Pesticide Exposure and Human Health (Part 1)

DONNA L. HOUGHTON, Ph.D., SYNGENTA CROP PROTECTION CAN. INC.

Being in the business of managing or researching turf, you no doubt have been asked many questions concerning the safety of pesticides and their impact on human health.

In this article, the first of a two part series, I will provide you with background information that will help you address public inquiries on this subject. This issue's article will focus on the regulation of pesticides in Canada, fundamentals of toxicology, acute toxicity of pesticides in comparison with common substances, misconceptions regarding the toxicity of natural chemicals and the difference between acute and chronic toxicity. Part two of this article will address the concept of risk and allegations that pesticide exposure is responsible for various health effects such as cancer and asthma.

Pesticides are products that are designed to kill unwanted living organisms; therefore, they need to be handled with respect. They can be used safely because the dose required to cause serious health effects in humans is significantly higher than the dose required to control the target pest. The fundamental principle of toxicology, which is the study of noxious effects of chemicals on living systems, is that "the dose makes the poison." This principle was recognized many centuries ago but was not put into writing until the early 1500s. "All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy" [Paracelsus (1493-1541), the father of toxicology].

Despite what the general public has been led to believe, either by the media or various environmental groups, pesticides are indeed regulated in Canada. In fact, Canadian regulations are the most stringent in the world and it is very important to communicate this fact to the public. In addition, pesticides are the most highly researched and regulated group of chemicals sold in this country.

Canadian Regulation

A pesticide cannot be sold in Canada until it is "registered" by the federal government. The term "registered" means that the product can be legally sold and used as per regulations outlined in the Pest Control Products Act (PCP Act). The Canadian Pest Management Regulatory Agency (PMRA) is responsible for reviewing the scientific data on new products submitted for registration by chemical companies. The PMRA is very thorough when reviewing data and it requires a lengthy review period due to the large quantity of scientific information that *must* be submitted by the pesticide manufacturers (100's of studies). New pesticide reviews conducted by the PMRA generally take a minimum of 2 years. Pesticide submissions consist of the results of scientific studies that address the following subjects/questions regarding the newly proposed product:

Chemistry (chemical information regarding the active ingredient and the end-use product). The active ingredient is the chemical in the pesticide formulation that provides the desired mode of action, e.g. it provides the herbicidal, insecticidal or fungicidal activity. The terms "end-use

product" or "formulation" refer to the active ingredient plus the liquid or solid materials added to the active ingredient to make it suitable for handling, application or storage, e.g. water, solvents, clay, thickeners and stabilizers. Formulations can be liquids, wettable powders, granulars, etc.

Toxicology. Results of studies conducted on laboratory animals to evaluate the potential for health effects such as cancer, birth defects, genetic mutations and effects on the reproductive and nervous systems

Metabolism. To determine how the chemical is metabolized (broken down) by mammals and plants

Residues. In the crop (agricultural scenarios) and its by-products

Dietary, Occupational and Bystander Exposure. To determine the potential for pesticide exposure to workers and bystanders during application or contact with treated surfaces such as turf and/or dietary exposure through consumption of treated produce (agricultural uses)

Environmental Impact. To determine residues in soil and water, environmental fate and effects on non-target organisms

Effectiveness. Results of performance trials.

It can take up to 12 years from the time a chemical is discovered in the lab through to the complete research and registration process and cost in excess of $100 million (CDN) to bring one new active ingredient and one of its corresponding end-use products to market.

Due to the stringent registration requirements in Canada, not all pesticides submitted to the PMRA are granted a registration. In fact, it is currently very difficult for a company to gain a registration in this country. The PMRA's mandate is to protect occupational workers, the general public and the environment by ensuring that pesticides to be registered are effective and can be used safely provided label directions are followed, and thus the agency plays a critical role in protecting Canadian citizens. The PMRA employs more than 350 individuals to perform this task and, understandably, they err on the side of caution to ensure that their mandate is achieved.

