveys by the U.S. Geological Survey (USGS), also documents similar risks from residues, most commonly neonicotinoids, frequently in surface waters, and in 70 percent of the native bees.[18][19] Morrissey at al. confirms all this in a review which finds that neonicotinoid concentrations detected in aquatic environments pose risks to aquatic invertebrates and the ecosystems they support.[20]

Once in soil, neonicotinoids have a high propensity to leach into groundwater, streams, and ponds. For instance, one California study (2012) reports 89% of water samples taken from rivers, creeks, and drains in the state contain imidacloprid.[21]

Additionally, Rundlof et al., (2015) reports that pesticide coated seed plantings reduced wild bee density, solitary bee nesting, and bumblebee colony growth and reproduction under field conditions.[22] Furthermore, environmental levels of neonicotinoid and other systemic pesticides frequently exceed federal standards and are thus likely to have large-scale and wide ranging negative biological and ecological impacts on a wide range of non-target invertebrates in terrestrial, aquatic, marine and benthic habitats.[23]

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[15] Goulson, D. 2013. REVIEW: An overview of the environmental risks posed by neonicotinoid insecticides. *Journal of Applied Ecology.* 50: 977–987. doi: 10.1111/1365-2664.12111.

[16] Mineau P, Whiteside M. 2013. Pesticide Acute Toxicity Is a Better Correlate of U.S. Grassland Bird Declines than Agricultural Intensification. PLoS ONE 8(2): e57457.

[17] Hallmann CA, et al. 2014. Declines in insectivorous birds are associated with high neonicotinoid concentrations. *Nature* doi:10.1038/nature13531.

[18] Hladik, M and Kolpin, D. 2015. First national-scale reconnaissance of neonicotinoid insecticides in streams across the USA. Environ Chem http://dx.doi.org/10.1071/EN15061.

[19] Hladik, Michelle, et al. 2015. Exposure of native bees foraging in an agricultural landscape to current-use pesticides. *Science of The Total Environment*, doi:10.1016/j.scitotenv.2015.10.077.

[20] Morrissey, C. et al. 2015. Neonicotinoid contamination of global surface waters and associated risk to aquatic invertebrates: A review. *Environment International.* doi:10.1016/j.envint.2014.10.024.

[21] Starner, K et al. 2012. Bulletin of Environmental Contamination and Toxicology

[22] Rundlöf M, Andersson GK, Bommarco R, Fries I, et al. 2015. Seed coating with a neonicotinoid insecticide negatively affects wild bees. *Nature.* 521(7550):77-80.

[23] Pisa LW, Amaral-Rogers V, Belzunces LP, Bonmatin JM, et al. 2015. Effects of neonicotinoids and fipronil on non-target invertebrates. *Environ Sci Pollut Res Int.* 22(1):68-102.

In 2014, an international meta-analysis of approximately 800 peer-reviewed studies on the impact of systemic pesticides, conducted by the International Union for the Conservation of Nature, known as the Task Force on Systemic Pesticides (IUCN Task Force) found that:[24]

- Neonicotinoids are present in the environment "at levels that are known to cause lethal and sublethal effects on a wide range of terrestrial (including soil) and aquatic microorganisms, invertebrates and vertebrates."
- The active ingredients persist, particularly in soils, with half-lives of months and, in some cases, years, and they accumulate. This increases their toxicity by increasing the duration of exposure of non-target species.
- The metabolites of neonicotinoids are often as or more toxic than the active ingredients.
- The weight of the published evidence is very strong that the acute and chronic effects pose a serious risk of harm to colonies/populations of honey bees, bumblebees, and other pollinators.
- The most affected group of species include soil invertebrates and insect pollinators, with high exposure through air and plants and medium exposure through water. Invertebrates exposed to contaminated pollen, nectar and fluids are harmed at "field-realistic" concentrations.

The European Food Safety Authority (EFSA) determined that the most widely used neonicotinoids –imidacloprid, clothianidin and thiamethoxam– pose unacceptable hazards to bees, prompting the European Union to suspend their use on agricultural crops in 2013. This agency also published an opinion report linking two neonicotinoids to adverse effects on the developing human nervous system.[25] According to the report, data suggests that the neonicotinoid chemicals (imidacloprid, acetamiprid) under review are responsible for the excitation or desensitization or both of nicotinic acetylcholine receptors (nAChRs), which may affect the developing mammalian nervous system, as is known to occur with nicotine. The agency concludes that the two neonicotinoid compounds may affect neuronal development and function.

In recognition of the long-term impacts systemic pesticides have on the environment, the U.S., the Fish and Wildlife Service (FWS) announced in June 2014 its decision to phase out neonicotinoid use. The service states that neonicotinoids "can be effective against targeted pests, but may also adversely impact many non-target insects," and that "the prophylactic use of neonicotinoids and the potential broad-spectrum adverse effects to non-target species do not meet the intent of IPM principles or the Service's Biological Integrity, Diversity, and Environmental Health (BIDEH) policy.

Atrazine Ecological Risk Discussion by EPA

EPA has released its triazine ecological risk assessments for atrazine and its chemical cousins simazine, and propazine. The assessments evaluated risks to animals and plants including,

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[24] Van der Sluijs JP, et al. 2014. Conclusions of the Worldwide Integrated Assessment on the risks of neonicotinoids and fipronil to biodiversity and ecosystem functioning. *Environ Sci Pollut Res.* doi:10.1007/s11356-014-3229-5.

