Health and environmental impacts of pyrethroid insecticides: *What we know, what we don't know and what we should do about it*

Executive summary and Scientific Literature Review

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Abstract

Although regulatory agencies still consider registered pesticides to be an essential pest management tool whose benefits counterweight health and environmental risks, history has shown that no pesticide, particularly insecticides, is harmless. Banning DDT led to the use of alternate insecticides, such as organophosphates, of varying degrees of toxicity. Now, organophosphates are gradually being replaced because updated regulatory assessment protocols have uncovered novel potential toxicity. However, the common trend of replacing organophosphates with putatively safer pyrethroids may not be a benign alternative. Pyrethroids rapidly immobilize and kill insects by affecting their nervous system. While lethal doses for humans are quite substantial, sub-lethal neurotoxic effects may be expected in humans. Regulatory science may adapt slowly to new findings from fundamental science laboratories. Recently, independent research has suggested certain pyrethroids have a potential for neurotoxicity, carcinogenicity, reproductive toxicity and endocrine disruption; these have sometimes been considered and refuted during national regulatory registration assessment reviews and evaluations by international authorities.

The enhanced sensitivity of children to pesticide is a widely accepted fact and children may be subject to greater exposure to pyrethroids than adults. However, developmental neurotoxic data gaps exist in pyrethroid regulatory assessments and Canadian and US academic research increasingly supports possible correlations between sub-lethal neurotoxicity in children and pyrethroid exposure. For instance, a Canadian study revealed that pyrethroids were significantly associated with behavioural problems in children. Furthermore, pyrethroid and organophosphorus exposure during pregnancy were associated with the increase risk of Autism Spectrum Disorder and Developmental Delays and an *in utero* exposure to a common pyrethroid synergist, piperonyl butoxide, was statistically related to mental development delays in three-year-old children. A better understanding of behavioural endpoints and strengthening our knowledge on developmental neurotoxicity mechanisms is critical in the light of this recent epidemiological evidence. Already, a mechanism linking pesticides to autism has been described. Meanwhile, we should apply the precautionary principle on all uses which may lead to direct and indirect children exposure.

Emerging evidence also suggests that pyrethroids might have reproductive toxicity. A US study of males, corroborated by a Chinese study, revealed that pyrethroid exposure (measured as metabolite concentrations in the urine) is correlated with a decrease in sperm count, decreased mobility of sperm, an increase of abnormal morphology as well as an increase in DNA damage which may result in decreased fertility and pregnancy. In mice reduced sperm counts were related to decreased testosterone levels with *cis*-Permethrin exposure. Pyrethroids may alter hormones in males (antiandrogenic activity) and females (estrogenic and lutropic activities). Our societies have been facing a secular trend of decreasing testosterone and semen quality in males, consequently seemingly subtle associations found in epidemiological studies may result in large changes in human reproductive capacity or in other endocrine-mediated diseases and this is the cause for great public concern.

At the turn of the millennium, the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) concluded that animal carcinogenesis evidence provided no clear indication of carcinogenicity for humans, while the US Agency for Toxic Substances and Disease Registry considered some pyrethroids to be possible human carcinogens. In the face of new evidence, including mutagenesis in hamster and human cell cultures, IARC assigned a high priority to reviewing Permethrin

carcinogenicity in the 2015 to 2019 period. Associations between some pyrethroids and breast, testicular, prostate and thyroid cancers have been suggested, based on pyrethroids endocrine disruption potential.

Although pyrethroids have been observed in Canadian surface waters in agricultural areas, sometimes at concentrations above the legal thresholds intended to protect aquatic life, we know very little about groundwater and urban water contamination. Permethrin has recently been observed in Quebec groundwaters (the synergist piperonyl butoxide has also been observed in 24% of the 2014 samples). Urban water contamination has been shown to be substantial in US cities. Since pyrethroids are not among the 25 pesticides for which Quebec's environmental legislation require drinking water supplies to be tested, we know very little about our exposure via drinking water. Furthermore, contamination of fruits and vegetables has been found in Canada, though most food conform to the maximal residues guidelines. A US study suggests that the risks of contamination of food frequently consumed by children should be better quantified. While several Quebec municipalities have banned the use of pesticide for aesthetic purposes within their jurisdictions, residents may still purchase and apply pyrethroids in and around their houses with very few restrictions. The majority of registered pyrethroid formulations are actually designed for domestic use, in settings where the public is little informed of the potential health and environmental consequences of such application.

The Pesticide Management Code of Quebec already restricts pyrethroids from daycares and schools. As this code is being reviewed, new discoveries concerning pyrethroid toxicity for children should be integrated in the risk assessment to restrict pyrethroids to other sites children visit. While a cluster of pyrethroids is currently reviewed for registration in Canada, transparency and easy permanent public access to information should be improved. It is noteworthy that Americans have easier access to pesticide registration documents, from early Data Call-In to the final decision, in addition to instantaneous access to all comments submitted by the public and interest groups via the regulations.gov website. Meanwhile, Canadians do not have such easy and transparent access to pyrethroid documents: many documents are not cohesively archived grouped by pesticide chemical family, they do not have a permanent docket number or permalink on Health Canada's Pest Management Regulatory Agency website to facilitate consultation, and numerous documents are only accessible by submitting a personal request with a lengthy processing time.

Executive Summary[1]

History and registration

Pyrethroids comprise several active substances used for their insecticidal properties. Pyrethrins were the first groups of pyrethroids isolated from chrysanthemum flowers. To increase activity and persistence, synthetic pyrethroids were created, starting with Allethrins in 1949. Today, pyrethroids dominate the worldwide insecticide markets. Some 614 products are registered in Canada and over 3500 products in the US. Pyrethroids are used in domestic, commercial, industrial, agricultural, veterinary and medical settings. They are used against agricultural pests (e.g., aphids and weevils), crawling or flying domestic pests (cockroaches, wasps, ants and spiders), animal parasites (fleas and ticks), human parasites (head lice) and for public health concerns (mosquitoes). Contrary to general pesticide use in Quebec, sales of pyrethroids increased from 2004 to 2010, reaching more than 12 tonnes of active ingredients for all sectors together. During that same period, domestic sales nearly doubled, reaching 2780 kg of active ingredients (kg a.i.) in 2010 while sales to exterminators were at 6210 kg a.i. in 2010. Cypermethrin and Permethrin are among the most widely sold pyrethroids in the Province of Quebec, with more than 1000 kg per year each. Pyrethroid use has risen in the past few years because they are heavily used to replace the more toxic organophosphates.

Physico-chemical characteristics

Pyrethrins names can often be recognized by the suffix *–thrin*. Common Canadian pyrethroids include Allethrins, Cyfluthrin, Cypermethrin, Deltamethrin, *d*-Phenothrin, Lambda-cyhalothrin, Permethrin, Pyrethrins, Resmethrin and Tetramethrin. They have been divided into two major groups, based on the absence (type I) or presence (type II) of a cyano group (formed with carbon and nitrogen) in the first position attached to a functional group (called alpha) on the molecule. Each active molecule may be sold as a mixture of different arrangements of the same atoms (called isomers). Along with the active ingredients, the composition of formulations sold on the market also includes co-formulants (called adjuvants or synergists). Common synergists include piperonyl butoxide and MGK-264, each has its own intrinsic toxicity and physico-chemical characteristics which may enhance the pyrethroid molecule's toxicity.

Pyrethroids are more soluble in fats than in water, though they may be washed off from surfaces by rain. Their volatility is low, and in air, they are primarily associated with dust particles. Natural Pyrethrins are rapidly degraded by sunlight (photodegradation) and in the presence of humidity (hydrolysis). Synthetic pyrethroids, however, are more stable, though this family of pesticides is generally considered to degrade rapidly in the environment, compared to other insecticides.

[1] *References for this executive summary can be found in the full-length technical report. The observations, conclusions and recommendations displayed in this literature review were those expressed by the primary science authors quoted. The sole purpose of providing commercial product examples is so that the public can recognize common household or professionnal use products, by referring to brand names they may know. Other brands and products are registered by the PMRA. No specific claims regarding products brands are made in this review.*

Mode of action

Pyrethroid insecticides interfere with signal propagation in neurons, which is why they are called neurotoxic. Specifically, they act on the sodium channels which are located along the cell membrane on the neuron tail (axon). By blocking open gates, they may create repetitive firing and depolarization that lead to symptoms like tremors, involuntary movements and salivation.

Domestic uses

Due to our modern lifestyle, we stay indoors for long hours; because the majority of homes have at some point been treated with pesticides, this exposes us to a cocktail of chemical pollutants. There are 478 pesticide products registered for domestic use in Canada, with familiar names like Raid and OFF! Products are sold in a variety of forms, including powders, sprays and coils. By far, pressurized cans and aerosol bombs are the modes of application resulting in the greatest number of poisoning reports. Permethrin, Cypermethrin and Piperonyl Butoxide are commonly detected in house dust. Unfortunately, in trying to eradicate domestic pests like cockroaches which may cause asthma in humans, we use pyrethroids—which may also cause asthma. Besides health issues associated with children exposure, when treating head lice with pyrethroids may lead to development of resistance among the lice targeted, making further eradication more difficult and more heavily dependent on higher doses and mixtures of insecticides. Flea treatment of pets with pyrethroid shampoos have been linked with poisoning in children. All the while, less toxic alternatives, such as careful combing and monitoring may suffice to control head lice problems. Pyrethroid sprays are also dangerous especially when used indoor since limited air circulation may lead to greater inhalation exposure. More information on how pyrethroids enter the body following domestic uses is detailed in the exposure section. Alternatives to synthetic pesticides are preferable. If pesticide use is unavoidable, it should be limited to the minimum requirement, always following the manufacturer's recommendation on labels. Rooms should be well ventilated after treatment and before re-entry; unused products should be locked safely away from children.

Agricultural uses

The environmental and health risk index associated with Quebec's agricultural production has decreased over the past decade. Agricultural workers are commonly exposed to pyrethroids, and this may represent a cause for concern, especially when good agricultural practices are not followed. Pyrethroids are commonly used in animal rearing and on food production. Several vegetables (sweet corn, potatoes, carrots, lettuces, onions, green onions and members of the cabbage family) and fruits (apples, strawberries and other berries) may be treated with pyrethroids registered in Canada, and several imported produce may be treated with pyrethroids not registered in Canada. Agricultural uses will leave residues on food, which will lead to exposure via ingestion of contaminated food. While pesticide residues on food are regulated and mostly compliant with tolerated residue levels, not all food items available on the market comply with these regulations.

Exposure

Pyrethroids mainly enter the body through ingestion, commonly via contaminated food or water, but also through ingestion of soil or dust particles, especially in children. Absorption through the skin when exposed to products during application or when touching treated surfaces is slower but it is also possible because pyrethroids are fat soluble and cells, such as those of the skin, are composed of a lipid bi-layer. Hence, using flea shampoo leads to limited absorption by the skin. Finally, breathing fine droplets or airborne dust particles may also occur, especially when using pyrethroids in an enclosed space. Once pyrethroids have entered the body, they are transformed through degradation into products called metabolites prior to excretion in the urine. Metabolites common to several pyrethroids include *cis*- or *trans*-DCCA (dichlorovinyl-dimethyl-cyclopropane carboxylic acid), 20 different pyrethroids may transform into 3BPA (3-phenoxybenzoic acid), while Cyfluthrin may also become 4F3PBA (also known as 4-fluoro-3-phenoxybenzoic acid). Hence, identifying which pyrethroid exposure corresponds to which metabolite detected in the body is difficult. Furthermore, metabolites may only be detectable in the blood or urine for a few hours or a few days. This is why proving a direct link between pyrethroid exposure and clinical symptoms of toxicity is so difficult.

Workers manufacturing, packaging, handling or applying pesticides are particularly prone to skin exposure. However, not all workplace poisoning with pyrethroids is related to such direct manipulation of pesticides. For instance, inhalation may occur when re-entering incorrectly ventilated work places and skin exposure may occur via contact with treated surfaces, something known to occur among flight attendants working in disinsected airplanes. Since the 1930s, pyrethroids have been used, pre-flight or even during a flight, to prevent the transport of disease vectors or harmful pests to other countries. Although this practice ceased in the US in 1979, it is still commonly used in other countries.

Acceptable exposure

Pyrethroid dietary exposure may be reduced by washing food because much of the pesticide does not get through the skin of fruits and vegetables. However, simple dipping in water is insufficient, and better removal is achieved via peeling and cooking. To prevent unwanted health side effects, pyrethroids residue on food and in water is regulated. Food tolerances set by the United States Environmental Protection Agency vary from 0.01 to 75 ppm, depending on the pyrethroid molecule. An Acceptable Daily Intake may also be calculated based on the average human body weight. These range from 0.002 to 0.07 mg/kg body weight per day depending on the legislation and the pyrethroid molecule. According to the World Health Organization, water concentration of Permethrin should not exceed 20 μ*g/l* in drinking water. However, the Quebec Regulation on drinking water does not include any pyrethroids among the 25 targeted pesticides for which regular testing at water purification plants is required. Drinking water contamination risks are unmonitored in Quebec despite documented surface water contamination in agricultural areas and groundwater contamination.

Enhanced sensitivity of children

Children may be more sensitive than adults to pyrethroids because they have a lower body weight but breathe and eat proportionally more than adults, and they often play on the ground, exhibiting hand-to-mouth behaviour. Their detoxification systems may not be as mature and their rapid development may lead to windows of particular sensitivity, for instance, during brain development. Normally, children are primarily exposed to pyrethroids in food; however when their homes have been recently treated, dermal absorption may be more important. Pyrethroids may be found in 5% of food regularly consumed by children, but not all food is systematically tested, nor is it tested on an annual basis. Unstructured eating habits of children may enhance their exposure, for example when food is dropped on treated surfaces and then eaten. A Montreal-based study revealed that children, compared to adults, excreted more of a pyrethroid metabolite most common in domestic or commercial extermination applications, even though home treatments with pyrethroids were seldom reported. Furthermore, children are more prone to head lice infestations, hence more susceptible to being treated with pyrethroid shampoo. Online forums contain numerous questions and testimonies of parents using dog shampoo to treat head lice infestations in children at a lower cost. Such uses are not evaluated in the registration of the products, are beyond the instruction label guidelines and should be prevented; however, since inappropriate use is in response to financial and health issues, simple recommendations to read and follow the label may not suffice.

Poisoning symptoms

Short-term skin exposure to pyrethroid may lead to abnormal facial sensations (paresthesia). Ingestion may cause sore throat, nausea, vomiting and abdominal pain, with or without mouth ulcers, increased secretions and swallowing difficulty. Most patients recover within 12-48 hours. Doses required to induce death range from approximately 55 mg/kg of body for Bifenthrin or lambda-Cyhalothrin to > 10,000 mg/kg body weight (extremely high dose) with *D*-Phenothrin. Hence, death following exposure is uncommon, though high doses will lead to trembling, convulsions and coma.

The effects of longer-term exposure are not well characterized for pyrethroids. Most of the data on pyrethroids toxicity was gathered from animal studies, with only few epidemiological studies in humans. Sub-lethal effects of long-term exposure in animals include perturbations in behaviour or development, reproduction, cancer and hormonal balance. In humans, non-specific symptoms like nausea, dizziness, respiratory pain, skin rashes, memory loss or immune system disruptions are difficult to link to one cause and may be confounded with other syndromes (e.g., Chronic Fatigue Syndrome).