Toxicology Principles

Before addressing whether or not exposure to pesticides causes an increased risk of certain health effects such as asthma and cancer (Part 2), it is critical to explain the fundamental principle of toxicology, the difference between acute and chronic toxicity, and misconceptions regarding natural and man-made chemicals.

No doubt you have heard people talk about how "toxic" one substance is compared to another. In this context, the term "toxic" generally refers to the *acute toxicity*, or the adverse effects that occur following a single or multiple exposures to a substance within a 24-hour period. However, some chemicals can also cause persistent health effects following exposure to lower doses continuously for long periods of time. This type of toxicity is referred to as *chronic toxicity*.

Toxicologists measure the *acute toxicity* of a chemical using a value known as the LD50, which stands for Lethal Dose 50%. Determining this value also makes it possible to roughly compare the relative toxicity of various substances in a general sense (technically, the slope of the dose-response curve should also be studied). The LD50 is derived from studies conducted on laboratory animals (rats, mice and rabbits). Animals are exposed to the chemical either orally (via diet or stomach tube), dermally (applied to the skin), or via the inhalation route (breathing air containing the pesticide).

The dose, in milligrams per kilogram of body weight (mg/kg), which is lethal to 50% of the test animals within a stated period of time (usually 24hrs), is the LD50. When the chemical is administered in the air, as it is in inhalation studies, toxicity is measured using the LC50 or lethal concentration in milligrams/litre of air (mg/L) required to kill 50% of the test animals. The important point to remember is that the lower the LD50 or LC50 value, the more *acutely* toxic the substance because a smaller quantity will be lethal to 50% of the test animals.

Chemical Origins

There is a common misconception among the general public that natural substances are "safer" than those that are man-made. The word "chemical" unfortunately conjures up negative images in the minds of the public. In reality, all matter is composed of chemical building blocks called atoms. Examples of atomic elements are

hydrogen, oxygen, carbon and nitrogen – there are over a 100 of them. Everything in our world, natural and man-made, is chemical and is made of the same atoms – the food and water we consume, our clothing, medicine, cosmetics, furniture, the plants in our garden, even our own bodies ... and of course, the pesticides we use.

What differentiates one substance from another is the number, combination and configuration of atoms that make up the substance. Once we accept that everything around us is chemical, we realize that what people are really concerned about are *man-made* chemicals. Scientists have created new combinations and configurations of these basic building blocks not found in nature. Consequently, a whole host of synthetic products are now available e.g. plastics, pharmaceutical drugs and pesticides, to name a few. Many drugs and pesticides, however, are synthetic mimics of compounds found in nature e.g. synthetic pyrethroids.

While pharmaceutical drugs have a perceived health benefit in the minds of the public, pesticides are viewed as hazardous to human health because they are used to kill living things. In reality, there are many substances to which people are routinely exposed that are much more acutely toxic than most pesticides. The most toxic substance known to man is not man-made, it is a natural compound called botulinus toxin that causes botulism and is produced by a bacteria *Clostridium botulinus*. However, this toxin has been applied successfully in cosmetic surgery because extremely low doses are used. Remember, "The dose makes the poison." Nature has also produced many natural pesticides such as pyrethrins and nicotine from chrysanthemums and tobacco, respectively.

Some chemicals have been used as both drugs and pesticides and may even have additional uses. For example, hydrochloric acid has been regulated as a household product when used in cleaning agents, a drug when used to treat people with low gastric acidity and a pesticide adjuvant when used to enhance the germicidal activity of chlorine in swimming pools. Hydrochloric acid is natural when produced by the stomach and synthetic when made in the lab – even though its chemical structure (arrangement of atoms) is the same regardless of whether it occurs naturally or is man-made. The toxicity of hydrochloric acid is the same when it is used as a drug, a pesticide, a cleaning agent or when produced by the stomach. It is the ***dose*** in each of these cases that is different.