[25] EFSA Panel on Plant Protection Products and their Residues (PPR). Scientific Opinion on the developmental neurotoxicity potential of acetamiprid and imidacloprid. EFSA Journal 2013;11(12):3471. doi:10.2903/j.efsa.2013.3471.

amphibians, birds, mammals, fish, reptiles, aquatic invertebrates, aquatic plant communities, and terrestrial plants. EPA is currently in the registration review process for these chemicals. For atrazine, EPA concludes, "aquatic plant communities are impacted in many areas where atrazine use is heaviest, and there is potential chronic risks to fish, amphibians, and aquatic invertebrate in these same locations. In the terrestrial environment, there are risk concerns for mammals, birds, reptiles, plants and plant communities across the country for many of the atrazine uses." Levels of concerns were exceeded by as much as 200-fold for some organisms! When it comes to amphibians, impacts which have been extensively documented by researchers like Tyrone Hayes, PhD, at the University of California, Berkeley, EPA finds that "there is potential for chronic risks to amphibians based on multiple effects endpoint concentrations compared to measured and predicted surface water concentrations."[26] Previous scientific reviews, like the 2009 analysis of more than 100 scientific studies conducted on atrazine, found evidence that atrazine harms fish and frogs.[27]

The results are similar for simazine and propazine, since all three triazines show similar effects at similar concentrations. Simazine, which is frequently detected in surface water and groundwater, was found to have potential chronic risks to mammals and birds. Simazine spray drift and runoff can also impact non-target plants. For propazine, which has minimal uses (preemergent control in sorghum and container grown ornamentals in greenhouses only), the agency identified chronic risks to mammals, birds and non-target plants. All three chemicals are mobile and persistent in the environment, which results in water contamination. According to the U.S. Geological Survey (USGS), atrazine is one of the most frequently detected pesticides, found at concentrations at or above aquatic benchmarks, and is also frequently detected in shallow ground water in agricultural areas, and in urban streams.[28]

Children's Vulnerability

Children face unique dangers from pesticide exposure. The National Academy of Sciences reports that children are more susceptible to chemicals than adults and estimates that 50% of lifetime pesticide exposures occur during the first five years of life.[29] In fact, studies show children's developing organs create "early windows of great vulnerability" during which exposure to pesticides can cause great damage.[30] Additionally, according to researchers at the University of California-Berkeley School of Public Health, exposure to pesticides while in the womb may increase the odds that a child will have attention deficit hyperactivity disorder (ADHD).[31]

As EPA points out in its document, *Pesticides and Their Impact on Children: Keep Facts and Talking Points*:[32]

- "Due to key differences in physiology and behavior, children are more susceptible to environmental hazards than adults."

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[26] Hayes, Tyrone, 2004. Wreaking Havoc with Life, *Pesticides and You* (2)24: 10-13

[27] Rohr, Jason R.; McCoy, Krista A. 2009. A Qualitative Meta-Analysis Reveals Consistent Effects of Atrazine on Freshwater Fish and Amphibians *Environ Health Perspect* 118:20-32 (2010)

[28] Tillitt, Donald E. et al. 2010, Atrazine reduces reproduction in fathead minnow (Pimephales promelas) Aquatic Toxicology, (2)99:149-159

[29] National Research Council, National Academy of Sciences. 1993. Pesticides in the Diets of Infants and Children, National Academy Press, Washington, DC: 184-185.

[30] Landrigan, P.J., L Claudio, SB Markowitz, et al. 1999. "Pesticides and inner-city children: exposures, risks, and prevention." Environmental Health Perspectives 107 (Suppl 3): 431-437.

[31] Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, et al. 2010. Organophosphate Pesticide Exposure and Attention in Young Mexican-American Children: The CHAMACOS Study. Environ Health Perspect 118:1768-1774.

[32] See: https://www.epa.gov/sites/production/files/2015-12/documents/pest-impact-hsstaff.pdf

- "Children spend more time outdoors on grass, playing fields, and play equipment where pesticides may be present."
- "Children's hand-to-mouth contact is more frequent, exposing them to toxins through ingestion."

In 2012, the American Academy of Pediatrics (AAP) released a landmark policy statement, *Pesticide Exposure in Children*, on the effects of pesticide exposure in children, acknowledging the risks to children from both acute and chronic effects.[33] AAP's statement notes that, "Children encounter pesticides daily and have unique susceptibilities to their potential toxicity." The report discusses how kids are exposed to pesticides every day in air, food, dust, and soil. Children also frequently come into contact with pesticide residue on pets and treated lawns, gardens, and indoor spaces.

Pesticides, such as glyphosate and its formulated products (Roundup) and 2,4-D, both widely used on turf and lawns, can be tracked indoors resulting in long-term exposures. Scientific studies show that pesticides, like 2,4-D, that are applied to lawns drift and are tracked indoors where they settle in dust, air and on surfaces and may remain in carpets.[34,35] Pesticides in these environments may increase the risk of developing asthma, exacerbate a previous asthmatic condition, or even trigger asthma attacks by increasing bronchial hyper-responsiveness.[36] This is especially important as infants crawling behavior and proximity to the floor account for a greater potential than adults for dermal and inhalation exposure to contaminants on carpets, floors, lawns, and soil.[37]

A study published in the Journal of the National Cancer Institute finds that household and garden pesticide use can increase the risk of childhood leukemia as much as seven-fold.[38] Similarly, a 2010 meta-analysis on residential pesticide use and childhood leukemia finds an association with exposure during pregnancy, as well as to insecticides and herbicides. An association is also found for exposure to insecticides during childhood.[39]

Prenatal exposures to pesticides can also have long-lasting impacts on infants and children. Herbicides, like glyphosate, can adversely affect embryonic, placental and umbilical cord cells, and can impact fetal development. Preconception exposures to glyphosate were found to moderately increase the risk for spontaneous abortions in mothers exposed to glyphosate products.[40] One 2010 analysis observed that women who use pesticides in their homes or yards were two times more likely to have offspring with neural tube defects than women who did not use pesticides.[41] Studies also find that pesticides, like 2,4-D, can also pass from mother to child through umbilical cord blood and breast milk.[42,43]