Because pyrethroids are generally rapidly metabolized and excreted, only transient (non-permanent) effects may be apparent in humans. The main mode of action of pyrethroids is an effect on the nervous system and there is animal evidence of developmental neurotoxicity. For instance, Cyfluthrin was shown to affect the growth, survival and function of specific brain and spinal cells (called astrocytes). Nevertheless, regulatory agencies estimate that evidence is equivocal and advanced neurotoxicity studies are only mandatory for the registration of pesticides strongly suspected to have an impact on the nervous system. In lieu of conducting specific neurodevelopmental toxicity tests, registrants may cite results obtained on similar active ingredients, but not all active ingredients may lead to the same effects. Furthermore, common regulatory protocols may not be sensitive enough to detect certain toxic effects, while academic research using novel protocols may reveal previously unsuspected or unacknowledged

toxicity. Newborns may also be more sensitive than adults, and neurobehavioral changes to exposed youth may persist in adulthood. An association between pre-natal exposure to pyrethroids and neurodevelopmental toxicity has been suggested, whereby concentrations in air samples of the common synergist piperonyl butoxide is associated with poorer mental development in three-year-old children. Several other studies suggest an association between pesticides and impaired neurodevelopment in children and between pesticide exposure and Autism Spectrum Disorder or pervasive Developmental Delays. According to recent research, exposure to pyrethroids is common in American and Canadian children and seems associated with behavioural and cognitive difficulties. Specifically, children who had ten times the urinary concentration of the metabolite *cis*-DCCA as the average were twice as likely to exhibit behavioral problems according to parental observations. Highly exposed children had a higher likelihood of having learning disability and attention deficit disorder combined.

Recent research involving animal testing and epidemiological studies in humans shows potential adverse effects on human fertility, such as alterations of the male reproductive system, decreased sperm count, and mobility and DNA damage, which all led to lower fertility and pregnancy rates. Pyrethroids have been shown to alter hormones (endocrine disruptors), for example, by decreasing concentrations of testosterone (an important male hormone) and interfering with luteinizing hormone (involved in the production of sperm and ova) or altering thyroid function. *In vitro* studies on Cypermethrin and Fenvalerate show that pyrethroids may alter female and male hormones (estrogenic and antiandrogenic activity). The World Health Organization recognizes that tumours have been induced in rodents exposed to pyrethroids during their whole life, however, in 2001 the WHO concluded that there were no clear indication of carcinogenicity relevant for human health risk assessments. Permethrin was shown to be mutagenic in human and hamster cell cultures.

Environmental occurrence and persistence

When pyrethroids are used, sprays may drift with the wind, rain may wash the insecticides into surface water and pesticides may travel further in groundwater and sewer systems. Since pyrethroids have high affinity for particles, they tend to sink into sediment rather than stay dissolved in the water column, but nothing prevents eventual redissolution. Even if only 1% of applied doses reach open water bodies, this may be sufficient to harm aquatic life. In Quebec, stream contamination (Lambda-cyhalothrin, Permethrin and Cypermethrin) near vegetable production and orchards regions has been documented. In these follow-up studies, peak concentrations of Permethrin exceeded both the acute and chronic toxicity criteria for aquatic life by 32 and 350 times, and concentrations above said criteria were surpassed in 14-33% of the samples. Unfortunately, pyrethroids in ground water are not routinely monitored in the province. A 2015 report on groundwaters in the lower Saint-François region detected Permethrin in 6% of the tested wells in 2014. In the US, pyrethroids have also been detected in surface waters and sediments of agricultural regions, with even higher concentrations in urban areas. While research has revealed the presence of multiple pyrethroids in US waters (Cyhalothrin, Cypermethrin, Permethrin, Resmethrin, etc.), Bifenthrin is the most abundant. However, due to budgetary constraints, Permethrin is the only pyrethroid routinely surveyed in surface and groundwater.

In the environment, sunlight (photodegradation), chemical reactions in water (hydrolysis) and the action of microbes (biodegradation) will eventually break down pyrethroids, with factors like temperature, pH, presence of oxygen, and adsorption to soil or sediment particles affecting the time it takes until complete degradation. For instance, cold will slow decomposition, and will also increase toxicity in animals.

However, a compound which would break down outdoors in a matter of days may remain active for years inside buildings, where it is protected from the elements. On average, it may take 30-100 days to decompose most pyrethroids in soil exposed to oxygen, but inside a grain elevator or subway tunnel, it may take up to a year, and certain formulations intended to have residual effects (like those protecting wood from termites) may persist up to 5 years. In general, pyrethroids will break down faster in alkaline environments, so washing treated surface with alkaline water may help to cleanse surfaces following indoor treatments.

Toxicity to non-target organisms

Though mammals may be sensitive to long-term exposure to pyrethroids, slow absorption through the skin, rapid metabolism and excretion of metabolites may protect them to some extent. Birds are considered moderately to be affected by pyrethroids; however this does not take into account the indirect effects of reduced insects available for dietary intake in treated areas. Reptiles, fish and frogs have all been shown to be increasingly affected by pyrethroids at lower temperatures, however reptiles are rarely studied in registration eligibility decisions. Obviously, insecticides will affect insects, not only targeted pests, but untargeted ones as well. Bees may be particularly at risk from pyrethroid insecticides (generally considered toxic to highly toxic). If direct spraying does not harm them, secondary contact as they forage on wild or crop flowers exposes bees to "cocktails" of up to nine active substances. Seventy-five percent of human food crops relies on pollination, most often by bees, and this worldwide service was valued at 153 billion euros (CAD $214 billion) annually in 2005. Massive bee colony losses have been documented in the US and Europe and pesticides are one of the several factors causing this serious and complex threat. Earthworms, which play a critical role in organic matter cycling may also be exposed to long-term risks of pyrethroid exposure. All tested pyrethroids are toxic to fish, sometimes highly toxic. Unfortunately, important data gaps in toxicity assessment of pyrethroids to crustaceans, mollusks, marine and estuarine fish and benthic organisms exist. Concentrations used to kill mosquitoes or blackflies larvae in surface water bodies may suffice to harm sunfish and lake trout, though such uses are not documented in Canada. Sub-lethal effects may include inhibition of olfaction which can affect salmon, rainbowfish or sunfish reproduction, since they rely on pheromones to synchronize egg spawning by females and fertilization by males.

Cumulative risk assessment

Water and sediment in the US and Canada have been shown to contain a mixture of pesticides, including several pyrethroids. Pesticides may lead to cumulative or antagonistic interactions which are difficult to quantify and predict. Nevertheless, legislation requires assessment of interactions in cocktails of pesticides, but this type of research can hardly test all possible permutations of the thousands of chemicals we are exposed to on a daily basis. Research has shown that a mixture of organophosphorus and pyrethroids may increase toxicity by 140 to170 times in fish because of effects on the detoxification capabilities of animals under multiple exposure. Pyrethroids and neonicotinoids have been found to co-occur in Quebec surface waters, and in laboratory conditions both pesticides were shown to synergistically affect bees. Household dust may also contain quite a cocktail of pesticides, with 64% of kitchen floor wipe samples containing six pesticides together. Mixtures may occur randomly, but may also be voluntary, for instance with organophosphorus and pyrethroids being used together to manage increasing insect pest resistance. These two classes together are known to increase laboratory animal

sensitivity, and epidemiological evidence associates their combined presence to decreased sperm count in man. Further research on the effect of mixtures is required.

Registration review

Several pyrethroids are currently undergoing registration review in Canada and the United States. Decisions should be taken before 2016, and registrations may be harmonized between the two North American neighbours. In Canada, the Pesticide Management Regulatory Office of Health Canada is responsible for registration oversight. Though federal laws supersede all others, provincial governments also play a role in pesticide management. For instance Quebec's environmental ministry (*ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques*) oversees the Pesticides Act and the Environment Quality Act which mandate record keeping for pesticide sales, delivery of authorization certificates, training and licensing of pesticide applicators and retailers, among other requirements. Drinking water regulations under the Environment Protection Act requirements include the regular monitoring of pesticide concentrations in drinking water, however, pyrethroids are not currently targeted. In 2003, Quebec put forward a Pesticide Management Code (*Code de gestion des pesticides*) designed to reduce the health and environmental impacts of pesticide use. The Code did not restrict the use of pyrethroids, except in places used by children (daycares, elementary and secondary schools). In 2015, the government plans to review this Code, hence the importance of bringing new pyrethroid health and environmental issues to its attention, in the hope of further minimizing their impact on our wilderness and population. Beyond federal and provincial government jurisdictions, some 131 Quebec municipalities have placed further restrictions, for example on the uses of pesticides for aesthetic purposes within their boundaries. For instance, the city of Montreal requires the use of low impact pesticides outdoors, a regulation bound to fines where unapproved use is reported. However, this regulation only applies to outdoor uses of pesticides.

Several alternatives to pyrethroids do exist. In order to manage growing insect resistance to pyrethroids, we should seek less toxic alternatives like physical actions (heating or freezing), biological actions, low impact pesticides or complex natural plant extracts. Low impact pesticides like diatomaceous earth rely on its dehydration potential of the targeted insects, like cockroaches. Biological insect control has been proven efficient against a wide variety of agricultural pests without any reliance on synthetic pesticides. A US survey revealed that a majority of people would prefer non-pesticidal alternatives to eliminate insect pests in their homes. It is possible to eradicate bed bugs with advanced detection means (i.e. sniffer dogs) coupled to a heat treatment (offered by professional exterminators). It is possible to eradicate head lice with combing and manual nit picking following a strict time schedule. However, it is not always easy to properly train people and motivate them to make behavioural changes, i.e. a Pyrethrin shampoo appears so easy to apply for many who have not been instructed in potential lice resistance or consequences for treated children. Hence, studies on potentially safer alternatives to pesticides need to expand. For instance, essential oils may have great potential, but we need a good characterization of their efficiency and potential impacts, since even natural substances are not without risk: Remember that pyrethroids origins stem from a natural flower extract, and unmodified natural molecules bear some risk, a baseline which is often compounded via chemical optimization.

Scientific Literature Review

Introduction

Pyrethroids comprise a family of broad spectrum insecticides that have been used for more than 50 years. Pyrethroid insecticides are widely used because they are believed to be relatively safe for humans, their insecticidal potency is elevated at low dosages and they exhibit a rapid immobilization effect.[1] Pyrethroids are used against a wide range of insects considered pests, such as potato beetles and cotton boll weevil (*Coleoptera*), flies and mosquitoes (*Diptera*), aphids (*Homoptera*) and bed bugs (*Heteroptera*), ants and wasps (*Hymenoptera*), butterflies and moths like the cotton boll-worm (*Ledipodtera*), grasshoppers and crickets (*Orthoptera*), thrips (*Thysanoptera*) and head lice (*Phthiraptera*). Pyrethroids are extensively used in domestic, agricultural, public health (i.e. against public disease vectors like mosquitoes), medical and veterinary applications (see Table 1).

The extract of chrysanthemum flowers (*Chrysantemum cinerariaefolium* and *C. cineum*) called pyrethrum contains several active substances, one of which is Pyrethrin. This botanical extract was originally used in order to control body lice during the Napoleonic Wars.[2, 3] While pure Pyrethrins are moderately toxic to mammals, commercial preparations are considerably less toxic.[3, 4] Pyrethrins currently represents 80% of the total market of botanical insecticides.[3, 5] But because pyrethrum is unstable in sunlight (UV), its components were long ago chemically modified to enhance their stability, and that is when the synthetic pyrethroids (a man-made version of Pyrethrins) were born. The natural origin of this family of insecticides is not a guarantee of its safety. The first molecule synthesized in 1949 was called Allethrin,[6] but the first commercialization came about in 1978 with Fenvalerate.[1] Though more than 1000 pyrethroid molecules have been synthesized, approximately 40 are currently included in the pyrethroid class, and only a dozen of them are commonly used, with Permethrin being the most commonly used active ingredient worldwide and in the US.[1, 7] Now over 3,500 pyrethroids products are registered in the United States.[8] Worldwide, Pyrethrins and pyrethroids sales were less than 500 tonnes per year in 1976,[9] then ranked second behind organophosphorus in the insecticide market in 1995 with 23% of worldwide sales,[10] and now account for 17% of global insecticide sales with a market value of $7 billion.[11] In Canada, 744 pyrethroid formulations are registered for domestic, commercial, agricultural or industrial uses under Health Canada's Pest Management Regulatory Agency (PMRA), with 588 dedicated to domestic uses (representing 79% of all formulations) and only 4 with restricted uses (restricted products are not available to the general public and can only be used under certain circumstances by specifically trained individuals).[12] To appreciate the importance of the current registration review process, the current pyrethroid cluster pesticide registration review targets active substances which are present in 614 formulations, including 478 domestic products.

Table 1: Pyrethroid formulations registered by Health Canada classified by active substances. Asterisks (*) identify pyrethroids under current review. Information compiled from Health Canada website on 2015.02.23: http://pr-rp.hc-sc.gc.ca/ls-re/index-fra.php. The sole purpose of providing commercial product examples is so that the public can recognize common household or professionnal use products, by referring to brand names they may know. Other brands and products are registered by the PMRA. No specific claims regarding products brands are made in this review.

Active Substances	total	domestic	restricted	Examples of commercial product names	Examples of applications (which fruits, vegetables, crops, plants, animals or places)
Numbers	**744**	**588**	**4**		
Percentage (%)	*100*	*79*	*1*		
Allethrins*	150	128	0	Raid or OFF! Mosquito coils, Raid home insect killer	Used in grain mills, food processing plants (bakeries, canneries, freezing establishments, bottling plants, breweries, restaurants), food services, storage and food transport vehicles.
Cyfluthrin*	9	4	0	Tempo, Raid Spider Blaster, and & roach, crawling insect bug killer	CyLence is used against horn flies, lice on beef cows and lactating cows.
Cypermethrin*	7	0	0	Ripcord 400EC agricultural insecticide	Row crops (Wheat, Barley, Canola, Corn), Vegetables (Sunflowers, Asparagus, Celery, Crucifers like cabbage, cauliflower, broccoli and Brussels sprouts, Carrots, Lettuces, Onions, Potatoes, Rutabagas, Turnip, Tomatoes). Fruits (Apples, Pears, Peaches, Plums, Grapes, Strawberries). Eliminator in eartags against facial flies of bovids and lactating cows.
Deltamethrin*	1	0	0	Insecticide deltaguard SC	Lawns and flowers (no food)
d-Phenothrin (Sumithrin)*	125	110	0	Knockdown flying insect killer 1, Raid max house & garden multi-bug killer, Raid outdoor and nest destroyer 2, Wilson One Shot Garden Kille, Schultz House plant Insect Spray, Green Earth Homecare bed bug travel spray, C-I-L Wasp and Hornet Long Shot, X-Pire, Hartz Ultraguard flea & Tick treatment for dogs, WalMart Great Value Bed Bug Killer,	Not used on crops, allowed on house plants, away from food preparation area.
Lambda-cyhalothrin*	18	0	0	Syngenta Technical Insecticide, Matador, BASF residual effect insecticide, Silencer emulsifiable concentrate insecticide	All industrial crops including fruits, nuts, potatoes, oleaginous cultures, cereals, alfalfa, pasture, corn, legumes.
Permethrin*	381	313	4	Ambush, Pounce, KG insecticide against fleas and ticks for cats or dogs, Raid for ants, cockroaches, earwigs; Hagen anti-fleas carpet protector, spider killers; Horse flies sprays; Wasps and Hornets destructor; OFF outdoor mosquito repellant, Ortho home max defense ants eliminator; Raid fumigant; Eco-Guard; Knock Down, etc.	Asparagus, Beets, Carrots, Cereals, Colza, Cucumbers, Ginseng, Lettuces, Lentils, Linseed, Corn, Peas, Peppers, Potatoes, Sunflowers, Mushrooms, Peanuts, Chinese cabbage, Pak-Choi, Radishes, Horseradish, Snap beans, Tomatoes, Tobacco, Turnip, Apples, Pears, Nectarines, Grapes, Blueberries, etc.
Pyrethrins*	25	14	0	Knock Down flying insects, Doctor Lethal eco choice	Asparagus, Beans, Broccoli, Celery, Cranberries, Eggplants, Lettuces, Mustard leaves, Cabbage, Turnip, Peppers, Radishes, Potatoes, Spinach, Tomatoes
Resmethrin*	19	15	0	Schultz fungus gnats destructor; PPP shampoo for fleas and ticks; K-G vaporiser IV against wasps and hornets; Buzz-up? Wasps and hornets,	Wilson fungus gnats, destructor spray on house plants, in small gardens and greenhouses, but no mention of crops for this active substance.
Tetramethrin*	0	0	0	-	
Bifenthrin	3	0	0	Capture 240 EC	Raspberries and Potatoes.
Fenvalerate	0	0	0	No longer registered in Canada, historically three formulations including Bovaid ear tags.	For the control of horn and face flies in beefs and lactating cows.
Flucythrinate	0	0	0	No longer approved in Canada, 2 formulations previously approved in Canada (historical products) including Guardian Insecticide Cattle ear tag	For the control of stable, domestic, horn and face flies in beefs and lactating cows.
Fluvalinate	0	0	0	-	-
Tefluthrin	2	0	0	Syngenta Force 3.0G Insecticide	Field, sweet and seed corn only. Corn forage, grain cobs and other plant portions may be fed to livestock.