The fungicide thiabendazole has been used successfully as a deworming agent in humans and animals as well as a fungicide for agricultural crops. Coumarin compounds such as warfarin are excellent rodenticides, but these compounds are also valuable anti-coagulant drugs. Many compounds that are screened for pesticide activity and are not accepted become drugs and vice versa. In summary, *the toxicological properties of any chemical are independent of its uses and whether it is natural or man-made.*

Potential for Harm

Any chemical, if absorbed by the body in excessive amounts, can be poisonous, even substances that are natural and substances to which the public is exposed on a daily basis. It is well recognized that smoking is hazardous to human health because it increases the risk of various types of cancer including lung, mouth, throat, stomach, colon and prostate cancers. What the public may not know, or fails to consider, is that nicotine isn't only a carcinogen, it is a highly toxic substance and it is natural – produced by tobacco. (In fact, nicotine was once used as a pesticide). Death does not occur after smoking a pack of cigarettes in a single day because the dose consumed is not high enough to approach an *acutely* toxic level; however, lower doses over the course of many years (chronic exposure) can be harmful.

Natural substances such as caffeine, salt, Vitamin D and gasoline are very acutely toxic. Similarly, many pharmaceutical drugs are also quite toxic and can be harmful if taken in large doses e.g. Aspirin and Tylenol. Table 1 (pages 15-16) is designed to put the acute oral toxicity of various chemicals into perspective. The reader should keep in mind that the lower the LD50 value, the more toxic the substance. Toxicologists do not calculate LD50s in humans for obvious reasons, but from poisoning cases, the lethal doses of certain compounds have been documented. Where available, these are included in the table. Table 1 demonstrates that the idea that natural substances are safe and man-made substances are toxic is a misconception. Over the centuries, many natural substances have been used deliberately to cause death (e.g. the execution of Socrates using Hemlock brew).

The purpose of Table 1 is **not** to convey that pesticides are no more acutely toxic than Tylenol and salt, but to demonstrate that people should keep *their dose, which in the case of pesticides is their exposure*, as low as possible to all of these substances. Most people would never consider swallowing an entire bottle of Tylenol or a salt shaker full of salt. *They keep their dose to a minimum or, as in the case of pharmaceutical drugs, they abide by the label recommendations regarding dose. The same is true of pesticides – the label regarding such items as application rate, personal protective clothing etc. must be followed in order to use the products safely and reentry periods should be observed to protect bystanders.*

The other basic type of toxicity is chronic toxicity, which can result from long-term daily exposure to a chemical over the course of a lifetime (which in laboratory animals is 18-24 months depending on species – this equates to a full human lifetime). Several different chronic toxicity tests are performed which help to predict whether a pesticide will cause long-term health effects including cancer.

Animals are exposed to a range of dose levels of the chemical, usually through their diet, but occasionally through the skin or lungs, daily, for up to two years. The doses administered in a single study range from very low in some groups of animals, to extremely high in others. There is always a "control" group that is fed the untreated diet and housed under identical environmental conditions. During the study, animals are examined for physical and behavioural effects. At the conclusion of the study, external and post-mortem examinations are conducted and tissues are examined microscopically. The results from the treated and untreated groups of

animals are compared. The results indicate whether or not a chemical has the potential to be neurotoxic (toxic to the nervous system), carcinogenic (cancer causing), teratogenic (causes birth defects) or a reproductive toxin. Tests to determine mutagenicity (effects on DNA) are done in culture and also in live animals. Some of the mutagens we consume daily in small quantities include chemicals in coffee.