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[33] Roberts JR, Karr CJ; Council On Environmental Health. 2012. Pesticide exposure in children. Pediatrics. 2012 Dec; 130(6):e1765-88.
[34] Nishioka, M., et al. 1996. Measuring lawn transport of lawn-applied herbicide acids from turf. Env Science Technology, 30:3313-3320.
[35] Nishioka, M., et al. 2001. "Distribution of 2,4-D in Air and on Surfaces Inside Residences. Environmental Health Perspectives 109(11).
[36] Hernández, AF., Parrón, T. and Alarcón, R. 2011. Pesticides and asthma. Curr Opin Allergy Clin Immunol.11(2):90-6.
[37] Bearer, CF. 2000. The special and unique vulnerability of children to environmental hazards. Neurotoxicology 21: 925-934; and Fenske, R., et al. 1990. Potential Exposure and Health Risks of Infants following Indoor Residential Pesticide Applications. Am J. Public Health. 80:689-693.
[38] Lowengart, R. et al. 1987. Childhood Leukemia and Parent's Occupational and Home Exposures. Journal of the National Cancer Institute. 79:39.
[39] Turner, M.C., et al. 2010. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. Environ Health Perspect 118(1):33-41.
[40] Arbuckle, T. E., Lin, Z., & Mery, L. S. (2001). An Exploratory Analysis of the Effect of Pesticide Exposure on the Risk of Spontaneous Abortion in an Ontario Farm Population. Environ Health Perspect, 109, 851–857.
[41] Brender, JD., et al. 2010. Maternal Pesticide Exposure and Neural Tube Defects in Mexican Americans. Ann Epidemiol. 20(1):16-22.
[42] Pohl, HR., et al. 2000. Breast-feeding exposure of infants to selected pesticides. Toxicol Ind Health. 16:65-77.
[43] Sturtz, N., et al. 2000. Detection of 2,4-dichlorophenoxyacetic acid (2,4-D) residues in neonates breast-fed by 2,4-D exposed dams. Neurotoxicology 21(1-2): 147-54.

Biomonitoring testing has also documented pesticide residues in children. Residues of lawn pesticides, like 2,4-D and mecoprop, were found in 15 percent of children tested, ages three to seven, whose parents had recently applied the lawn chemicals. Breakdown products of organophosphate insecticides were present in 98.7 percent of children tested.[44] In one study, children in areas where glyphosate is routinely applied were found to have detectable concentrations in their urine.[45] While glyphosate is excreted quickly from the body, it was concluded, "a part may be retained or conjugated with other compounds that can stimulate biochemical and physiological responses." A 2002 study finds children born to parents exposed to glyphosate show a higher incidence of attention deficit disorder and hyperactivity.[46]

Pesticides and Pets

Studies find that dogs exposed to herbicide-treated lawns and gardens can double their chance of developing canine lymphoma (1) and may increase the risk of bladder cancer in certain breeds by four to seven times (2).

(1) Scottish Terriers exposed to pesticide-treated lawns and gardens are more likely to develop transitional cell carcinoma of the bladder, a type of cancer.[47]
(2) "Statistically significant" increase in the risk of canine malignant lymphoma in dogs when exposed to herbicides, particularly 2,4-D, commonly used on lawns and in "weed and feed" products.[48]

Adverse Effects to Wildlife

While the data is pouring in on intersex species in waterways that surround urban and suburban areas and there are certainly a mix a factors, the contribution of runoff from suburban landscapes are seen as an important contributor. In Suburbanization, estrogen contamination, and sex ratio in wild amphibian populations, the authors from Yale University's School of Forestry and Environmental Studies and the U.S. Geological Survey (USGS) find the following: "While there is evidence that such endocrine disruption can result from the application of agricultural pesticides and through exposure to wastewater effluent, we have identified a diversity of endocrine disrupting chemicals within suburban neighborhoods. Sampling populations of a local frog species, we found a strong association between the degree of landscape development and frog offspring sex ratio. Our study points to rarely studied contamination sources, like vegetation landscaping and impervious surface runoff, that may be associated with endocrine disruption environments around suburban homes."[49]

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[44] Valcke, Mathieu, et al. 2004. Characterization of exposure to pesticides used in average residential homes with children ages 3 to 7 in Quebec. National Institute of Public Health, Québec.
[45] Acquavella, J. F., et al. (2004). Glyphosate Biomonitoring for Farmers and Their Families: Results from the Farm Family Exposure Study. Environ Health Perspect. 112(3), 321-326.
[46] Cox C. 2004. Journal of Pesticide Reform. Vol. 24 (4) citing: Garry, V.F. et al. 2002. "Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota." Environ. Health Persp. 110 (Suppl. 3):441-449.
[47] Hayes, H. et al., 1991. "Case-control study of canine malignant lymphoma: positive association with dog owner's use of 2,4-D acid herbicides," Journal of the National Cancer Institute, 83(17):1226.
[48] Glickman, Lawrence, et al. 2004. "Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers," Journal of the American Veterinary Medical Association 224(8):1290-1297.
[49] Lambert, M.R., Giller, G.S.J., Barber, L.B., Fitzgerald, K.C., Skelly, D.K., 2015. Suburbanization, estrogen contamination, and sex ratio in wild amphibian populations. Proc. Natl. Acad. Sci. 112, 11881e11886.

The Failure of EPA Regulatory System

Pesticides are, by their very nature, poisons. The Federal Insecticide Fungicide and Rodenticide Act (FIFRA), the law governing pesticide registration and use in the U.S., relies on a risk-benefit assessment, which allows the use of pesticides with known hazards based on the judgment that certain levels of risk are acceptable. However, EPA, which performs risk assessments, assumes that a pesticide would not be marketed if there were no benefits to using it and therefore no risk/benefit analysis is conducted or evaluated by the agency "up front." Registration of a pesticide by EPA does not guarantee that the chemical is "safe," particularly for vulnerable populations such as pregnant mothers, children, pets, and those with chemical sensitivities. Below are examples of concern within the pesticide registration process. These factors should give pause to lawmakers tasked with protecting public and environmental health, and supports action, such as Bill 52-14, to prohibit toxic pesticides and, in so doing, encourage alternatives.