Let us explore the volume of pesticide sales and specifically pyrethroids in a province like Quebec, Canada. Quebec sales of pesticides are on a decreasing trend with 4.6% fewer kilograms of active ingredients sold since 1992, the first record tracking year. However, contrary to overall pesticide trends, sales of pyrethroids have increased from 2004 to 2010, reaching 12,139 kg (all sectors together: domestic, agricultural, pest management, etc.). The environmental risk for the use of pyrethroid insecticides is increasing according to the latest Quebec report (data from 2011).[13] The use of adjuvants is also on the rise in the province, but they only account for 3.4% of all pesticides sales by weight (it is impossible to know if formulations contain an increasing amount of adjuvants relative to their active ingredient content, as formulations are secret proprietary information not disclosed in sales reports).[13] In Quebec, domestic sales of pyrethroids nearly doubled in half a decade (from 1482 kg a.i. in 2004 to 2780 kg a.i. in 2010) and extermination sales were at 6210 kg a.i. in 2010.[13] While domestic uses have increased, agricultural uses had decreased by a third (3036 kg a.i. in 2004 to 2011 kg a.i. in 2010).[13] Quebec agricultural use of pyrethroids involves animal rearing and other agriculture-related situations (not restricted to plant culture). Pyrethroids are not commonly used in landscaping nor for industrial purposes, but it is the first class of pesticide used by the extermination sector in the province. Cypermethrin alone is responsible for 1.9% of Quebec's pesticides Environmental Risk Index (IR_E) in 2010. Along with Cypermethrin, Permethrin is also one of the most widely sold pyrethroid in the province, with sales ranging from 1,001-10,000kg a.i. in 2010. Pyrethroids with sales below 1000 kg include, in alphabetical order: Cyfluthrin, Cyhalothrin-lambda, Deltamethrin, *d-cis*, *-trans*-Allethrin, *d-trans*-Allethrin, Fluvalinate, *d*-Phenothrin, Pyrethrins, Resmethrin, Tefluthrin and Tetramethrin and its active derivatives. Allethrins (other than the specific isomers mentioned above). No sales of Fenvalerate and Flucythrinate were reported in 2010. All of the above pyrethroids are part of Health Canada's cluster scheduled to undergo re-evaluation before 2016, except Fluvalinate, Tefluthrin, Fenvalerate and Flucythrinate (http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rev2011-05/index-eng.php).

Throughout the world, there is a trend to replace the more toxic organophosphorus insecticides with pyrethroids, due to a phase-out of organophosphorus pesticides for residential use[14-16]; but this trend is also observed in agricultural regions.[17] Pyrethroids are the pesticide most frequently associated with human acute poisoning despite their generally acclaimed lower toxicity, but fortunately few of the reported cases resulted in major effects or death, for example only 2% of cases reported in the US state of Oregon.[14]

The various pyrethroids active substances registered in Canada have different potential environmental and health impacts. Aggregated indices of potential impacts have been created by various organizations to help users and consumers assess the relative risk of applying or consuming pesticides. The human and environmental impact indices were created by the Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec (Quebec Ministry of agriculture, fisheries and food), with the Ministère du Développement durable, de l'Environnement et Parcs (Ministry of sustainable development, environment and parks) as well as the Institut national de santé publique du Québec (Quebec National institute for public health).[18] A description of the methodology appears in Samuel et al.[18] To quantify the risk associated with a particular pesticide use, farmers, agronomists and other users are encouraged to consult the database.[19] Based on specific cultivation and pest scenarios, appropriate registered products can be located, and their environmental and health impacts may be compared. As an example, Table 2 shows a summary of the pyrethroids which can be used to fight a Colorado Potato Beetle infestation in a potato field. Note that the other classes of pesticides recommended for this scenario were not considered

in this pyrethroid-focused summary. These indices represent potential risk for users of the pesticide and due to its presence in the environment, however because food is a major pathway for pesticide intake, indices focusing on this specific risk have also been developed.

Table 2: Various aggregated environmental and health consumption risks assigned to various pyrethroid active ingredients based on a simulation intended to eradicate the Colorado Potato Beetle from a potato field.

Active Substances	Environmental Impact Index	Human health risk index
Cypermethrin*	124-127	183-211
Deltamethrin*	15	56
D-Phenothrin (Sumithrin)*		
Lambda-cyhalothrin*	48-96	81
Permethrin*	130	212

While some Canadians may chose organic foods to circumvent potential failures of the pesticide registration system, many more chose to consume conventionally grown fruits and vegetables. To answer the need for ethical information on consumers' risks, various tools were created. A well-known American tool created by the Environmental Working Group two decades ago is an annual publication of the Dirty Dozen (Plus) and Clean Fifteen, helping consumers to rapidly identify the worst and best fruits and vegetables found on the market, among 48 common varieties.[20] This index is derived from the reports from the US Department of Agriculture and the Food and Drug Administration on food contaminated by pesticides residues.

To circumvent two methodological flaws identified in the EWG method,[21] Soumis[22] developed a novel index in 2015 which is adapted from the Indice de Risque Toxicologique created by the Quebec national institute for public health mentioned above. The adapted Toxicological Risk Index, is abbreviated TRI'. First, it considers the relative importance of the toxicological risk for each substance, instead of relying solely on the average concentration of each active substance. Secondly, it decreases the systematic disadvantage imposed on food items which contained multiple pesticide residues simultaneously, by introducing the relative toxicity of individual pesticides and not simply summing the number of pesticides present. Together with the detection frequency for each pesticide within a food sample and the frequency that food items are contaminated with more than the maximal residual limit, we obtain an adapted Toxicological Risk Index associated with the consumption of fruits and vegetables. Food produced by organic farming, food from imprecise origin and uncommon varieties, and food items insufficiently tested (fewer than three specimens) were left out. A total of 179 products, 45 from Canada and 134 from 23 different countries were quantified. From this list, all food items, even the "most contaminated ones" are *a priori* edible based on current maximal residue limits, and even when these limits are surpassed, the consumer is still protected by safety margins because residue limits are well below admissible daily doses of the pesticides, and the Canadian Food Inspection Agency neither washes nor peels fruits and vegetables prior to testing, leading to a precautionary worst-case scenario portraits for the consumers. Finally, this list is not an absolute ranking, but a relative one.

The TRI' index was further refined to specifically address pyrethroids. In order to do this among 179 food produce found on the Canadian markets as per the Canadian Food Inspection service report,[23] fruits and vegetables which scored positive for detection of pyrethroids which are registered in Canada for direct use on crops (row crops, fruits and vegetables) or which may enter the human food chain indirectly (registered for use on lactating cows or cattle, or for use in areas where human food is transported, stored, transformed, prepared or served). Finally, from this sub-set of pyrethroids, only those which appeared in the SAgE Pesticides database were retained.[19] Use of only this database had the objective to reduce the variability in the source data values to facilitate chronic risk weighting based on the Environmental and Human Health Risk Indices described above.[18] Consequently, the calculated values presented in
Table 3 may not necessarily equate with those presented in Soumis' earlier report.[18] The higher the risk according to the TRI', the greater the risk associated with the consumption of a particular pyrethroid. However, because the TRI' is an index, it does not correspond to a real measurable quantity, and hence does not have any units. Furthermore, due to the mathematical methodology used to establish their values, a linear relationship (proportionality) cannot be used to compare different values, i.e., a substance with a TRI' of 1000 is not necessarily ten times more toxic than another substance with a TRI' of 100. The best way to compare these substances is to rank them.

Table 3: Various aggregated health risks based on food consumption risks attributed to different pyrethroid active ingredients registered in Canada, as per Soumis.[22] ND indicates unquantified TRI' due to absence of toxicology data in the SAgE Pesticide database despite the possibility of encountering the pesticides in fruits and vegetables.

Active Substances	Adapted Toxicological Risk Index from food consumption (TRI')
Allethrins*	289
Cyfluthrin*	169
Cypermethrin*	196
Deltamethrin*	16
D-Phenothrin (Sumithrin)*	36
Lambda-cyhalothrin*	16
Permethrin*	552
Pyrethrins*	210
Resmethrin*	812
Tetramethrin*	ND
Bifenthrin	ND
Fenvalerate	ND
Esfenvalerate	ND
Flucythrinate	ND
Fluvalinate	16
Tefluthrin	324
Etofenprox	ND

* Products currently included in the Canadian PMRA pyrethroid registration review cluster.

Chemistry: Classes, co-formulants

The botanical Pyrethrins are composed of a mixture of six ingredients with insecticidal activity: Pyrethrin 1 and 2, Cinerin 1 and 2 and Jasmolin 1 and 2.[8] Although pyrethroids have evolved considerably over the past few decades, synthetic pyrethroids retain a common structure, composed of a chrysanthemic acid linked to an aromatic alcohol by an ester linkage (Figure 1).[24] Newly synthesized molecules tend to be more active, but are also used at lower doses. Synthetic pyrethroids can often (but not always) be recognized by the suffix *–thrin*; they include Allethrins stereoisomers, Bifenthrin, Beta-Cyfluthrin, Cyfluthrin, Cypermethrin, Cyphenothrin, Deltamethrin, Esfenvalerate, Fenpropathrin, Tau-Fluvalinate, Lambda-Cyhalothrin, Gamma Cyhalothrin, Imiprothrin, 1RS *cis*-Permethrin, Permethrin, Prallethrin, Resmethrin, Sumithrin (D-Phenothrin), Tefluthrin, Tetramethrin, Tralomethrin, and Zeta-Cypermethrin.[8] Synthetic pyrethroids can be divided in two broad classes, based on the absence (type I) or presence (type II) of an α-cyano group which enhances toxicity. Different spatial organization of the same chemical formula (termed isomers) can be sold as a mixture of the different isomers or separately, depending on the commercial formulation.[25, 26] The different isomers can be more or less toxic, but generally the stereoisomer most toxic to insects (desirable attribute of insecticides) is also the most toxic to mammals (undesirable side effect).[25, 26]

Similarly to all other pesticides, pyrethroids are used as commercial formulations which consist of mixtures of the active ingredient (the pyrethroid itself), with co-formulants, also called adjuvants, synergists or *inert ingredients*. But so-called *inerts* are not necessarily devoid of intrinsic toxicity; this is why the US Environmental Protection Agency requested that formulators voluntarily changes the term *inert* to *other* ingredient on pesticide labels.[2] Synergists implies enhancement of the toxicity of pyrethroids. Piperonyl butoxide and MGK-264 are common sygergists[8] and both represent some risk of toxicity. Piperonyl butoxide, for instance, can be present at concentrations ten times higher than the pyrethroids themselves in a commercial formulation, and their role is to inhibit natural detoxification by an enzyme (Cyt P_{450}) in order to extend the useful life and hence the activity of the active principle. As such, it can synergistically increase human sensitivity not only to pyrethroids, but also to other environmental toxicants. MGK-264 is the short name for N-Octyl bicycloheptene dicarboximide. Used in pyrethroid formulations, it is intended to act as a synergist and not to have instrinsic insecticidal properties alone. However, there are potential endocrine dusruption evidence for MGK-264 in the literature.[27] Many human epidemiological studies reporting pyrethroid toxicity are limited by the difficulty in differentiating the effect of the active ingredient, or pyrethroid, with that of the additives used in the commercial preparation.[14]

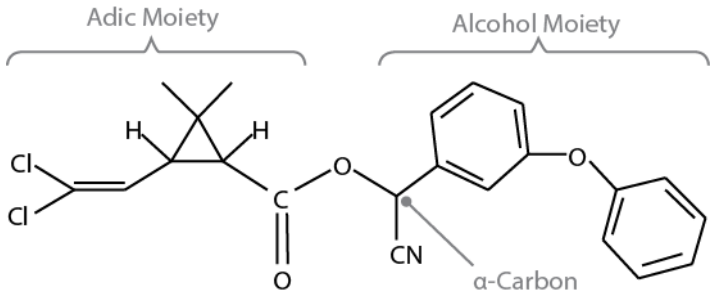

Figure 1: Typical structure of pyrethroids illustrated in Cypermethrin.[24]

Mode of action

The majority of insecticides sold in the US are neurotoxic, either inhibiting neurotransmitters or affecting voltage-gated sodium channels.[28] Pyrethroids are insecticides which act by interfering with the nerve transmission influx.[25,6] Simply put, pyrethroids interfere with sodium (Na) channels in the tail (axon) of neurons (see Figure 2). Sodium channels are common across a wide variety of animals. By blocking these gates open, they elongate the time of the nerve impulse. This leads to muscular paralysis and death.[1] At higher concentration, pyrethroids may also interfere with chloride channels. Other proposed mechanisms, likely representing secondary modes of action, include antagonism with gamma-aminobutyric acid (GABA) receptors, modulation of nicotinic cholinergic transmission, increase of noradrenaline release and action on calcium channels.[1, 25]