Chronic toxicity testing is extremely complex. Health effects *must* occur in the study or it is deemed invalid and must be repeated at higher dose levels. *All substances, natural or man- made, will cause health effects of some sort if given at a high enough dose.*

The purpose of the chronic study is to stress the animals' system sufficiently for effects to be seen. This allows the toxicologist to determine which organs are the target organs and to determine the highest dose level tested that will *not* cause health effects (a "safe" dose in the species tested). A minimum safety factor of 100 is then applied to this dose (e.g. the dose is reduced 100 fold, 10x to account for the study being conducted in animals not humans and an additional 10x to account for differences between individuals within a population) to obtain a dose level that is considered "safe" for human exposure. An additional 10x safety factor is invoked if there is evidence of increased susceptibility of young animals to ensure our children are protected (total safety factor = 1000 fold). A risk assessment is then performed by the PMRA to determine the exposure of the general public, bystanders and occupational workers to the new pesticide. Exposure values must be below the "safe dose" determined from the animal studies following implementation of the required safety factors or registration is not granted.

Turf Specific

PMRA reviewed the data on the products currently registered for use on turf and concluded that they could be applied safely without risking human health or the environment (provided label directions are followed). Consequently, these products are registered. As part of their ongoing review program, PMRA is conducting re-evaluation of older pesticides that were registered prior to some of the newer study protocols and standards being required. Through re-registration, chemical companies will be asked to fill data gaps on older chemicals. These data will be reviewed and any products not meeting the standard will have their registrations revoked.

Since the exposure incurred by occupational workers, bystanders and the general public has been thoroughly studied for each registered pesticide and found to be well below any level of concern, the public's hysteria regarding their exposure to pesticides and risk to their health is currently not warranted from a scientific point of view. Pesticides **can** be used safely, provided label directions are followed; therefore, any pesticide ban approved by a municipality is really a political decision based on emotion and not one based on sound science. ♦

Table 1: Toxic Hazards of Common Materials

Note: Acute toxicity is measured following a single exposure. Where human data are available, the dose presented is the *lethal dose* for adults unless otherwise noted. Lethal dose in mg/kg body weight has been calculated based on an average adult body weight of 65 kg. Acute oral toxicity from animal studies is assessed using the quantity required to kill half of a group of test animals when given orally (Oral LD_{50}); therefore, the *higher the LD_{50}, the lower the toxicity e.g. A larger quantity of a less toxic substance is required to cause harm. Compounds in* **BOLD** *type are natural in origin.*

LIST OF MATERIALS	LETHAL DOSE FOR HUMANS (from poisoning records; dose presented in mg/kg body weight where possible)	LD_{50} VALUES FROM ANIMAL STUDIES (mg/kg body wt unless otherwise stated)	REF.
PRIMO MAX		>5050 (rat)	a
HERITAGE		>5000 (rat)	b
ROUND-UP		>5000 (rat)	b
ALCOHOL (ethanol)	10-14 oz or 300-400 mL pure ethanol, or 600-800 mL 100 proof whiskey, if consumed in < 1 hr (3643-4860 mg/kg)[1]	13 mL/kg (rat)	c, d
KILLEX Lawn Weed Killer	8 oz or 227 mL (3751 mg/kg)[2]	>5000 (rat)	b
ANTIFREEZE (Ethylene glycol)	100 mL = 100 g (1540 mg/kg)[1]	8540 (rat)	c, d, h
GLYPHOSATE (active ingredient)		5600 (rat)	e
RUBBING ALCOHOL (isopropyl alcohol)	250 mL (3021 mg/kg)[1]		c, d
DACONIL 2787		4200 (rat)	b
SALT	Lethal Dose for 1 yr old is 2 tbsp	3000-3750 (rat)	f, g, d
DUAL® 960 (herbicide)		2780 (rat)	b
DISINFECTANT (Lysol®, 7% O-phenylphenol)	10 g (2200 mg/kg)	2480 (rat)	c, d
HORIZON® Herbicide		2276 (rat)	a
AATREX NINE-0® (atrazine)		1600 (rat)	b
BANNER 130EC		>1550	b
ASA (Aspirin)	200 g (3077 mg/kg)	1350-1500 (rat)	c, d, g
DICAMBA (active ingredient)		1040-1707 (rat)	d, e
BLEACH	15-30 mL (child) (500-1000 mg/kg)[3]		c
BATHROOM CLEANSER (Sodium phosphate 24%, eg. Comet®)	Approx. 50 g (769 mg/kg)		c
MECOPROP (active ingredient)		930-1166 (rat)	e
2,4-D herbicide formulations		600-764 (rat)	b, e