Conditional Registration. EPA will often approve the use of a pesticide without all of the necessary data required to fully register the chemical, and will assign it a "conditional" registration. The agency assumes that while it waits for additional data the product would not cause adverse impacts that would prevent an eventual full registration. A recent report (2013) from the Government Accountability Office, entitled *EPA Should Take Steps to improve Its Oversight of Conditional Registrations,*[50] strongly criticizes this process, citing poor internal management of data requirements, constituting an "internal control weakness." The report states, "The extent to which EPA ensures that companies submit additional required data and EPA reviews these data is unknown. Specifically, EPA does not have a reliable system, such as an automated data system, to track key information related to conditional registrations, including whether companies have submitted additional data within required time frames." However, these recommendations do not go far enough. Pesticides without all the data required for a full understanding of human and environmental toxicity should not be allowed on the market. Several historic examples exist of pesticides that have been restricted or canceled due to health or environmental risks decades after first registration. Chlorpyrifos, an organophosphate insecticide, which is associated with numerous adverse health effects, including reproductive and neurotoxic effects, had its residential uses canceled in 2001. Others, like propoxur, diazinon, carbaryl, aldicarb, carbofuran, and most recently endosulfan, have seen their uses restricted or canceled after years on the market due to unreasonable human and environmental effects. Recently, a product manufactured by DuPont, Imprelis, with the active ingredient aminocyclopyrachlor, was removed from the market only two years after EPA approval under conditional registration.[51] Marketed as a broadleaf weed killer, Imprelis was found to damage and kill trees. However, in EPA's registration of the chemical, the agency noted, "In accordance with FIFRA Section 3(c)(7)(C), the Agency believes that the conditional registration of aminocyclopyrachlor will not cause any unreasonable adverse effects to human health or to the environment and that the use of the pesticide is in the public's interest; and is therefore granting the conditional registration."[52]

Failure to test or disclose inert ingredients. Despite their innocuous name, inert ingredients in

[50] Government Accountability Office. August 2013. EPA Should Take Steps to Improve Its Oversight of Conditional Registrations. GAO-13-145. http://www.gao.gov/products/GAO-13-145.

[51] Environmental Protection Agency. June 2012. Imprelis and Investigation of Damage to Trees. http://www.epa.gov/pesticides/regulating/imprelis.html.

[52] Environmental Protection Agency. August 2010. Registration of the New Active Ingredient Aminocyclopyrachlor for Use on Non-Crop Areas, Sod Farms, Turf, and Residential Lawns. http://www.regulations.gov/contentStreamer?objectId=0900006480b405d8&disposition=attachment&contentType=pdf.

pesticide formulations are neither chemically, biologically, or toxicologically inert; in fact they can be just as toxic as the active ingredient. Quite often, inert ingredients constitute over 95% of the pesticide product. In general, inert ingredients are minimally evaluated, even though many are known to state, federal, and international agencies to be hazardous to human health. For example, until October 23, 2014,[53] creosols, chemicals listed as hazardous waste under Superfund regulations and considered possible human carcinogens by EPA,[54] were allowed in pesticide formulations without any disclosure requirement. EPA recently took action to remove cresols and 71 other inert ingredients from inclusion in pesticide formulations as a result of petitions from health and consumer groups. However, numerous hazardous inerts remain. For example, a 2009 study, entitled *Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells*,[55] found that an inert ingredient in formulations of the weed killer Roundup (glyphosate), polyethoxlated tallowamine (POEA), is more toxic to human cells than the active ingredient glyphosate, and, in fact, amplifies the toxicity of the product – an effect not tested or accounted for by the pesticide registration process. A 2014 study, *Major pesticides are more toxic to human cells than their declared active principle*, found inert ingredients had the potential to magnify the effects of active ingredients by 1,000 fold.

Pesticide manufacturers argue against the disclosure of inert ingredients on pesticide product labels, maintaining that this information is proprietary. Limited review of inert ingredients in pesticide products highlights a significant flaw with the regulatory process. Rather than adopt a precautionary approach when it comes to chemicals with unknown toxicity, EPA allows uncertainties and relies on flawed risk assessments that do not adequately address exposure and hazard. Then, when data becomes available on hazards, these pesticides, both active ingredients and inerts, have already left a toxic trail on the environment and people's well-being.

Label Restrictions Inadequate. From a public health perspective, an inadequate regulatory system results in a pesticide product label that is also inadequate, failing to restrict use or convey hazard information. While a resident may be able to glean some acute toxicity data, chronic or long-term effects will not be found on products' labels. Despite certain pesticides being linked to health endpoints, such as exacerbation of asthma,[56] learning disabilities,[57] or behavioral disorders,[58] this information is not disclosed on the label. Furthermore, data gaps for certain health endpoints are also not disclosed.

Mixtures and Synergism

In addition to gaps in testing inert ingredients and their mixture with active ingredients in pesticide products, there is an absence of review of the health and environmental impacts of pesticides used in combination. A study by Warren Porter, PhD., professor of zoology and environmental toxicology at the University of Wisconsin, Madison, examined the effect of fetal

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[53] Environmental Protection Agency. October 2014. EPA Proposes to Remove 72 Chemicals from Approved Pesticide Inert Ingredient List. http://yosemite.epa.gov/opa/admpress.nsf/bd4379a92ceceeac8525735900400c27/3397554fa65588d685257d7a0061a300!OpenDocument.
[54] Environmental Protectin Agency. October 2013. Cresol/Cresylic Acid. http://www.epa.gov/ttnatw01/hlthef/cresols.html.
[55] Benachour and Seralini. 2009. Glyposate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells. *Chemical Research and Toxicology. http://pubs.acs.org/doi/abs/10.1021/tx800218n.*
[56] Hernandez et al. 2011. Pesticides and Asthma. *Current opinion in allergy and clinical immunology.* http://www.ncbi.nlm.nih.gov/pubmed/21368619.
[57] Horton et al. 2011. Impact of Prenatal Exposure to Piperonyl Butoxide and Permethrin on 36-Month Neurodevelopment. *Pediatrics.* http://www.ncbi.nlm.nih.gov/pubmed/21300677
[58] Furlong et al. 2014. Prenatal exposure to organophosphate pesticides and reciprocal social behavior in childhood.

exposures to a mixture of 2,4-D, mecoprop, and dicamba exposure —frequently used together in lawn products like Weed B Gone Max and Trillion— on the mother's ability to successfully bring young to birth and weaning.[59] A 2011 study, entitled *Additivity of pyrethroid actions on sodium influx in cerebrocotorial neurons in primary culture,*[60] finds that the combined mixture's effect is equal to the sum of the effects of individual pyrethoids. This equates to a cumulative toxic loading for exposed individuals. Similarly, researchers looked at the cumulative impact the numerous pesticides that may be found in honey bee hives in the 2014 paper *Four Common Pesticides, Their Mixtures and a Formulation Solvent in the Hive Environment Have High Oral Toxicity to Honey Bee Larvae*.[61] The findings of the study send no mixed messages —pesticides, whether looked at individually, in different combinations, or even broken down into their allegedly inert component parts have serious consequences on the bee larvae survival rates. The synergistic effects in most combinations of the pesticides amplify these mortality rates around the four-day mark.