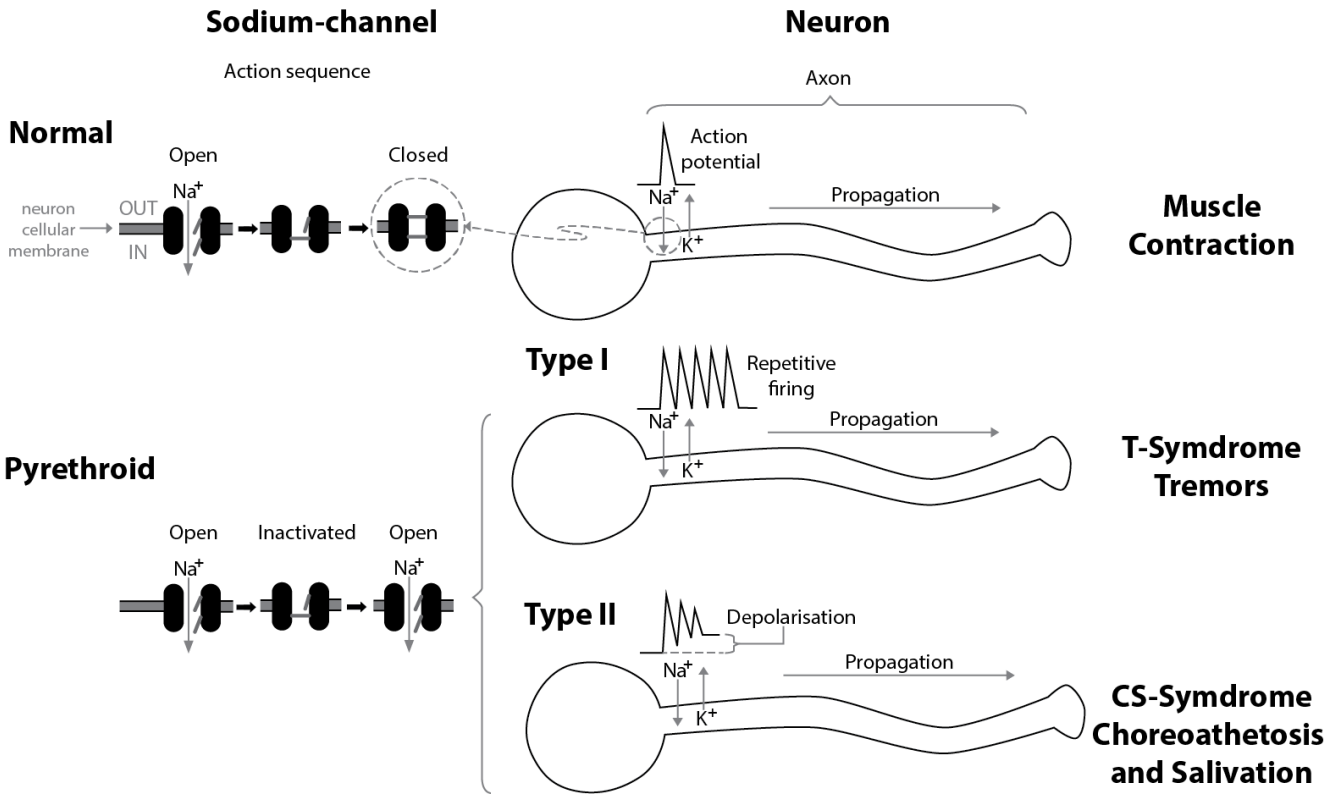

Figure 2: Mode of action of pyrethroids on neurones. The top diagram shows the normal functioning of sodium channels which open, allowing sodium to pass, but then close after the action potential. This single action potential propagates through the nerve tail (axon) and triggers muscle contraction. Upon exposure to pyrethroids, the sodium channels malfunction, and may remain opened instead of returning to a closed state after initiation of the action potential. This will lead to repetitive firing (in type I pyrethroids) or depolarization (in type II pyrethroids) leading to tremors or involuntary movements (choreoathetosis) depending on the type of pyrethroid. Note that the T (fine tremors) and CS (choreoathetosis and salivation) syndromes are not as clearly differentiated as initially characterized in the pyrethroid literature, and mixed symptoms may occur.

Domestic uses

Pyrethroids are commonly used as a treatment for vector borne diseases (e.g., mosquito carrying malaria plasmodium) and against residential pests and parasites (e.g., fleas, ticks, head lice, cockroaches, etc.).[2, 29] As mentioned above, Quebec domestic sales of pyrethroids nearly doubled in half a decade (from 1482 kg a.i. in 2004 to 2780 kg a.i. in 2010) and extermination sales were at 6210 kg a.i. in 2010.[13] Among the pyrethroid formulations available to consumers, the vast majority (79%) are available for domestic use, i.e., for the members of the general public, who are not required to have any specific training in pesticide handling and application, and who are expected to carefully follow label instructions.

Modern life is characterized by long hours spent indoors, and because indoor use of pesticide is common, this results in high exposure levels. For instance, in the US, it is estimated that citizens spend 90% of their times indoor and that 74% of homes are treated with pesticides.[30] Favoured choices of pest management in urban dwellings include traps (41%), sprays (34%), smoke bombs (27%) and non-volatile gels (25%).[30] Most US households have measurable levels of insecticides (as detected in floor wipe samples); the most commonly detected is Permethrin (89%).[31] Cypermethrin (46%) and piperonyl butoxide (52%) are also commonly detected.[31, 32] Urban multiunit dwelling are often plagued with pests problems, for which control with excessive, restricted or banned pesticides has been documented. An example of restricted pesticide misuse is application of a Cyfluthrin-based pyrethroid wettable powder by residents, without following recommended dilutions on the label, compounded by the fact that this insecticide is normally restricted to professional pest managers.[31] Banned organophosphorus pesticides residential use has also been documented in questionnaires and quantified by sampling.[32] Urban multiunit housings are expected, and observed, to have high loads of pyrethroids.[31] Domestic pests may create health consequences, but so do treatments with pesticides. For example both cockroaches and insecticides used against them are associated with asthma problems.[30] Exposure to pyrethroid (Permethrin) was associated with non-atopic asthma in farm women and maternal exposure to pesticides (predominantly assumed to be organophosphates and pyrethroids) is associated with allergic asthma in children.[33]

Lice are treated with pyrethroid formulations often used on the scalp, with a high proportion of children receiving treatment due to contamination in daycare and schools. Natural Pyrethrins were introduced on the worldwide market in 1948 to control the head louse, synergized Pyrethrins (piperonyl butoxide) were introduced in the US in the 1980s, and finally synthetic pyrethroids were authorized in the US in 1986 (1% Permethrin) and launched worldwide in 1992 (Phenothrin and Permethrin).[34] When head lice treatment fails to exterminate the undesirable insect from children's heads, parents are often told that reinfestation occurred or that they failed to appropriately use the product or to follow through correctly.[34] However, head lice resistance to pyrethroids was first documented over a decade ago, and this resistance leads to the use of increased concentrations of pyrethroids, alternating between various families of pesticides, and requires the introduction of new insecticidal molecules.[35] Beyond this documented drug resistance, some specialists even question the global effectiveness of pediculicides (insecticides targeting lice).[34]

In homes, pyrethroids may be used in vaporizers or as powders to eradicate several crawling and flying insects like cockroaches, ants and wasps. Indoor uses in confined spaces may lead to exposure by breathing during application (inhalation). After application, children who play on the floor and exhibit

hand-to-mouth behaviour may further be exposed via their skin (dermal) and digestive tract (ingestion). In a treated home, floors, sofas and carpet fabrics are important reservoirs for pyrethroids, and may lead to exposure of occupants.[30] In addition, some commercial formulations of pyrethroids (with each product containing a different assemblage of pyrethroids active ingredients and co-formulants to target different pests) may have a repulsive effect on cockroaches (they augment locomotor activity). This may render eradication via less toxic alternatives more difficult because the exposed insects then migrate from their usual kitchens and bathrooms habitats to unusual zones such as bedrooms. Permethrin was detected in all (100%) urban public housing units surveyed in Boston (Mass., USA), while Cypermethrin and Cyfluthrin had a prevalence of more than 90% and 71%, respectively.[30] Finally, flea treatment of pets often relies on pyrethroids in shampoos and collars. These have been linked to poisoning in children.[29] Misuse of pyrethroids in domestic settings (e.g., using Cyfluthrin wettable powder without mixing with water) has been documented and leads to greater than necessary exposure.[30] Exposure to pyrethroids in homes and other treated areas varies with the age of residents, income, but can also be affected by how pesticides are applied, such as whether or not recommended guidelines are followed.

The poison control centres receive initial contacts in case of pesticide incidents and accidents, but we could not obtain a compilation of incident reports from the Quebec or National association. The Quebec government does not compile statistics on pesticides incidents or accidents. The Canadian government (Health Canada) compiles incident reports on various pesticides, and the last report, published in 2013, contains a section related to pyrethroid.[36] This report analyzed trends from 2007 to 2011 for the 2,420 incidents related to pyrethroids. The majority of Canadian incidents surveyed were considered minor in nature, but pyrethroid-related incidents nevertheless accounted for more than a third of all human incidents and more than half of all domestic animal incidents reported to the PMRA. Lambda-cyhalothrin was involved in 15 incidents reported since 2007, 11 of which were classified as Canadian. The number of incidents associated with this active ingredient increased from 2007 to 2011. The increase in pyrethroid-related incidents led to a recommendation to review label warnings to make sure that they are clear to the consumers and consistent. Reported symptoms include respiratory (e.g., irritation of the throat), dermal (e.g., skin rash), neurological (e.g., headache), and gastrointestinal (i.e., nausea). The majority of incidents occurred during application or following contact with a treated area. Domestic product application in homes, leading to single short-term human exposure, with insecticide sprays, predominate in the reports. On the other hand, animal incidents occurred with flea and ticks control products directly applied on animals. Few reported cases involved a violation of the label instructions. In fact, even when the label instructions are respected, inhalation and dermal exposure to domestic insecticide sprays occurred. Despite the label instructions, which are intended to reduce risk, incidents may occur at a rate higher than what would be expected based on sales reports. In order to reduce the number of incidents, potential poisoning symptoms and more precise instructions for the consumers will be listed on the labels. A list of incident reports associated with different active substances can be found in Table 4. Each incident report may be consulted online by accessing the Health Canada portal.[37]

Table 4: Incident reports by active substance based on Health Canada database.[37] Data compilation on 2015.04.16.

Active Substances	Current Applications	Registered Products	Current re-evaluation	Incident reports
Allethrins*				NA
Cyfluthrin*	0	9	1	91
Cypermethrin*	1	7	1	32
Deltamethrin*	4	8	1	52
D-Phenothrin (Sumithrin)*	10	126	1	264
Lambda-cyhalothrin*	8	18	1	122
Permethrin*	17	377	1	3659
Pyrethrins*	17	521	1	1201
Resmethrin*	0	19	0	13
Tetramethrin*	0	145	1	121
Bifenthrin	2	3	0	2
Fenvalerate				NA
Esfenvalerate				NA
Flucythrinate				NA
Fluvalinate	1	2	0	20
Tefluthrin	3	2	0	4
Etofenprox	0	2	0	483

Agricultural uses

While pyrethroids are commonly used to control several insects affecting agricultural production, their main agricultural uses are for animal rearing. Between 1997 and 2010, the environmental (IR_E) and health risk index (IR_S) of pyrethroids have decreased in Quebec agriculture from 7.4 to 2.6%, and from 2.6 to 0.9%, respectively.[13] However, the environmental risk index had increased in the report for the year 2011.[13] The use of pyrethroids in animal husbandry increased marginally from 1,683 kg a.i. sold in 2004 to 1767 kg a.i. sold in 2010.

Table 1, above, lists common crops treated with pyrethroids against various insect pests in Canada, and similar product uses are listed elsewhere for the US.[2] In Quebec, pyrethroids may be applied to several vegetables (sweet corn, potatoes, carrots, lettuces, onions, green onions and members of the cabbage family) and fruits (apples, strawberries and other berries).[38] Until resistance is found in certain insect pests, pyrethroids are commonly the first choice in conventional growing systems.[39] Agricultural uses are linked to exposure of workers, especially when good agricultural practices are not followed. Faulty practices for pyrethroids were documented in other countries, such as China in the late 1980's,[40] but inappropriate use and distribution of general pesticides has also been documented more recently in Quebec, where a 2010 report found pesticides not registered by Pest Management Regulatory Agency of Canada on sale.[13] Among specialized workers, use of pyrethroids before it has been approved by Health Canada and uses outside approval limits is known to occur in Quebec.[39] Agricultural use will leave traces of residues on food, and this leads to exposure via ingestion.[41, 42] As long as pesticides are used according to the recommended practices (within approval limitations and according to good agricultural practices), this leads to human pesticide exposure which has been deemed safe by Health Canada. Any abusive or non-intentional misuse exposes us to residue levels of for which the safety is not attested (further discussed below).

The most recent data from Health Canada's National program for the surveillance of chemical residuals from the Canadian Food Inspection Agency reveals that the vast majority of fruits and vegetables produced in Canada (97.64%) or imported (94.30%) and found on the Canadian market conform to maximum residue limits (MRL). However, most of them are contaminated by at least one pesticide residue.[23] As would be expected, imported fruits and vegetables are more likely to be contaminated than Canadian-grown food, and part of this is explained by the greater number of registered products used outside of the country compared to within Canada. With respect to pyrethroid contamination, no Canadian nor imported dairy products, eggs or meat were found to be contaminated. Less than 1% of Canadian and imported honey samples contained Permethrin. For honey, Tau-Fluvalinate was not found even though it is used in apiaries and flowering crops pollinated by bees.[43, 44] Fruits and vegetables samples which had a pyrethroid residue above the maximum residue limit are listed in Table 5.

Table 5: Contamination of fresh fruits and vegetables produced in Canada (C) or Imported (I) based on the Canadian Food Inspection Agency 2014 report.[23] Non-conformity is the opposite (100% - X) of the conformity value given in the source report, and it represents the percentage food samples having a pyrethroid residue level above the maximum allowed. Only the pyrethroids are listed in for the non-conform residues detected, so other pesticides were commonly detected along with the pyrethroids, but only the pyrethroids (which are the focus of the current review were listed here). Readers are encouraged to consult the original report for details.

Source	Food product	% Non-conformity	Non-conform pesticide residue
C	Dill	33	Cypermethrin, Permethrin
C	Cabbage	33	Deltamethrin
C	Herbs	30	Lambda-cyhalothrin
C	Asian vegetables	28.5	Permethrin
C	Beets	2.5	Cyfluthrin
C	Potatoes	2.5	Permethrin
I	Basil	75	Bifenthrin, Lambda-cyhalothrin, Cypermethrin, Deltamethrin
I	Dill	47	Cyfluthrin
I	Mint	50	Lambda-cyhalothrin
I	Herbs	40	Piperonyl Butoxide
I	Peas	39.5	Cypermethrin
I	Spinach	39.5	Cyfluthrin, Lambda-Cyhalothrin, Cypermethrin
I	Asian vegetables	36	Cypermethrin, Permethrin
I	Cabbage	21	Cypermethrin
I	Kohlrabi	19	Permethrin
I	Peppers	16	Bifenthrin, Lambda-cyhalothrin, Cypermethrin
I	Lettuce	15.5	Cypermethrin
I	Parsley	15	Permethrin
I	Rapini	14.5	Permethrin
I	Strawberries	12	Bifenthrin, Fenpropathrin, Piperonyl Butoxide
I	Blackberries	11	Bifenthrin
I	Starfruit	10	Esfenvalerate, Fenvalerate
I	Artichoke	10	Esfenvalerate, Permethrin
I	Various vegetables	8	Cypermethrin
I	Orange	8	Lambda-Cyhalothrin
I	Yellow or green beans	8	Fenvalerate
I	Apricot	7	Fenpropathrin
I	Nectarine	7	Fenpropathrin
I	Grapefruit	6.5	Fenpropathrin
I	Eggplant	6	Lambda-Cyhalothrin
I	Peaches	6	Bifenthrin
I	Cherries	5.5	Fenpropathrin, Permethrin
I	Lemon	5	Piperonyl Butoxide

Physico-chemistry

Pyrethroids are more soluble in fats than in water, though they may be washed off from surfaces by rain. Their volatility is low, and in air, they are primarily associated with dust particles. Natural Pyrethrins are rapidly degraded by sunlight (*photodegradation*) and in presence of humidity (*hydrolysis*). Synthetic pyrethroids, however, are more stable, though this family of pesticides is generally considered to degrade rapidly in the environment compared to other insecticides.