LIST OF MATERIALS	LETHAL DOSE FOR HUMANS (from poisoning records; dose presented in mg/kg body weight where possible)	LD_{50} VALUES FROM ANIMAL STUDIES (mg/kg body wt unless otherwise stated)	REF.
CREAM OF TARTER (tartaric acid)	30 g (462 mg/kg)		c
TURPENTINE	15 g (230 mg/kg)		c
PROZAC	200-400 mg (14-17 yrs) (4-8 mg/kg)[4]	425-467 (rat)	i, j, k
2,4-D (active ingredient)		375 (rat)	b
CAFFEINE (coffee)	183-250 mg/kg 100 cups of strong coffee	355 (male rat) 247 (female rat)	c, f, d
TYLENOL (acetaminophen)	10 g (140 mg/kg)	338 (mice)	c, d
DURSBAN TURF INSECTICIDE		776 (male rat), 300 (female rat)	b
NICOTINE	40 mg (0.6 mg/kg = 1 drop = quantity in 2 g of tobacco or 2 cigarettes)	230 (mice)	c, d
GASOLINE	10-250 mL (112-2807 mg/kg)[2]		c
MOTH BALLS (naphthalene)	2 g (31 mg/kg)		c
SODIUM FLUORIDE (fluorine)	5-10 mg/kg	35 (species not specified), 180 (rat)	c, f, d
ARSENIC (Arsenic trioxide)	400 mg (6.2 mg/kg)	15.1 (rat)	f, d
PARATHION	2 mg or 0.1 mg/kg (5-6 year olds) 120 mg/kg (adult male) 1.8 mg/kg (no age specified)	2 to 13 mg/kg (rat)	c, f, e, d
VITAMIN D		10 mg/kg	f
STRYCHNINE (Strychnine sulfate)	15-30 mg (0.2-0.5 mg/kg)	Approx. 5 mg/kg (rat)	c, d
TUBOCURARINE CHLORIDE	6 mg/kg	0.63 mg/kg (mice, i.p.)	c, d
BOTULIN (Clostridium botulinum) Food Poisoning	<0.000,014 mg/kg		g

References

a) Internal Novartis/Syngenta Toxicology reports
b) Material Safety Data Sheets, various manufacturers
c) Dreisbach, RH (1983) Handbook of Poisoning, 11th Edition, Lange Medical Publications. Note: amount fatal for adult divided by 65 kg typical weight to get values in mg/kg
d) Merck Index, Encyclopedia of Chemicals, Drugs and Biologicals (1983) 10th Edition, Windholz, M. Editor, Merck and Co. Inc., Rahway, N.J.
e) The Pesticide Manual (2000), 12th Edition, British Crop Protection Council
f) Ottoboni, A (1984) The Dose Makes the Poison, Vincente Books, Berkeley, California
g) Hayes, WJ and Laws, ER (1991) Handbook of Pesticide Toxicology, Academic Press, Vol. 1, 2 and 3
h) Emsley J (1994) The Consumer GOOD Chemical Guide: A jargon-free guide to the chemicals of every day life. W.J. Freeman Co., New York, pg. 291
i) Personal communication between Syngenta Crop Protection Canada Inc. and Eli Lily Canada Inc.
j) Product Monograph for Prozac, Eli Lily manufacturer, Feb. 21, 2000
k) China Chemical and Pharmaceutical Co. Ltd., Taiwan

Footnotes

1. Calculated using fatal dose converted to mass using density from Ref. d and body weight of 65 kg.
2. Calculated using fatal dose converted to mass using density from Ref. b and body weight of 65 kg.
3. Calculated assuming density of bleach containing 3-6% sodium hypochlorite in water is approx. 1, and 30 kg body weight.
4. Assuming 50 kg body weight.