Research by Tyrone Hayes, PhD, professor of integrative biology at UC Berkeley has compared the impact of exposure to realistic combinations of small concentrations of pesticides on frogs, finding that frog tadpoles exposed to mixtures of pesticides took longer to metamorphose to adults and were smaller at metamorphosis than those exposed to single pesticides, with consequences for frog survival. The study revealed that "estimating ecological risk and the impact of pesticides on amphibians using studies that examine only single pesticides at high concentrations may lead to gross underestimations of the role of pesticides in amphibian declines."[62]

A Systems Approach without Toxic Chemicals

Chemical-intensive turf and landscape management programs are generally centered on a synthetic product approach that continually treats symptoms with toxic chemicals, rather than focuses on the root causes of pest problems, which lies in the soil. Experience finds that toxic pesticides are not needed for successful turf management. Rather, a systems approach incorporates preventive steps based on building soil biomass to improve soil fertility and turf grass health, organic products based on a soil analysis that determines need, and specific cultural practices, including mowing height, aeration, dethatching, and over-seeding.

Organic turf management, which meets the standards of the *Organic Foods Production Act*, is a "feed-the-soil" approach that centers on natural, organic fertilization, microbial inoculants, compost teas, and compost topdressing as needed. This approach builds a soil environment rich in microbiology that will produce strong, healthy turf able to withstand stress. The aim of a natural approach to land care is not to simply swap one herbicide or insecticide for another, but instead build a soil environment rich in microbial diversity that will produce strong, healthy landscapes able to withstand stress from weeds, pests, fungus and other disease.

Cost of Organic is on Par with Conventional in the Long Term

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[59] Cavieres MF, Jaeger J, Porter W. Developmental toxicity of a commercial herbicide mixture in mice: I. Effects on embryo implantation and litter size. Environmental Health Perspectives. 2002;110(11):1081-1085.

[60] Cao et al. 2011. Additivity of Pyrethroid Actions on Sodium Influx in Cerebrocortical Neurons in Primary Culture. *Environmental Health Perspectives. http://ehp.niehs.nih.gov/1003394/.*

[61] Zhu et al. 2014. Four Common Pesticides, Their Mixtures and a Formulation Solvent in the Hive Environment Have High Oral Toxicity to Honey Bee Larvae. PLOS One. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0077547.

[62] Hayes TB, Case P, Chui S, et al. Pesticide Mixtures, Endocrine Disruption, and Amphibian Declines: Are We Underestimating the Impact? *Environmental Health Perspectives.* 2006;114(Suppl 1):40-50. doi:10.1289/ehp.8051.

Cost of implementing an organic systems approach is not likely to be substantially more than current costs, and there is likely to be savings in the long term.

In considering cost, County governments should reflect on the externalities associated with pesticide use, including its effect to reduce the risk of exposure to carcinogens, prevent the contamination of groundwater, and the poisoning of wildlife. These are costs that residents are already paying for, through hospital visits, expensive clean-ups, and the need for species conservation and habitat restoration. A natural land care program is not only generally on par with and in the long run less expensive than a conventional chemical based program, it also reduces and in many cases eliminates costly externalities borne by the community at large.

The following provide select examples of the experience of towns and institutions with organic land care programs:

- There is report produced by nationally renowned turfgrass expert and Beyond Pesticides' board member Chip Osborne in coordination with Grassroots Environmental Education, which looks specifically at the cost of conventional and organic turf management on school athletic fields. The report concludes that once established, a natural turf management program can result in savings of greater than 25% compared to a conventional turf management program.[63]
- There is also the research from Harvard University which determined that, ultimately, total operating costs of its organic maintenance program are expected to be the same as the conventionally based program. In a 2009 *New York Times* article,[64] the school determined that irrigation was reduced by 30%, saving 2 million gallons of water a year as a result of reduced irrigation needs. The school was also spending $35,000/year trucking yard waste off site. The university can now use those materials for composting and has saved an additional $10k/year due to the decreased cost and need to purchase fertilizer from off-campus sources. [65]
- The Department of Energy and Environmental Protection in the state of Connecticut, which itself has a successful ban on pesticide use in school playing fields up to 8th grade, notes in its information on organic lawn care that "If your lawn is currently chemically dependent, initially it may be more expensive to restore it. But in the long term, an organic lawn will actually cost you less money. Once established, an organic lawn uses less water and fertilizers, and requires less labor for mowing and maintenance."[66]
- The experience in Reno, NV may also be instructive. As part of their pesticide-free pilot program there, the Parks Department stated, "There will be no cost implications as staff will implement changes within its adopted budget." [67]

Local Success Stories

Beyond Pesticides has seen first-hand the success of this approach in communities throughout the country. Beyond Pesticides' Tools for Change[68] webpage highlights over 50 communities that have enacted some level of lawn and landscape pesticide reduction policy. The vast majority of these policies occurred in states subject to pesticide preemption on private property. This list is also not comprehensive. The following are select examples of the towns,