General physico-chemical properties of various pyrethroids are presented in Table 6. Briefly, hydrophobicity is measured as the logarithm of the octanol vs. water partition coefficient (or K_{ow}) and represents how much of a substance will dissolve in organic solvents compared to water. The variation is nearly four orders of magnitude from the most hydrophilic, Esfenvalerate (K_{ow} = 4), to the most lipophilic, Tralomethrin (K_{ow} = 7.6). Since K_{ow} serves as a predictor of environmental fate (adsorption to sediments, bioaccumulation, etc.) and animal toxicity (absorption, distribution, storage, degradation and excretion), it is apparent that pyrethroids, as a family of chemicals, have a wide range of properties.

Similarly, the organic carbon vs. water partition coefficient (or K_{OC}), gives an approximation of how much the chemical will adsorb and desorb from organic matter in the environment.[45] Here, not all pyrethroids are characterized, but a much lower range of variability has been observed. Normally, lower values ($\leq$ 2.7) represent compounds which are very mobile in the environment because of their water solubility; larger values characterize compounds have a tendency to strongly adsorb to soil organic matter, which minimizes environmental movement, and this appears to be the case for pyrethroids (at least under controlled laboratory conditions). The partition coefficient measures the relative affinity of the pyrethroids with organic solvents or organic carbon. In contrast, solubility is simply how much of a compound will dissolve in water, generally under fixed parameters of temperature and pH. Pyrethroids like Bifenthrin (0.1 mg/l) are two orders of magnitude more water soluble than Cyfluthrin, Deltamethrin, Esfenvalerate or Fluvalinate ($\leq$ 0.002 mg/l).

When a pure chemical is in equilibrium with its liquid or solid form, vapour pressure is a relative measure which indicates the relative volatility of a substance (via the pressure exerted by the gaseous phase). Greater vapour pressure (i.e., Bifenthrin = 1.8×10^{-4} mm Hg at 25°C) means higher volatility; however, pyrethroids are generally recognized for their low volatility (as much as seven orders of magnitude lower than Bifenthrin in the case of Tralomethrin (3.6×10^{-11} mm Hg). Henry's Law Constant then puts vapour pressure, molecular weight of the compound and water solubility in relation to estimate exposure via the aerial pathway. On the extreme ends of the pyrethroids family spectrum, is Bifenthrin, which is the most likely to lead to significant aerial exposure and Tralomethrin which is the least likely (with four orders of magnitudes separating the extrema).

Finally, pyrethroids may degrade differently depending on the environmental compartments (soil or water) where they end up, and environmental conditions (aerobic or anaerobic). The measurement is days for half-life ($t_{1/2}$), which means the number of days required to disintegrate half of the original product concentration. For example, if Cyfluthrin ends up in a soil which is well supplied with oxygen, microbes may break it down rapidly, with $t_{1/2}$ as little as 11.5 days. On the contrary, should Bifenthrin be spilled in a poorly aerated soil, it may remain there for years ($t_{1/2}$ = 425 days). Notice the important variability for compounds like Cypermethrin ($t_{1/2}$ =1.9-619) indicating that changing environmental conditions may lead to radically different persistence in the environment and remember that the longer

an active chemical stays in the environment, the higher the chances of environmental and human toxicity. To summarize persistence, pyrethroids are generally considered to have a low environmental persistence, but keep in mind that this varies with the active ingredient of interest and with environmental conditions.

Table 6: Physico-chemical properties of selected pyrethroids.[8, 17, 19]

Active ingredient	Log K_{ow}	Log K_{oc}	Solubility (mg/l)	Vapour Pressure (mm Hg at 25°C)	Henry's Law Constant (atm-m^3/mol at 25°C)	Soil aerobic half-life (days)	Soil anaerobic half-life (days)	Hydrolysis half-life (days)
Allethrins	>5	3.13	4.6	1.2×10^{-6}	6.1×10^{-7}	17-43		4.3 at pH 9; >>> at pH 7
Bifenthrin	6	5.4	0.1	1.8×10^{-4}	$<1.0 \times 10^{-3}$	96.3	425	>30
Cyfluthrin	5.9	5.1	0.002	2.03×10^{-9}	9.5×10^{-7}	11.5	33.6	1.8-183
Cyhalothrin	6.9	5.5	0.003	1.5×10^{-9}	1.8×10^{-7}	42.6		8.7->30
Cypermethrin	6.6	5.5	0.004	3.07×10^{-9}	4.2×10^{-7}	27.6	55	1.9-619
Deltamethrin	6.1	5.7	<0.002	1.5×10^{-8}	1.2×10^{-4}	>26		17
Esfenvalerate	4	5.4	0.0002	5.5×10^{-6}	4.1×10^{-7}	38.6	90.4	>30
Fenpropathrin	6		0.014	1.8×10^{-10}	1.8×10^{-4}			
Fluvalinate	4.3	5.0	0.002	5.7×10^{-7}	3.05×10^{-5}	8-15	84-88	22.4
Permethrin	6.5	5.4	0.0055	2.2×10^{-8}	1.4×10^{-6}	39.5	197	>30-242
D-Phenothrin (Sumithrin)	6.01	5.15	<0.0097	1.43×10^{-7}*	1.43×10^{-7}	18.6-25.8	173.3	36.1
Pyrethrins	4.30-5.90	4.09-4.57	0.0002-0.009**	2×10^{-5} – 4×10^{-7}	-	10.5	86.1	0.6-0.7 at pH 9; >>> at pH 7
Resmethrin	5.4	2.71-3.50		1.13×10^{-8}	$<8.9 \times 10^{-7}$	198	682	37
Tetramethrin	4.6	3.09-3.47	1.83	7.08×10^{-6}	1.7×10^{-6}	<0.04-0.13	-	0.89-1.06
Tralomethrin	7.6		0.08	3.6×10^{-11}	3.9×10^{-15}			

*at 21°C

** at 20°C

Exposure

Unsurprisingly, the method employed to apply pyrethroids will influence the likeliness of contamination: Pressurized cans and aerosol bombs are, by far, the modes of application resulting in the most reports of contamination (according to a study made in the northwestern US[29] but likely similar in the rest of North America). In order to better understand the risk of exposure in different groups, exposure is generally assessed separately for workers, children and the general public.[46] However, assessing the exact exposure of short-lived (non-persistent) pesticides like pyrethroids is challenging, in part because body fluid samples (i.e., urine or blood in biomonitoring studies) only allow an estimate of current levels of pyrethroids in the body (tracking history is difficult). Also, questionnaires often target work exposure but neglect environmental exposure, and often overlook the mode of application of a pesticide or the wearing of personal protection equipment. Combining samples and questionnaires is thus essential.[46]

The following sections detail how pyrethroids are absorbed, metabolized and excreted from the body (toxicokinetics) and distinguish occupational from domestic exposure. To set a reference frame for the reader, Acceptable Daily Intake and food tolerances of pyrethroids is discussed. Finally, since children are particularly sensitive to pesticides in general, including pyrethroids, a special section focuses on their enhanced exposure and metabolic sensitivity. Pertinent toxicological information is summarized in Table 7.

Table 7: Classification, Acute and Chronic toxicity of pyrethroids with references doses determined by Health Canada's Pesticide Management Regulatory Agency (PMRA), the US Environmental Protection Agency (EPA), the World Health Organization (WHO) or Australia's Health Ministry, based on a compilation by Quebec's SAgE Pesticide. Substances currently in the pyrethroid registration review cluster of Environment Canada are marked with an asterisk.

	Classification		Acute toxicity							Acute toxicity reference dose				Acute toxicity summary			Chronic toxicity reference dose			Acceptable daily intake
	EPA	WHO	LD_{50} oral mg/kg	LD_{50} cutaneous mg/kg	LC_{50} inhalation mg/L	Cutaneous irritation	Ocular irritation	Cutaneous sensitization	Cholinesterase Inhibitor	PMRA mg/kg/day	EPA mg/kg/day	target population	WHO mg/kg/day	oral	cutaneous	inhalation	PMRA mg/kg/day	EPA mg/kg/day	WHO mg/kg/day	Australia mg/kg/day
Allethrins*	III	II	709 (rats)	>3000 (rabbits)	2.51	very little or not at all	Slightly	No	No	-	0.03	General population	-	Moderate	Low	Low	-	0.008	-	-
Cyfluthrin*	I	Ib	>16.2 (rats)	>5000 (rats)	>0.468 (rats)	very little or not at all	Slightly	No	No	-	0.02	General population and children	0.04	Moderate	Low	Low (US EPA) to high (EU)	-	0.024	0.04	0.01
Cypermethrin*	II	III	247 (rats)	>4920 (rabbits)	2.50 (rats)	very little or not at all	Slightly	Yes	No	-	0.023-0.07	General population and children	0.04	Moderate	Low	Low	-	Refer to Acute[a]	0.02	0.05
Deltamethrin*	II	II	>135 (rats)	>2000 (rabbits)	2.2 (rats)	very little or not at all	Slightly	No	No	-	0.001-0.01	For newborns and children - For general population	0.05	Low-Moderate	Low	Low	-	0.001-0.01 For newborns and children - For general population	0.01	0.01
D-Phenothrin (sumithrin)*	III	U	>5000 (rats)	>5000 (rats)	>2.1 (rats)	very little or not at all	Slightly	No	No	ND[b]	0.03-NA	Women of childbearing age; none for other groups[c]	-	Low	Low	Low	ND[b]	0.007	0.07	0.02
Lambda-cyhalothrin*	II	II	54 (rats)	632 (rats)	0.065 (rats)	very little or not at all	Slightly	Possible	No	0.025	0.005	General population	0.02	High	Moderate	Moderate	0.005	0.001	0.02	0.02
Permethrin*	III	II	2280 (rast)	>2000 (rabbits)	>5.32 (rats)	very little or not at all	very little or not at all	No	No	-	0.25		1.5	Low	Low	Low	-	0.25	0.05	0.05
Pyrethrins*	III	II	700 (rats)	>2000 (rabbits)	2.5 (rats)	very little or not at all	Slightly	No	No	-	0.07	General population	0.2	Low	Low	Low	-	0.044	0.04	-
Resmethrin*	III	III	4639 (rats)	>2000 (rabbits)	5.28 (rats)	very little or not at all	very little or not at all	No	No	-	-		-	Low	Low	Low	-	0.035		0.1
Tetramethrin*	III	U	4600 (rats)	>2000 (rabbits)	>2.73 (rats)	very little or not at all	very little or not at all	No	No	-	-	ND[d]	-	Low	Low	Low	-	ND[d]		0.02
Fluvalinate	II	III	261 (rats)	>2000 (rabbits)	>0.56 (rats)	very little or not at all	Slightly	No	No	-	0.005	General population including infants and children	-	Moderate	Moderate	Low	-	0.005	-	0.005
Tefluthrin	I	Ib	22 (rats)	177 (rats)	>0.04 (rats)	very little or not at all	Severely to extremely	No	No	0.001[e]	0.05		-	High	High to Moderate	High	0.0005[f]	0.005	-	0.005

Notes from the table:

[a] Due to reversibility of the most sensitive effects studied in neurotoxicity, it is assumed that danger does not increase with duration, consequently, the acute reference dose is considered protective for long-term exposure.

[b] Not determined because it is not used on food in Canada.

[c] Women of childbearing age are 13-49 years old; None determined for other groups because no effect from single dose administration was concluded from animal studies.

[d] Not determined because it is not used on food in the US, and water exposure is not expected.

[e] An additional safety factor of ten was added to compensate for data gaps in acute and developmental neurotoxicity.

[f] Safety factor of ten normalized uncertainty, ten for interpolation between species and ten to account for data gaps in acute and developmental neurotoxicity studies (total = 1000).

Toxicokinetics

Entry of pyrethroids in the human body (absorption) can occur through the intestinal tract (ingestion), the skin (dermal contact) and the lungs (respiration of particles).[1, 25] Skin absorption is generally slow.[1] Following absorption, pyrethroids are distributed rapidly throughout the body including in fatty tissues (adipose tissue), stomach, intestine, liver, kidney and the nervous system.[1] Pyrethroids will be degraded in the body via two principal routes (oxidation and hydrolysis, followed by conjugation with amino acids, sugars or sulphate) and this will transform this originally fat-loving compound (lipophilic) into water soluble products (hydrophilic) which can then be excreted in the urine, but also in the feces.[1, 2, 25, 46] This process typically occurs in the liver through the action of enzymes like cytochrome P_{450} monooxygenase and hydrolases. The transformation of pyrethroids in the body (metabolism) is generally considered to reduce their toxicity.[1, 25] However, some studies suggest that metabolism of pyrethroids may in fact bioactivate the product by creating breakdown intermediate products (called metabolites) which are more toxic than the original parent molecule, and this new hypothesis deserves further attention.[26] The concentration of intact pyrethroids in the urine and blood plasma is much lower than that of the metabolites (breakdown products),[46] though non-metabolized pyrethroids have been detected in occupational workers[1, 47] and in the breast milk of occupationally exposed women.[1] Pyrethroids are rapidly metabolized in the body with the metabolites, with half-lives varying from two hours to a few days, being excreted in the urine.[48, 49]

Quantifying pyrethroids and metabolites (breakdown products) concentrations in body fluids can be done in laboratories, using gas or liquid chromatography techniques with relatively good detection limits, as low as 0.08 µg/l urine.[50] Interest in pyrethroid metabolites only arose about a decade ago, coinciding with increased agricultural and residential use of pyrethroids.[46] However, so far few studies have quantified pyrethroid metabolites[46] in the general population, pregnant women, infants, children and flight attendants (work-related exposure of airline crew members due to the *disinsection* [insect eradication] of planes flying internationally required under certain legislations).[50] Different pyrethroid parent compounds can be metabolized into common degradates. For example, *cis*- and *trans*- isomers of Permethrin, Cypermethrin and Cyfluthrin will transform into *cis*- or *trans*-DCCA (dichlorovinyl-dimethyl-cyclopropane carboxylic acid), but Cyfluthrin may also transform into 4F3PBA (3-(4'-hydroxyphenoxy) benzoic acid) and 20 different pyrethroids may transform into 3BPA (3-phenoxybenzoic acid).[15, 49] This makes it hard when relying strictly on blood or urine sampling to track which parent compound can be linked with observed human health effects. In addition, pyrethroids are rapidly metabolized in the body and do not tend to bioaccumulate,[1] but with continuous exposure to stable dietary or environmental doses, urinary metabolites may reach a pseudo-steady-state whose analysis may allow a better understanding of chronic toxicity.[16] For instance, because of airplane mandatory insect control protocols, regular international air travellers may regularly be exposed to wave-like short-term build-up of pyrethroids, despite rapid metabolism, and this may lead to a steady-state concentration in their body.[50] Development of pesticide biomarkers allowing longer-term quantification of exposure, such as metabolites found in hair or meconium (the earliest stool of infants) should continue.[46] For now, biomarker studies allowing snapshots of rapidly metabolizing pyrethroids should not stand alone in toxicity assessments or regulatory decisions, as they may not always represent everyday exposure.[46] In 2008, the first pyrethroid exposure study was conducted, in Montreal, with the use of questionnaires and urinary metabolite sampling and analysis. The results indicate that exposure levels of Montrealers are similar to those in the United States, but some individuals had higher exposure levels than an earlier study in Germany.[51]