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[63] Osborne, Charles and Doug Wood. 2010. A cost Comparison of Conventional (Chemical) Turf Management and Natural (Organic) Turf Management on School Athletic Fields. Grassroots Environmental Education. http://www.grassrootsinfo.org/pdf/turfcomparisonreport.pdf
[64] Raver, Anne. 2009. The Grass is Greener at Harvard. http://www.nytimes.com/2009/09/24/garden/24garden.html?_r=2
[65] Harvard University. 2009. Harvard Yard Soils Restoration Project Summary Report. http://www.slideshare.net/harvard_uos/harvard-yard-soils-restoration-project-summary-report-22509-4936446
[66] Connecticut Department of Energy and Environmental Protection. 2016. Organic Land Care: Your neighbors will "go green" with envy. http://www.ct.gov/deep/cwp/view.asp?a=2708&q=382644#Expensive
[67] City of Reno, Nevada Staff Report. 2015. Update, discussion and potential approval of a Pesticide-Free Parks program for twelve City Parks.
[68] Beyond Pesticides. 2016. Tools for Change. http://beyondpesticides.org/programs/lawns-and-landscapes/tools-for-change

cities, and counties that have enacted laws which promote lawn care practices which protect their resident's health from toxic pesticides.[69]

- **Takoma Park, Maryland** passed an ordinance known as the *Safe Grow Act* in 2013. The act generally restricts the use of cosmetic lawn pesticides on both private and public property throughout the city. The Act does this by creating a list of restricted use pesticides based on chemical toxicity and international standards, and does not allow the use of these restricted chemicals for turf management. Ornamental and garden plants are exempted from this ban, as are control of poisonous plants, venomous insects, and invasive species. The city has a waiver process through which homeowners may request the use of disallowed pesticides. Takoma Park developed a website that includes educational materials to help homeowners maintain a healthy lawn without the use of toxic pesticides.[70]

- **Ogunquit, Maine** voters went to the polls in November 2014 and passed a pesticide ordinance with a similar scope to law adopted in Takoma Park. This ordinance amended a previous law that restricted pesticide use only on town-owned property, allowing it to expand pesticide restrictions to public and private property. Agricultural activities, control of poisonous plants, invasive species applications mandated by state or federal law, and applications to control venomous or disease carry insects are exempted by the law.[71]

- **Cuyahoga County, Ohio's** Organic Pest Management ordinance was passed in 2012. The ordinance prohibits the use of synthetic pesticides on property owned by the county. The ordinance does exempt the use of larvicides and rodenticides as public health measures or by a mandatory finding by the Department of Public Works (DPW). It also adopted an Integrated Pest Management program for all county-own properties, which requires that "all non-chemical and organic treatments available for the targeted pest should be exhausted prior to the use of synthetic chemical treatments."[72]

- **Irvine, CA** recently amended the City's Integrated Pest Management Policy as a result of significant community concern regarding the pesticides used on public property within City limits. The amendments ensure the city will prioritize the use of organic pesticides on parks, fields, playgrounds, and other City properties and rights of way. EPA registered pesticides will be used only when deemed necessary to protect public health or economic loss, and other methods have proven ineffective

- **Marblehead, Massachusetts** adopted Organic Pest Management Regulations in 2005 for all turf and land management. According to the regulations, the use and application of toxic chemical pesticides, either by Town of Marblehead employees or by private contractors, is prohibited on all Town-owned lands. The town employees who work with turf grass and the landscape receive education and training in natural, organic turf and

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[69] A longer list of communities which have enacted pesticide restrictions is available on Beyond Pesticides' Tools for Change webpage: http://www.beyondpesticides.org/lawn/activist/index.php

[70] City of Takoma Park, Maryland. 2013. Safe Grow Act. http://www.codepublishing.com/MD/TakomaPark/?TakomaPark14/TakomaPark1428.html

[71] Ogunquit Conservation Commission. 2014. http://ogunquitconservation.org/ogunquitconservation.org/PROPOSED_PESTICIDE_ORDINANCE.html

[72] County Council of Cuyahoga County, Ohio. 2012. Ordinance No 02011-0047. http://council.cuyahogacounty.us/pdf_council/en-US/Legislation/Ordinances/2012/O2011-0047.pdf

landscape management. This ordinance was forwarded by the Chairman of Marblehead's Recreation and Parks Department and turfgrass expert Chip Osborne.[73]

These examples prove in practice that organic, least-toxic methods of managing landscapes are feasible and cost-effective for local governments of all sizes. As land managers are trained and familiarize themselves with organic methods and new practices and products continue to emerge, more and more communities are moving toward common-sense, sustainable approaches to land care. These practices do not put humans, pets, and the environment, particularly pollinators and other wildlife at risk of non-target pesticide impacts, in unnecessary danger.[74] Furthermore, the current and past pesticide testing and labeling protocols used by the U.S. Environmental Protection Agency have failed to address full range of hazards and allow for too many data gaps to adequately protect against harm. The hazards and uncertainties that put people and the environment in harm's way are, in our view, unreasonable given that they are unnecessary to achieve beautiful lawns and gardens.

Thank you for the opportunity to present this statement to local leaders in Las Cruces. We appreciate your consideration of the information and citations presented here in support of organic and sustainable turf and landscape practices. We remain available to discuss the importance and finer details of this issue at any time through email at dtoher@beyondpesticides.org or by phone at 202-543-5450.

Thank you,

Beyond Pesticides
Drew Toher
Public Education Associate

[73] Town of Marblehead Board of Health. 2005. Organic Pest Management Regulations. http://www.beyondpesticides.org/documents/MarbleheadOPM%20REGS%2012%2022%2005.pdf

[74] (See Appendix A for additional information about these issues).

Appendix A. Health Effects of 30 Commonly Used Pesticides

A Beyond Pesticides Factsheet – A Beyond Pesticides Factsheet – A Beyond Pesticides Factsheet – A Beyond Pesticides Factsheet

Health Effects of 30 Commonly Used Pesticides

Pesticides	Health Effects						
	Cancer	Endocrine Disruption	Reproductive Effects	Neurotoxicity	Kidney/Liver Damage	Sensitizer/ Irritant	Birth Defects
Herbicides							
2,4-D*	X[4]	X[10]	X[7]	X[8]	X[9]	X[1]	X[11]
Benfluralin					X[1]	X[1]	
Bensulide				X[2]	X[1]	X[2]	
Clopyralid			X[7]			X[2]	X[7]
Dicamba*			X[1]	X[2]	X[2]	X[1]	X[1]
Diquat Dibromide			X[12]		X[11]	X[1]	
Dithiopyr					X[1]	X[1]	
Fluazipop-p-butyl			X[1]		X[1]		X[1]
Glyphosate*	X[12]	X[8]	X[1]		X[8]	X[3]	
Imazapyr					X[7]	X[2]	
Isoxaben	X[3]				X[2]		
MCPA		X[6]	X[2]	X[2]	X[11]	X[1]	
Mecroporp (MCPP)*	Possible[3]	X[6]	X[2]	X[1]	X[9]	X[1]	X[1]
Pelargonic Acid*						X[1]	
Pendimethalin*	Possible[3]	X[6]	X[1]			X[2]	
Triclopyr			X[7]		X[9]	X[1]	X[7]
Trifluralin*	Possible[3]	X[6]	X[1]		X[2]	X[1]	
Insecticides							
Acephate	Possible[3]	X[6]	X[11]	X[9]		X[2]	
Bifenthrin*†	Possible[3]	Suspected[6,10]		X[8]		X[1]	X[9]
Carbaryl	X[3]	X[10]	X[8]	X[1]	X[11]	X[11]	X[7]
Fipronil	Possible[3]	X[6]	X[8]	X[8]	X[8]	X[8]	
Imidacloprid ‡			X[7]		X[2]		X[7]
Malathion*	Possible[3]	X[10]	X[11]	X[9]	X[2]	X[2]	X[2]
Permethrin*†	X[3]	Suspected[6,10]	X[1,7]	X[9,7]	X[9]	X[1]	
Trichlorfon	X[3]	X[6]	X[11]	X[2]	X[2]		X[2]
Fungicides							
Azoxystrobin					X[2]	X[2]	
Myclobutanil		Probable[6]	X[2]		X[2]		
Propiconazole	Possible[1]	X[6]	X[2]		X[1]	X[1]	
Sulfur						X[1]	
Thiophanate methyl	X[3]	X[1]	X[1]	Suspected[1]	X[1]	X[2]	X[1]
Ziram	Suggestive[3]	Suspected[6]		X[2]	X[2]	X[2]	
Totals:	16	17	21	14	25	26	12

**These pesticides are among the top 10 most heavily used pesticides in the home and garden sector from 2006-2007, according to the latest sales and usage data available from EPA (2011), available at http://www.epa.gov/oppb00001/pestsales/07pestsales/market_estimates2007.pdf.*
† EPA lists all synthetic pyrethroids under the same category. While all synthetic pyrethroids have similar toxicological profiles, some may be more or less toxic in certain categories than others. See Beyond Pesticides' synthetic pyrethroid fact sheet at bit.ly/TLBuP8 for additional information.
‡ Imidacloprid is a systemic insecticide in the neonicotinoid chemical class, which is linked to bee decline.

Description

Most toxicity determinations based on interpretations and conclusions of studies by university, government, or organization databases. Empty cells may refer to either insufficient data or if the chemical is considered relatively non-toxic based on currently available data.

The list of 30 commonly used lawn chemicals is based on information provided by the General Accounting Office 1990 Report, "Lawn Care Pesticides: Risks Remain Uncertain While Prohibited Safety Claims Continue," U.S. Environmental Protection Agency (EPA) National Pesticide Survey (1990), Farm Chemicals Handbook (1989), The National Home and Garden Pesticide Use Survey by Research Triangle Institute, NC (1992), multiple state reports, current EPA Environmental Impact Statements, and Risk Assessments, EPA national sales and usage data, best-selling products at Lowe's and Home Depot, and Beyond Pesticides' information requests.

For more information on hazards associated with pesticides, please see Beyond Pesticides' *Gateway on Pesticide Hazards and Safe Pest Management* at www.beyondpesticides.org/gateway. For questions and other inquiries, please contact our office at 202-543-5450, email info@beyondpesticides.org or visit us on the web at www.beyondpesticides.org.

Citations

1. U.S. EPA. Office of Pesticide Program *Reregistration Eligibility Decisions (REDs), Interim REDS (iREDs), and RED factsheets.* http://www.epa.gov/pesticides/reregistration/.

2. National Library of Medicine, TOXNET, *Hazardous Substances Database*, http://toxnet.nlm.nih.gov/.

3. U.S. EPA. 2012. Office of Pesticide Programs, *Chemicals Evaluated for Carcinogenic Potential.* http://npic.orst.edu/chemicals_evaluated.pdf.

4. California Environmental Protection Agency. *Proposition 65: Chemicals Known to the State to Cause Cancer or Reproductive Toxicity.* Office of Environmental Health Hazard Assessment. http://www.oehha.org/prop65/prop65_list/files/P65single052413.pdf.

5. The Pesticide Management Education Program at Cornell University. *Pesticide Active Ingredient Information.* http://pmep.cce.cornell.edu/profiles/index.html.

6. The Endocrine Disruption Exchange. 2011. *List of Potential Endocrine Disruptors.* http://www.endocrinedisruption.com/endocrine.TEDXList.overview.php.

7. Northwest Coalition for Alternatives to Pesticides (NCAP), *Pesticide Factsheets.* http://www.pesticide.org/get-the-facts/pesticide-factsheets.

8. Beyond Pesticides *ChemWatch Factsheets*, http://www.beyondpesticides.org/pesticides/factsheets/index.htm.

9. U.S. EPA. *Chronic (Non-Cancer) Toxicity Data for Chemicals Listed Under EPCRA Section 313.* Toxic Release Inventory Program. http://www.epa.gov/tri/trichemicals/hazardinfo/hazard_chronic_non-cancer95.pdf.

10. European Union Commission on the Environment. *List of 146 substances with endocrine disruption classifications, Annex 13.* http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#report2.