Occupational exposure

Occupational studies generally follow pesticide sprayers, farmers, sheep dippers (workers controlling parasites on livestock) and workers in the chemical, manufacturing and packaging sector.[46] However, pesticide application or related handling may only be secondary components of work-related pyrethroid poisoning cases reported: the majority of pyrethroid poisoning cases occurred during normal work-related activities not related to pesticide application,[29] for example flight attendants working in a previously treated airplane.[50] Occupational exposure occurs mainly via skin absorption.[6, 47] Inhalation exposure is less common unless use occurs in confined spaces,[6] but despite this generally reported statement, inhalation exposure was the most common form of exposure in a study monitoring pyrethroids-related illnesses covering the states of Washington and Oregon.[29] To protect workers, maximum air concentrations of 5 mg/m^3 of Pyrethrins for 8-hour shifts and 40-hour work weeks should be respected, according to the US Occupational Safety and Health Administration.[7]

To protect people, fauna and flora from non-native disease vectors and harmful pests, some countries have required airplanes disinsection since the 1930s.[50] Disinsection has not been required in the US since 1979, but is still required in Australia, New Zealand, Barbados, Cooks Islands, Fiji, Panama and certain other countries.[50] Currently used insecticides in airplanes include 2% solutions of pyrethroids such as Permethrin (for residual treatment, pre-embarkation and pre-flight) as well as D-Phenothrin (top of descent, upon arrival). Treatment in airplanes is done by maintenance staff or professional exterminators prior to takeoff or after landing but, in flight, is done by flight attendants.[50] The World Health Organization determined that this practice caused no risk to human health, if carried out according to recommendations, however, new and unquantified general exposure risks have been recognized since production of the WHO report,[50] including suppression of immune system, damage to lymph node and spleen, developmental neurotoxicity, chronic symptoms and kidney poisoning, as well as gynecomastia (development of male breasts).[50, 52] Though pyrethroids are not very volatile, inhalation exposure by flight attendants may not be ruled out (even of flight attendants not personally responsible for spraying the pesticides in the airplane), but exposure may also occur via contact with contaminated seats, carpets and food trays leading to skin contact and unintentional ingestion.[50] Flight attendants working on disinsected planes were found to have significantly higher urinary levels of pyrethroid metabolites (3-PBA, *cis*- and *trans*-Cl2CA) in pre, post- and 24-h-post flight samples than those on planes which did not report having been disinsected.[50] Interestingly, none of the flight attendants followed in the study sprayed pyrethroids themselves, but the average work shift was 15 hours, leaving ample time for indirect exposure via contaminated surfaces.[50] The type of metabolites observed in urine was consistent with the type of pyrethroids used on aircraft.[50]

In a Chinese cotton grower survey, 68% of participants reported wiping off sweat with hand or sleeve, leading to secondary pyrethroid exposure. If there was leakage or a blockage in the spray nozzle during field application, 65% of workers cleared the nozzle with their mouth or hand. Pyrethroid preparation was often conducted using the packaged product lid instead of a measuring cup with a handle. The occurrence of hand contamination reached 92% of the workers, with 69.8% not aware of pyrethroid toxicity, wearing unsatisfactory personal protection equipment (no masks nor gloves, bare upper extremities, only open sandals during spraying). Most did not comply with basic safe handling recommendations (spray every other row, while walking backward or against the wind, and not eating or smoking in the field). Shoes and trousers were contaminated in 93.1% and 65% of the workers respectively, with body contamination reaching nearly 30% of the total skin surface. Sloppy handling yields the greatest risks of contamination.[47, 40] No Canadian studies of this type could be located.

Domestic exposure

Daily exposure of the general population to pyrethroids occurs mainly via contaminated food (originating from agricultural uses), contaminated waters (from general environmental contamination, usually a minor route), breathing contaminated air (right after spraying occurred, otherwise a minor route) or by skin contact.[2] In the northwestern US, the majority of pyrethroid-related incidents reported to local authorities occurred during normal outdoor or indoor living activities, which had nothing to do with pesticide handling; pesticide application or general pesticide handling came in only second.[29] Dermal exposure occurs upon direct application against lice or scabies, or upon indirect contact with an animal treated for fleas, or with flooring and upholstery treated against domestic pests.[2] Involuntary inhalation or ingestion of contaminated dust occurs in confined spaces treated against cockroaches, bed bugs or other domestic invaders, due to hand-to-mouth behaviour, or via electronic vaporizers which release pyrethroids in the air to control domestic insects.[2, 53] Improper use of pyrethroids may also lead to accidental exposure.[2]

Acceptable daily intake

Tolerances on foods vary from 0.01 to 75 parts per million depending on the pyrethroid molecule of interest, according to EPA standards.[7] Tolerance levels of pesticides on food items are set for raw produces at the farm gate, however, they do not consider potential contamination of food in homes nor do they account for multiple pesticide exposure mixtures.[42] Concentrations of pyrethroids in water are also regulated; for example, the WHO recommends that Permethrin concentration should not exceed 20 µg/l in drinking water. However, the Quebec Regulation on drinking water does not include pyrethroids among the 25 targeted pesticides for which regular testing at water purification plants is required.[54] Furthermore, only 26% of water purification plants in Quebec are equipped with systems such as ozonation or activated charcoal which are known to further remove pesticides. Hence, to avoid unmonitored hazards, it is essential to ensure no pyrethroid contamination reaches our surface and ground water supplies.[55]

Because humans are bound to consume pesticides via dietary intake and in order to correctly assess and mitigate this risk, the World Health Organization calculates Acceptable Daily Intake of different pesticides based on the available regulatory testing results and published literature. A human can be exposed to the Acceptable Daily Intake for his or her whole life without appreciable risk predicted by the facts known at a given time.[1] The WHO Acceptable Daily Intake of pyrethroids varies from 0.002 to 0.07 mg/kg body weight per day depending on the molecule,[1] while the US Acceptable Daily Intake ranges vary from 0.005 to 0.05 mg/kg body weight per day.[2] The daily average intake of Permethrin (US top seller) is estimated at 3.2 µg/day, which is three orders of magnitude lower than the WHO Acceptable Daily Intake for a 70 kg adult male,[2] although this does not consider the enhanced sensitivity of children and multiple exposures pathways.

Enhanced sensitivity of children

Children are particularly sensitive to pyrethroids and pesticides in general for several reasons. They have a lower body weight but proportionally higher food and respiratory intake, commonly play on the ground and outdoors, exhibit hand-to-mouth behaviour, may have an immature detoxification system and go through critical developmental windows, e.g., enhanced neuronal plasticity (rapid brain development).[15, 46, 56-58] Specifically, in the case of pyrethroids, the increased sensitivity of the young is likely attributable to an incomplete maturation of the enzymes that detoxify pyrethroids, such as carboxylesterases and cytochrome P450s.[24] In addition, different pyrethroid receptors (voltage-gated sodium channels) are expressed during embryonic development and adulthood, and the specific sensitivity of these different channels (isomers) could explain the greater sensitivity of the young.[24] The skin of children might be more permeable to pyrethroids, and children may be exposed to higher internal body concentrations than adults because exercise, flu and colds make them more prone to dehydration.[2]

Large studies following groups of children over time (prospective cohorts) have been conducted in the United States and Canada. Even before birth, children are exposed to pyrethroids. In a Baltimore hospital, Permethrin was measured in the umbilical cords of newborns, but the association with developmental effects is inconclusive.[33] In Poland, there was a small but significant decrease in birth weight of babies exposed *in utero* during the first or second trimester (this study is considered mid-quality).[33] A Health Canada study (Canadian Health Measures Survey) detected pyrethroids metabolites in nearly 100% of surveyed children, a finding of concern.[33] For the age cohorts of 6-11 and 12-19, respectively, 3-BPA (metabolite of Permethrin, Deltamethrin, Cypermethrin, etc.) was found in 99% and 100% of children, Cis-DCCA (metabolite of *cis*-Permethrin, *cis*-Cypermethrin) was found in 97% and 99% of children, and 4-F-3-PBB (metabolite of Cyfluthrin & Flumethrin) was found in 42% and 51% of children.[33] Other researchers showed that dietary ingestion is more important than non-dietary ingestion as the dominant exposure routes for children, except in homes with frequent pesticide applications where dermal exposure is first, followed by dietary ingestion.[41] The US Food Quality Protection Act has long required monitoring and management of children's dietary exposure to pesticides, but the application of this legislation is still a challenge.[42] Pyrethroids are found in 5% of fruits and vegetable consumed by children, with concentrations of 93 ng/g of Bifenthrin in strawberries or 1133 ng/g in a composite sample of lettuce-broccoli-mushrooms.[42] In a worst-case scenario, assuming that 100% of these food items on the market were as contaminated as the lettuce-broccoli-mushroom dish stated above, and with the WHO Acceptable Daily Intake of 0.02 mg/kg bw/day,[59] adults would approach the safety limit if they ate one kilogram of highly contaminated food in one day. While eating such a quantity may seem farfetched for an adult (whose average weight is assumed to be 60kg), remember that a 3-yeard-old or an 11-year-old child may weigh 15kg or 35kg, hence 250g or 500g of a highly contaminated meal would suffice to approach the safety margin of the Acceptable Daily Intake. Such dietary exposure is greater than the US Department of Agriculture Pesticide Data Program assumptions used to calculate exposure risk, which highlights the importance of measuring the actual concentration in food eaten by children, taking into consideration that some food samples may have a higher risk of being contaminated.[42] The US Pesticide Data Program does not test all food eaten by children, nor does it test all the food annually.[42] In Canada, children food are also tested.[60] However, the sampling is done in a fashion which prevents statistical extrapolations. Pyrethroids were found in food, but the nature of the food and the concentrations measured were not disclosed in the report, which simply stated that the allowed tolerances were respected. Another information found in this report is that organic food destined for children was less contaminated with pesticides than conventional food, although not completely

devoid of pesticides residues.

In addition, children's unstructured eating habits and activities may lead a greater environmental exposure than assessed by the US Environmental Protection Agency.[61] Pyrethroids may be transferred on food by crawling ants, with efficacy depending on food characteristics. For instance, there is less transfer on bread and cookies, but more transfer on apple slices and bologna. As long as pyrethroids are measurable in a children's environment, unintentional transfer on food will take place.[61]

A Montreal-based study[51] revealed that children, compared to adults, excreted more of a pyrethroid metabolite (CDCA per kg of body weight) most common in domestic or commercial extermination applications (Allethrins, Tetramethrin, Resmethrin, Phenothrin, Prallethrin) rather than agricultural uses. However, application of pesticide in homes was seldom reported within the three weeks prior to urine sampling (considering the short lifespan of pyrethroids metabolites within the body, this reveals exposure to sources outside of the home during the course of the study). Furthermore, head lice treatments significantly increased metabolite excretion in children, while certified organic diets significantly decreased pyrethroid metabolite excretion in children.[51] Hence, pyrethroid exposure in children may be controlled by reducing pediculocide treatments or eating organic food, but other sources of exposure outside of the home may nevertheless expose children in a large metropolitan region like Montreal.

Poisoning symptoms

Acute toxicity

Pyrethroids are generally regarded as having one major mode of action (action on sodium channels), which may lead to two distinct toxicity syndromes depending on the nature of the pyrethroid (at least in historical records currently recognized by registration authorizations, a recent review suggest that this type of classification is archaic and not truly supported by the literature).[25] The two historic syndromes include T (fine tremors) and CS (choreoathetosis and salivation) as characterized in rats, and have been linked to type I and type II pyrethroids (with or without α-cyano group, through this is not consensual[25] and mixed syndromes are known for some pyrethroids such as Esfenvalerate and Fenpropathrin).[24] Choreoathetosis is the occurrence of involuntary movements which combine irregular muscle contractions and twisting and writhing. Type I Pyrethrins appear to repetitively fire voltage-gated sodium channels while type II pyrethroids appear to block the action potential of depolarization-dependent sodium channels.[24]

Acute toxicity via dermal exposure commonly leads to abnormal skin sensations (paresthesia), especially in the face, presumably due to hyperactivity of skin (cutaneous) sensory nerve fibres.[6] Ingestion exposure may lead to sore throat, nausea, vomiting and abdominal pain, and there may be mouth ulceration, increased secretions and/or difficulty to swallow (dysphagia).[6] Effects appearing on the body remote from the original contact point (systemic effects) generally start within an hour of exposure and peak within 4-8 hours[24] and most patients recover within 12-48 hours,[24] though occurrence of symptoms within 4 to 48 hours after exposure and recovery up to 6 days after is also cited in the literature.[6] Dizziness, headache and fatigue are common, and palpitations, chest tightness and blurred vision less frequent.[6] There are anecdotal reports of flight attendants experiencing irritation to the skin

and mucosa, sore throat, vomiting, abdominal pain, headaches, dizziness and nausea.[50] Among 3,113 cotton farmers interviewed and followed 72h after spraying pyrethroids, 26.8% suffered from abnormal facial sensations, dizziness, headaches, fatigue, nausea and loss of appetite.[47] Despite extensive worldwide use, there are relatively few reports of lethal human pyrethroid poisoning, although deaths have been documented.[6] In oral toxicity studies, it takes only approximately 55 mg/kg of body weight to kill half of the exposed rats (LD_{50}) with Bifenthrin or lambda-Cyhalothrin, but D-Phenothrin and Etofenprox require nearly 200X that dose (> 10 000 mg/kg body weight).[1] Via dermal toxicity, lambda-Cyhalothrin and alpha-Cypermethrin appear as the most toxic (> 100 and 632 mg/kg body weight, respectively).[1] At high doses, trembling may occur and convulsions and coma are the principal life-threatening features.[6]

Chronic toxicity and Sub-lethal effects

Chronic toxicity, which generally occurs via repetitive low doses exposure, is not well characterized for pyrethroids. The US Environmental Protection Agency highlights that because pyrethroids are rapidly metabolized and eliminated from the body, repeated doses (as in dietary studies) may not yield the same toxicity effects as a single dose (gavage studies).[24] Below lethal doses, pyrethroids generally only exhibit transient effects in humans. Claims of cumulative or irreversible effects, and accumulation of small doses in the body in the long term have been refuted.[53] Nevertheless, long-term effect of pyrethroids is unclear since most knowledge is gathered from animal studies, and only few epidemiological studies have been conducted.[46] Information on chronic toxicity of various pyrethroid molecules can be found in Table 8 and Table 9.

In animals, sub-lethal effects of pyrethroids include perturbations of behaviour, development and hormonal balance.[46, 62] In mammals exposed to pyrethroids, motor, sexual, learning, anxiety and fear behaviours may be altered. Thresholds for changes in motor activity were found well below doses that produce overt signs of poisoning.[62] Some pyrethroids alter several types of behaviour such as schedule-controlled responses[63] (defined as behaviours that can be controlled by reinforcement or punishment and which are administered in a time-controlled manner), they may also decrease grip strength, produce incoordination and may increase or decrease the startle response to a noise.[62] Such behavioural endpoints in test animals can be considered to capture the heterogeneity of pyrethroids-induced adverse effects and should be taken into consideration in risk assessment which guides pesticide policy decisions (e.g., registration, Acceptable Daily Intake, etc.).[62]

In humans, symptoms claimed following chronic domestic exposure include nausea, dizziness and respiratory pain; delayed loss of weight and hair, skin rashes, loss of muscular response, memory and immune response.[64,53] However, these unspecific symptoms are difficult to link to one cause and they may be confounded with or involved in Chronic Fatigue Syndrome, Sick-Building Syndrome, Gulf War Syndrome and Multiple Chemical Sensitivity.[53, 65] Only a few clinical, experimental and epidemiological studies have been conducted on pyrethroids-induced illness, but this may be due to vaguely defined diagnostic criteria.[53] To complicate diagnosis further, different individuals may experience different susceptibility to pyrethroids because of different detoxification capabilities.[66]

For now, there is no consensus on the specific low concentrations which may lead to hazard, and claims vary from 100-500 µg of pyrethroids/kg of house dust, a threshold which is influenced by sampling methods and the analytical limit of detection. Because very low concentrations of pyrethroids are common in households,[53, 67] it is critical to deepen our understanding of chronic low-dose toxicity of pyrethroids.