11. Extension Toxicology Network (EXTOXNET) *Pesticide Information Profiles.* http://extoxnet.orst.edu/ghindex.html.

12. International Agency for Research on Cancer, World Health Organization (IARC) category 2A, the agent (mixture) is probably carcinogenic to humans based on sufficient evidence of carcinogenicity in laboratory animal studies. http://monographs.iarc.fr/ENG/Classification/index.php.

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Appendix B. Environmental Effects of 30 Commonly Used Lawn Pesticides

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Environmental Effects of 30 Commonly Used Lawn Pesticides

Pesticides	Health Effects					
	Detected in Groundwater	Potential Leacher	Toxic to Birds	Toxic to Fish/ Aquatic Organisms	Toxic to Bees	Toxic to Mammals
Herbicides						
2,4-D*	X[1,2,3,4,7]	X[3,4]	X[1,2,3,11]	X[1,2,3,11]	X[1,11]	X[3,4,12]
Benfluralin	X[7]		X[3,11]	X[3,11]	X[5,11]	
Clopyralid	X[2,7]	X[2,11]	X[11]	X[11]	X[11]	
Dicamba	X[2,7]	X[1,2,3]	X[10,11]	X[1,2,3,11]	X[5,10,11]	
Diquat Dibromide		X[5]	X[1,3,11]	X[1,3,11]	X[5,11]	X[1]
Dithiopyr				X[5,6,11]	X[5,11]	
Fluazipop-p-butyl				X[1,4,6,11]	X[1,4]	
Glyphosate+	X[8]	X[5]	X[1,3,11]	X[1,2,11]	X[11]	X[4]
Imazapyr	X[2]	X[2,3]		X[2,5,11]	X[5,11]	
Isoxaben		X[11]	X[11]	X[3,11]	X[11]	
MCPA	X[4,7]	X[1,4,11]	X[1,3,11]	X[1,3,11]	X[5]	X[3]
Mecoprop (MCPP)+	X[4]	X[1,2,3,11]	X[3,11]	X[2]	X[11]	X[3]
Pelargonic Acid+			X[3 §]	X[3 §]	X[5]	
Pendimethalin+	X[3,7]		X[1,3,11]	X[1,3,11]	X[5,11]	X[3]
Triclopyr	X[2,7]	X[1,2,3,11]	X[2,3,11]	X[2,3,11]	X[5,11]	
Trifluralin+	X[4,7]			X[3,11]	X[5,11,12]	
Insecticides						
Acephate		X[1]	X[1,3,10,11]	X[3,11]	X[1,3,10,11]	X[3]
Bifenthrin††			X[1,10,11]	X[1,10,11]	X[1,10,11]	X[1,4]
Carbaryl	X[1,3,7]	X[11]	X[2,11]	X[1,2,3,11]	X[1,2,3,11]	X[3,11]
Fipronil	X[7]	X[5,11]	X[2,4,10,11]	X[2,4,10,11]	X[2,4,10,11]	X[4]
Imidacloprid ‡	X[7]	X[1,2,10,11]	X[1,2,11]	X[1,2,11]	X[1,2,10,11]	
Malathion+	X[1,2,3,7]	X[1,3,5]	X[1,2,3,10,11]	X[1,2,3,10,11]	X[1,3,10,11]	X[3]
Permethrin††	X[2,7]			X[1,2,3,11]	X[1,2,3,11]	
Trichlorfon		X[1,3,11]	X[1,3,11]	X[1,3,11]	X[1,11]	X[4‖]
Fungicides						
Azoxystrobin	X[9]	X[3,4,11]	X[11]	X[3,11]	X[11]	
Myclobutanil	X[7]			X[5]		
Propiconazole	X[7]	X[3]		X[3,11]	X[5,11]	X[11]
Sulfur		X[1]	X[11]	X[11]	X[11]	
Thiophanate methyl		X[3]		X[3,11]	X[11]	
Ziram		X[3,4]	X[1,3,11]	X[1,3,11]	X[11]	X[3]
Totals:	19	20	22	30	29	14

**These pesticides are among the top 10 most heavily used pesticides in the home and garden sector from 2006-2007, according to the latest sales and usage data available from EPA (2011), available at http://www.epa.gov/opp00001/pestsales/07pestsales/market_estimates2007.pdf.*
† EPA lists all synthetic pyrethroids under the same category. While all synthetic pyrethroids have similar toxicological profiles, some may be more or less toxic in certain categories than others. See Beyond Pesticides' synthetic pyrethroid fact sheet at bit.ly/TLBuP8 for additional information.
‡ Imidacloprid is a systemic insecticide in the neonicotinoid chemical class, which is linked to bee decline.
§ Based on soap salts.
‖ Based on in-vitro mammalian cell study.

Description

Most toxicity determinations based on interpretations and conclusions of studies by university, government, or organization databases. Empty cells may refer to either insufficient data or if the chemical is considered relatively non-toxic based on currently available data. The column labeled "Potential to Leach" refers to a chemical's potential to move into deeper soil layers and eventually into groundwater. The column labeled "Toxic to Mammals" refers to conclusions based on evidence from studies done on non-human mammals.

The list of 30 commonly used lawn chemicals is based on information provided by the General Accounting Office 1990 Report, "Lawn Care Pesticides: Risks Remain Uncertain While Prohibited Safety Claims Continue," U.S. Environmental Protection Agency (EPA) National Pesticide Survey (1990), Farm Chemicals Handbook (1989), The National Home and Garden Pesticide Use Survey by Research Triangle Institute, NC (1992), multiple state reports, current EPA Environmental Impact Statements, and Risk Assessments, EPA national sales and usage data, best-selling products at Lowe's and Home Depot, and Beyond Pesticides' information requests.

For more information on hazards associated with pesticides, please see Beyond Pesticides' *Gateway on Pesticide Hazards and Safe Pest Management* at www.beyondpesticides.org/gateway. For questions and other inquiries, please contact our office at 202-543-5450, email info@beyondpesticides.org or visit us on the web at www.beyondpesticides.org.

Citations

1. Extension Toxicology Network (EXTOXNET) Pesticide Information Profiles. Available at: http://extoxnet.orst.edu/pips/ghindex.html.
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Last Updated May 2015