Developmental neurotoxicity

Recent developments in pyrethroid toxicity research suggest production of neuronal death, developmental neurotoxicity, and action mediated via pyrethroid metabolites,[26] the latter will not be further reviewed here. Concerning neuronal death, the regulatory tests conducted for the registration of many pyrethroids in the 1970s and 1980s were not as specific as more recent research protocols and only a few behavioural observations were made.[26] While high doses may lead to neuronal death, possibly as an indirect consequence of toxicity (i.e., seizures which cause oxygen deprivation and neuronal death as opposed to direct neuronal death imposed by pyrethroids), it is not obvious how repeated low doses affect the nervous system.[26] New evidence for neuronal death in the literature, although sometimes equivocal, calls for a review of the older regulatory tests.[26]

A 2005 report by the World Health Organization reviewed several developmental neurotoxicity effects of pyrethroids on animals, including delayed reflex (surface-righting reflex), decreased learning behaviour (shock-motivated visual discrimination in a Y maze) and changed neurotransmitters binding in the brain (acetylcholinesterase in the hippocampus) following *in utero* exposure to Deltamethrin; increased open-field immobility in male offspring exposed to Fenvalerate; decreased exploratory behaviour in rats exposed *in utero* to Cyhalothrin; changed brain neurotransmitter receptors (muscarinic cholinergic receptors) in neonates and adults treated *in utero* to Deltamethrin and Bioallethrin. Despite the quoted effects, the WHO concluded that neurotoxicity observations bear unclear biological significance, involve processes different in animals and humans, and lack standardization and comparability-highlighting the need for further investigation on developmental neurotoxicity of pyrethroids.[1]

Neurodevelopmental toxicity studies are not required for the registration of all pesticides and they may only be required by regulatory agencies in cases where neurodevelopmental toxicity is strongly suspected. In 2010, the US Environmental Protection Agency conducted a special review of the neurodevelopmental toxicity of the pyrethroids. They came to the conclusion that the developmental neurotoxicity protocols required for registration review of the pyrethroids did not adequately characterize the susceptibility of young individuals. However, instead of requiring pyrethroid manufacturers to conduct the missing developmental neurotoxicity tests for certain pyrethroids (Bifenthrin, Cyfluthrin, Cyhalothrin, Cypermethrin, Fenpropathrin and Deltamethrin), the EPA recommended that the registrants simply cite the existing literature reviews of other active substances that had been tested, considering that different pyrethroids active ingredients to be comparable in terms of developmental neurotoxicity.[8, 24] Because certain behaviours typically studied in neurodevelopmental regulatory protocols did not show a marked response to exposure to pyrethroids, the EPA suggested that neurodevelopmental studies were not sensitive indicators of pyrethroid toxicity, meaning that such tests would not be mandatory for registration.

Toxicity assessment protocols monitor certain behaviours or parameters of interest, but the optional developmental neurotoxicity protocols study unique behaviours or parameters which are not assessed in other toxicity assessment protocols. Those unique parameters include learning, memory, auditory startle and brain morphometrics. The EPA concluded that these parameters were not influenced (with some exceptions) by Pyrethrins, and thus it was not necessary to consider these indicators in pyrethroid toxicity. Simply stated, the EPA considered that gross measurements required in all toxicological assessments, like clinical signs of toxicity and body weight changes (of concern if they reach a threshold of 5% or more), were more sensitive indicators of toxicity than neurological effects (such as auditory startle response in rat pups) which are part of optional toxicity assessment protocols. The EPA considered that the large variability between developmental neurotoxicity studies, where the standard deviation of a recorded effect may be greater than the actual mean, led to inconclusive evidence and inappropriate statistical interpretation.[24] However, novel protocols to assess pyrethroid neurobehavioral effects may be more sensitive than those commonly recorded in regulatory protocols, hence if standard neurobehavioral endpoints are insensitive to pyrethroids,[24] this may require the use of alternate endpoints, a few of which are reviewed below. An endpoint is simply something to be looked for in a toxicity study, it could be weight loss, change in a target organ and tissues or a behavioural change.

Contrary to the regulatory agency conclusions mentioned above, an important peer-reviewed literature survey categorized pyrethroids as developmental neurotoxicants.[68] While acute neurotoxicity of pyrethroids to adult mammals is well characterized, information on developmental neurotoxicity is limited.[68] Pyrethroids may have an effect on Ca+ channels which are important in neuronal function during development and for neurotransmitter release, gene expression, and electrical excitability in the nervous system. However, proof of pyrethroid action on Ca+ channels is incomplete (only *in vitro*, lack of concentration-response relationships, contradictory effects, some data not peer-reviewed).[69] Many of the developmental neurotoxicity studies suffer from inadequate study design, problematic statistical analyses, use of formulated products, and/or inadequate controls. These factors confound interpretation of results.[68] An association between pre-natal exposure to pyrethroids and neurodevelopmental toxicity has been suggested, whereby the concentration in air samples of the common synergist piperonyl butoxide is associated with lower Mental Development Index scores.[46] Also, the replacement of organophosphorus insecticides with putatively safer pyrethroids may not be a perfectly safe alternative with respect to neurotoxicity. For instance Cyfluthrin was found equivalently or more toxic than Chlorpyrifos regarding growth, survival and function of primary human astrocytes. Astrocytes are star-shaped cells located in the brain or spinal cord which play several roles including supporting the blood-brain barrier, providing nutrients to neuronal cells, maintaining ionic balance and playing a role in repairing scarred nervous tissue after a trauma; inflammatory activity of these astrocytes can also mediate neurotoxicity.[70] Newborn rats are at least one order of magnitude more sensitive to pyrethroids than adults,[68,24,26] but there is no information on how neurotoxicity fluctuates with age for most pyrethroids.[68] Young mice administered pyrethroids, at a dose which does not exhibit acute toxicity, saw their behaviour and neurochemistry change, with the changes remaining into adulthood.[71] A better understanding of behavioural endpoints and the strengthening our knowledge on developmental neurotoxicity is critical in the light of recent epidemiological evidence of sub-lethal effects on children highly exposed to pyrethroids.[15, 72]

Epidemiological studies of children

Several studies suggest an association between pesticides and impaired neurodevelopment in children (consult Reference[28], and references therein), and between pesticide exposure and Autism Spectrum Disorder (ASD)[28, 73] or pervasive Developmental Delays (DD).[28, 74] Young children suffering from DD experience significant delays in reaching milestones in relation to cognitive or adaptive development including communication, self-care, social relationships and/or motor skills; it affects 3.9% of US children aged 3-10, and affects boys 1.7X more than girls.[28] Autism appears before age 3 and is characterized by deficits in social interaction, language, restricted or repetitive behavior, activities or movements.[28, 75] ASD is of lower severity than autism, and is generally linked with a language disorder affecting 4-5 times more boys than girls; 1.1% of American children age 8 are affected, a 78% increase since 2007.[28, 76]

Recent epidemiological research indicates widespread exposure of children to pyrethroids. As discussed in the toxicokinetics section of the current review, urinary metabolites of pyrethroids represent a snapshot of recent exposure. These metabolites were observed in 77% of 1,861 American children aged 6-15 between 1999-2002[72] and in as many as 97% of 779 Canadian children aged 6-11 between 2007 and 2009.[15] Not only is childhood exposure common, it seems associated with behavioural and cognitive difficulties. In 2007, an association between the pyrethroid Bifenthrin and ASD ($p=0.049$) was brought to light.[73] Pyrethroid metabolites are associated with high scores for total difficulties on Strengths and Difficulties Questionnaire (significant association of *cis*-DCCA and non-significant association with *trans*-DCCA metabolites).[15] Specifically, children who had urinary concentrations of the metabolite *cis*-DCCA ten times that of the average, were twice as likely to exhibit behavioral problems according to parental observations, and this was stronger for girls.[15] Also, a borderline significant association was found between another metabolite of pyrethroids (3-PBA) and special education utilization/early intervention (SEd).[72] Finally, highly exposed children had higher odds of having learning disability and attention deficit disorder combined.[72]

Even before birth, children are exposed to pyrethroids, though this may not affect fetal growth or gestation time (no association was found with the metabolite 3PBA).[77] According to the Childhood Autism Risk from Genetics and the Environment (CHARGE) study, children of mothers residing near to pyrethroid and organophosphorus insecticide application sites, just prior to conception or during the third trimester were at greater risk of Autism Spectrum Disorder (ASD) and Developmental Delay (DD).[28] Rather than exposure to the pyrethroid Permethrin itself, exposure to the common synergist, piperonyl butoxide, *in utero*, was linked to mental development delays in children when they reached the age of three.[78] This novel finding was obtained from a study where case and control populations were well defined, diagnostics were standardized, extensive information on covariates was available and confounding variables were identified and controlled. However, the study suffered from certain limitations including exclusion of institutional (schools, etc.), residential indoor uses, professional pesticide applications and dietary sources since these were not mandatory in California pesticide reporting. The mechanism linking pesticides to autism has been described by Shelton.[28, 79]

Reproductive toxicity

Earlier publications concluded that pyrethroids did not impair mating and fertility of laboratory animals, neither did exposure to pyrethroids lead to pre-implantation losses at low doses.[1] Humans exposed to Pyrethrins or pyrethroids showed no birth defects.[7] However, more recent research involving animal testing and epidemiological studies in humans shows potential adverse effects on human fertility.

The few studies conducted in this domain support pyrethroid-induced alterations to the male reproductive system.[46] Most studies highlighting effects on sperm concentration, motility and morphology were conducted on animals.[46, 80] Three studies significantly link pyrethroid exposure biomarkers and sperm parameters in humans, and four other studies show borderline or weak associations, while five studies significantly link sperm DNA damage with biomarkers levels.[46] In American males, urinary pyrethroid metabolites are correlated with a decrease in sperm count, a decrease mobility of sperm, an increase of abnormal morphology as well as an increase in DNA damage, which may result in decreased fertility and pregnancy.[16] These US findings are consistent with independent observations from China.[16] In a Finnish study which surveyed (via a questionnaire) 578 couples where the male was a greenhouse worker, the fecundability ratio was reduced in suggested association with increased pyrethroid exposure, but with no other family of pesticides surveyed.[33] Exposure of young mice to *cis*-Permethrin significantly reduced sperm counts in the testes (epididymis), motility, testicular testosterone production, and plasma testosterone levels in a dose-dependent manner.[81] As a secular trend of decreasing testosterone and decreasing semen quality is observed, and because so many people are exposed to endocrine disrupting compounds, a seemingly subtle association in epidemiological studies may result in large change in the reproductive capacity of human or other endocrine-mediated diseases. This is the cause for great public concern.[82]

Endocrine effects

Endocrine effects are those which create an imbalance in normal hormonal signalling in animals. While hormones are active in infinitesimal concentrations, most pyrethroid studies use doses that are higher than normal occupational exposure, thus higher doses may potentially mask what would happen at normal signalling concentrations.[82] *In vitro* studies on Cypermethrin and Fenvalerate show that pyrethroids may alter female and male hormones (estrogenic and antiandrogenic activity).[81, 83-85] Experimental evidence that pyrethroids affect the male endocrine system and reproductive function exist, but human data is limited.[82] Six out of seven studies using biomarkers have reported evidence of endocrine disruption.[46] Pyrethroids have been shown to alter hormones (endocrine disruptors), for example by decreasing concentrations of testosterone (important male hormone) and interfering with luteinizing hormone (LH; involved in the production of sperm and ovules).[81, 86] A significant positive dose-dependent association between the pyrethroid metabolites 3PBA and *cis*/*trans*-DCCA in urine and FSH concentrations has been observed.[82,46] In addition, testosterone levels have been inversely associated with pyrethroid metabolites, in a non-monotonic fashion. Monotonicity refers to the fact that a linear dose-response relationship (more poison leads to enhanced poisoning symptoms), is often a requirement to prove a toxicological relationship; however monotonicity is not always observed in endocrine disruptors.[46, 82] Furthermore, there is a negative dose-dependent association between pyrethroids and inhibin B, as well as free androgen.[82] FSH is a gonadotropin, secreted by the pituitary gland and acting on seminiferous tubules to initiate spermatogenesis.[82] Inhibin B is a protein hormone,

secreted by the Sertoli cells, which exerts a negative feedback on the anterior pituitary to inhibit FSH.[82] FSH and inhibin B are the two hormones most associated with semen quality, where increased FSH levels and decreased inhibin B levels, as observed with pyrethroids, both lead to poor semen. Pyrethroids have been shown to alter thyroid function.[87-89] The synergist MGK-264 is suspected to have endocrine disruption potential.[27] Based on the weight of evidence, the EPA did not recommend further endocrine disruption potential because further results would not change the EPA regulatory standpoint and endpoints for human health risk assessments.[27] Evidence of potential interaction with the estrogen pathway was observed in mammals (but not fish).[27] No convincing evidence of interaction with the androgen pathway was observed.[27] A potential interaction with the thyroid pathway of mammals was also observed (but not in amphibians).[27]

Cancer

Long-term pesticide exposure may lead to DNA damage and oxidative stress[46] and also disrupt the endocrine system, which may lead to cancer.[82] The World Health Organization recognizes that tumours have been induced in rodents which were exposed to pyrethroids during their whole life, however, in 2001 the WHO considered that were no clear indication of carcinogenicity relevant for human health risk assessments.[1] Animal evidence includes initiation (but not promotion or completion) of carcinogenic activity in mice exposed to Deltamethrin on their skin, initiation, promotion and complete carcinogenic activity in mice exposed to Permethrin on their skin, preputial gland adenomas and carcinomas in rats exposed to D-Phenothrin in their diet, lung adenomas in mice exposed to Permethrin, mammary adenocarcinomas in mice exposed to Cyhalothrin, urinary bladder haemangiomas in male mice following Bifenthrin exposure, and follicular cell adenomas in the thyroid of female rats exposed to Etofenprox. However, several of these findings were dismissed on the basis of non-statistical significance, no difference with the history of the control population, absence of joint genotoxicity (mutation of genes) or non-toxicological significance as assessed by groups of experts.[1] Some pyrethroids are considered possible human carcinogens in the US,[2] though the International Agency for Research on Cancer (IARC) considers them not classifiable (Deltamethrin, Fenvalerate, Permethrin) due to inconsistent evidence in animals or absence of evidence in humans.[7, 90] In a recent internal report, however, the IARC reviewed its earlier statement on Permethrin, and in the face of new carcinogenicity evidence, assigned a high priority for the revision of the carcinogenicity of this pesticide within the window of 2015 to 2019.[91]

Since these earlier WHO and IARC publications, Permethrin has been shown to be mutagenic in human and hamster cell cultures.[81] Pyrethroids have been shown to be endocrine disrupting compounds (EDC; see above), which may be associated with an increase in testicular, prostate and thyroid cancer.[82] Some pyrethroids may increase the levels of estrogens in breast cancer cells,[85] suggesting potential implications in human breast cancer.[92] The common synergist MGK-264 may be associated to increased thyroid follicular tumors in male rats.[27]

Table 8: Carcinogenicity, genotoxicity, endocrine disruption potential, reproductive toxicity, developmental toxicity and neurotoxicity of some Pyrethroids registered in Canada. An asterisk (*) denotes pesticides included in the current Health Canada pyrethroids cluster review program.

Active substance	Carcinogenicity	Genotoxicity	Endocrine disruption	Reproductive toxicity	Developmental toxicity	Neurotoxicity
Allethrins*	Possible	None	Not very likely	Suspected[a]	No effect reported[b]	Yes[c]
Cyfluthrin*	Not likely	None	Not very likely	Suspected[d]	No effect reported[e]	Yes[f]
Cypermethrin*	Possible	None	Not very likely	No effect reported	No effect reported[g]	Yes[h]
Deltamethrin*	Not likely in humans	None	Not very likely	No effect reported[i]	No effect reported[j]	Yes[k]
D-Phenothrin (sumithrin)*	Not likely in humans	None	Yes[l]	No effect reported[m]	Suspected effects in animals[n]	Yes[o]
Lambda-cyhalothrin*	Not likely in humans	None	Not very likely	No effect reported	No effect reported	Yes[p]
Permethrin*	Probable in human	Insufficient or nonexistent data	No very likely	No effect reported	No effect reported	Yes[q]
Pyrethrins*	Possible	None	Insufficient or inexistent data[r]	No effect reported[s]	No effect reported[t]	Yes[u]
Resmethrin*	Probable in human	None	No effect reported	No effect reported[v]	Suspected effects in animals[w]	Yes[x]
Tetramethrin*	Probable in human	None	Insufficient or inexistent data[y]	No effect reported[z]	No effect reported[aa]	Yes[bb]
Fluvalinate	Not Likely in Humans	None	None reported[cc]	None reported[dd]	No effect reported[ee]	Yes[ff]
Tefluthrin	Possible	None	Not likely[gg]	None reported[hh]	No effect reported[ii]	Yes[jj]

Notes from the table:

[a] On bi-generational rat study on esbiothrin, decreased viability of offspring, growth delays at a dose which would cause weight loss in adults. Not confirmed with d-allethrin.

[b] Rare anomalies considered genetic variations rather than skeletal malformations. Effects observed at maternal toxic doses.

[c] At high doses, near lethal doses, allethrin isomers may cause hyperactivity, trembling and convulsions.

[d] In bi-generation rat study, offspring has increased sensitivity compared to adults. At the lowest dose which had an effect (LOAEL), weight loss was observed in both adults and offspring, accompanied with tremors in offspring. No specific toxicity on reproduction. In a tri-generation study, no effect on animal appearance, behaviour, fertility or still-born offspring was observed. The only effect observed was decreased weight loss in adults. However, decreased lactation and reduced viability index of offspring were observed on F3a and F3b with intermediate (150 ppm) or high (450 ppm) exposure. The LOAEL was considered to be 50 ppm. This study considers increased susceptibility in the offspring compared to adults.

[e] In rats, a decreased weight and skeletal anomalies were observed at maternally toxic doses. At the highest doses, abortion and fetus resorption were observed in rabbits. Overall developmental toxicity is considered low.

[f] Na-channels alterations (like other pyrethroid insecticides). Short-term rat study revealed neurotubule dilation with neurofilaments proliferation and mitochondrial degeneration. These effects were caused by the treatments, but were reversible when exposition ceased. Two-week exposure in rats led to tremors and excessive salivation. A small and recent hemorrhage was observed in male rats that died during the study. Sub-chronic and chronic oral or inhalation exposure studies revealed behavioural changes, tremors, excessive salivation, abnormal locomotion and abnormal postures in rats. A chicken study reported in the US EPA assessment suggested delayed neurotoxicity accompanied with a degenerescence of nervous fibers. However, the European Union documentation does not reveal neurotoxicity in chicken.

[g] No toxicity in rats and rabbits exposed *in utero* at the highest dose tested. However, a recent neurotoxicity study in rats suggests increased sensitivity of fetus compared to adults; based on weight loss, the lowest dose where an effect was observable was lower in offspring than in mothers.

[h] Abnormal locomotion was observed in rats at high doses. Near lethal doses, histopathologic effects, like axon and sciatic nerves alterations, were observed. Additional studies on developmental neurotoxicity are required.

[i] In a multi-generation rat study, no increased sensitivity of offspring was observed compared to adults. Newborn may be more sensitive than adults in post-natal exposure.

[j] No adverse effects observed in rats and rabbits under standardized protocols according to US EPA and EU. Reproductive and developmental toxicity under re-evaluation for the US EPA and California EPA.

[k] No neuropathology observed in chicken or rats, but locomotor activity alterations observed in rats.

[l] Effects related to endocrine disruption were observed (estrogenicity, angdrogenicity or thyroid effects).

[m] Toxicity in offspring only observed at maternal toxic doses. In absence of maternal toxicity, second-generation offspring with reduced body mass were observed. At higher doses where maternal toxicity was also observed, mortality was observed in second generation rats expose *in utero*. However, this situation was considered to be of concern because decreased weight was only transient.

[n] Rats and mouse fetuses did not demonstrate increased sensitivity compared to adults, however, this was observed in rabbits. Increased occurrence of spina bifida was observed at doses below maternally toxic doses. At higher doses microphthalmia was also observed in offspring.

Hydrocephalia was also observed.

[o] Alters biochemistry and physiology of Na-channels. Incontinence and piloerection were observed at higher doses, but were reversible.

[p] Acute toxicity studies in rats revealed clinical signs of neurotoxicity such as decreased activity, ataxia, decreased stability, salivation, horripilation, walking on tip toes, convex deviation of vertebrae, urinary incontinence and/or tremors at high doses. No sub-chronic effects observed at higher doses, or in either sex.

[q] No neuropathological changes observed in chicken in acute or sub-chronic toxicity studies. At higher doses, muscle contractions, overexcitability, irritability and tremors were observed.

[r] Thyroid hormone and histopathologic effects (thyroid hyperplasia, hypertrophia of follicular cells, follicular adenomas and carcinomas) were observed in rats, but it is uncertain if this mode of action is pertinent in humans.

[s] Offspring showed enhanced sensitivity compared to adults, for instance by exhibiting a reduced body mass which was not observed in parents.

[t] Rats and rabbits fetuses did not exhibit enhanced sensitivity compared to their mother.

[u] Pyrethrins are toxic to axons. Clinical signs of toxicity include tremors, salivation, exaggerated or absence of fright reflex, lower prehension strength, increased locomotor activity, muscular contractions, spasms, etc. Neuropathological symptoms are also reported, including several types of neuronal degeneration following oral or inhalation exposure.

[v] No increased sensitivity in offspring compared to parents.

[w] Rabbit fetuses exhibited increased sensitivity compared to their mothers. Skeletal variations appeared at doses non toxic for mothers. In rats, maternal and fetal toxicity were observed at the same doses.

[x] No acute and sub-chronic neurotoxicity studies available in rats, but increased sensitivity observed in rabbits. Some studies demonstrated neurotoxic effects such as hypotonicity, ataxia, tremors, convulsions, dyspnea, sneezing, alteration of grooming behavior).

[y] No specific endocrine studies in animals, but studies in dogs revealed absence of estrus activity, confirmed by the absence of corpus luteus following histopathology, a result similar to that observed in rats. Chronic study in mice revealed lowered pituitary and thyroid/parathyroid gland mass in males above a certain dose, without appreciable histopathologic changes in microscopic examination of tissues. Interstitial testicular cells tumours observed may have a hormonal origin.

[z] No increased sensitivity in offspring compared to parents.

[aa] Rats and rabbits fetuses did not exhibit enhanced sensitivity compared to their mother though studies are considered inadequate due to the use of carboxymethylcellulose as a vehicle, which could have affected bioavailability of tetramethrin. Further studies are required.

[bb] Neurotoxicity studies of tetramethrin considered inadequate. Being a type I pyrethroid, tetramethrin is expected to lead to tremors (T-syndrome). Inhalation studies revealed irregular respiration, slight salivation and overexcitability, tremors, ataxia and depression. Mice appeared

slightly more sensitive than rats, but there was no difference between males and females.

[cc] None reported during registration

[dd] Tremors and reduced birth weight reported in second generations, but at concentrations producing parental toxicity.

[ee] Skeletal variations in rabbits not significantly higher than in control group, and effects observed at maternal toxic doses.

[ff] Acute nerotoxicity study in rats (7 doses per day) revealed nervous fibers degenerescence. Subchronic studies did not report degeneration of nerve fibres, but excessive grooming and protruding eyes.

[gg] No evidence reported in chronic, developmental or reproductive toxicity studies on members of the pyrethroid family during registration.

[hh] No increased sensitivity in youth compared to adults, i.e., toxicity in youth at parental toxic doses.

[ii] Maternal toxic doses are lower than doses which produced toxicity in rabbits and rats fetuses. Bone ossification was observed at fetal toxic doses.

[jj] Strong effects included ataxia (neuromuscular incoordination), weight loss, smaller food intake in mice, rats, rabbits and dogs. In reproductive toxicity study, nerotoxicity signs in young rats at doses where parents did not display signs of toxicity suggests enhanced sensitivity of the young. A specific developmental neurotoxicity study is required.

Table 9: Long-term effects of various pyrethroid active substances.

Active substance	Long-term effects
Allethrins*	Few studies. Decrease weight loss, enlarged liver and kidney >500ppm. Decreased enzymatic activity of ALAT and ASAT transaminases and alkaline phosphatase. Presence of macrophages containing crystals in the liver of animals exposed to >500ppm. The only carcinogenic evidence is benign kidney tumours in rats treated with esbiothrine. Mouse carcinogenic studies used doses considered inadequate. Potentially carcinogenic in humans, but insufficient data to confirm carcinogenicity in humans.
Cyfluthrin*	Long-term neurotoxicity in laboratory animals include locomotor and postural anomalies, tremors, reversible axonal degeneration squat legs, ataxia, etc. and decreased body mass. Some studies suggested reduced offspring viability at maternal toxic doses.
Cypermethrin*	
Deltamethrin*	Sub-chronic and long-term studies principally revealed hypersensitivity, stimulation of nervous system, altered locomotor activity, decreased body mass or weigh gain. No offspring effects at doses below maternally toxic doses. Currently under re-evaluation by the US and California EPAs concerning reproductive and developmental toxicity.
D-Phenothrin (sumithrin)*	Though oncogenesis was not witnessed in rats or mice under chronic exposure, at excessive doses tumours were observed in rats and hepatocellular adenomas were observed in mice, but considered not statistically significant due to high occurrence of this pathology in the mice strain used. Preputial gland cancer observed in a study could not be replicated in a following study, even at higher doses. Minor effects on body mass, liver, surrenal glands and circulatory system, depending on the species. Effects related to endocrine perturbations were observed (estrogenicity, angdrogenicity or thyroid effects).
Lambda-cyhalothrin*	
Permethrin*	In laboratory animals exposed to high doses, clinical signs such as overexcitability, tremors, body mass and liver effects were observed. Lung and liver tumours observed in mice, with equivocal carcinogenicity in Long-Evans rats. No in vivo tests in mammals to assess DNA damage, mutagenicity and clastogenicity.
Pyrethrins*	Weight of evidence concludes carcinogenicity of Pyrethrins, including occurrence of benign tumours in livers of female rats. Thyroid tumours were observed in rats of both sexes, but they developed via a mechanism not necessarily pertinent to humans. In laboratory animals, critical effects are (1) neurobehavioral after sub-chronic or chronic exposure; (2) thyroidian following chronic exposure in rats and dogs; (3) hepatic following sub-chronic or chronic exposure in rats, dogs and mice. Inhalation exposure yields neurobehavioral effects, followed by histopathologic lesions of lungs and respiratory tract. These effects and modes of action are likely to occur in humans. Animal studies did not reveal reproductive, developmental nor genetic toxicity.
Resmethrin*	Probably carcinogenic in humans as per very significant hepatocellular adenomas and carcinomas in male CD-1 mice and female Sprague-Dawley rats. Sub-chronic animal studies reported neurotoxicity, anemia, thyroid follicular cells vacuolation and hepatocyte hypertrophy. Chronic studies demonstrated target organ toxicity on liver and decreased body mass. Rabbit fetuses demonstrated enhanced sensitivity compared to their mothers. Estrogenic, endrogenic or thyroid toxicity potential were observed. No genotoxicity was reported.
Tetramethrin*	Animal carcinogenicity studies insufficient to evaluate human carcinogenic potential. Instertitial testicular cells adenomas were higher in treated rats, compared to controls, in two species of rats. Leydig cells tumours develop spontaneously in older rats and do not progress into malignant tumours. It is believed that these tumours are of hormonal origin. Mice did not develop benign nor malignant tumours. Hence, this carcinogenic potential in rats cannot be considered in establishing the carcinogenic potential in humans. At low chronic food exposure, mice displayed reduced pituitary, thyroid and parathyroid weight. In rats, in addition to testicular effects mentioned above, reduced weight gain and increased liver weight were observed. There are no specific studies on endocrine disruption potential of tetramethrin. However dog and rat studies revealed effects on estrus activity. Neurotoxicity studies were judged inadequate. No reproductive nor genotoxicity effects were reported.
Fluvalinate	No evidence of carcinogenesis in humans based on rats and mice studies. Dogs regularly fed Fluvalinate had reduced weight, increased liver weight, emesis (vomiting) and salivation. Rats had a reduced weight in chronic studies and a reduced weight with an enlarged liver in sub-chronic studies. In mice, chronic nephritis (kidney inflammation). Chronic neurotoxicity clinical symptoms were noted: Abnormal posture, hyperactivity, hypoactivity, excessive grooming and protruding eyes. No reproductive or developmental, or endocrine disruptions noted.
Tefluthrin	Chronic mice study revealed ataxia, changes in the uterus, and liver necrosis. Female rats exposed to high doses exhibited neoplastic lesions such as uterine adenocarcinoma. Although these effects are not statistically significant compared to the control, they are beyond the ranges historically observed in control populations. This suggests tumour and cancer potential in mice and rats. No carcinogenesis evidence in male mice and rats. Hence, this product was classified as non-carcinogenic by the US EPA and EU, but Canada added an extra safety factor in the calculation of the reference chronic dose. No reproductive or developmental toxicity in animal studies. No genotoxicity. We do not know if the effects observed in long-term studies are linked with endocrine perturbations. Neurotoxicity studies are considered unacceptable for Tefluthrin, but neurotoxic evidence was acquired from reproductive and chronic toxicity studies in rats. Pyrethroids are known neurotoxicants.

Environmental effects of pyrethroids

Environmental occurrence

Pyrethroids enter the environment via drift and deposition of sprays or leaching from agricultural and domestic uses applications.[38] In urban regions, pyrethroids are frequently used for golf course turf, ornamentals, residential lawns, rights-of-way, and structural pest control.[93] Since pyrethroids are extremely toxic to fish, they are generally not directly sprayed into water, but can leach off from treated areas[2] and may be released with tailwater for example in rice paddies.[17] Pyrethroids appear unaffected by secondary treatment systems at municipal wastewater treatment facilities.[94]

The two most important factors affecting pyrethroid concentrations in surface water include use patterns and precipitation.[17] Agricultural runoffs may lead to higher concentration in the summer than in the winter, but pyrethroids are nonetheless detected in surface waters following heavy winter rains.[17] Modelling has shown that less than 1% of all pyrethroids applied in agricultural fields of a California region were transported to the nearest bay. However, this was sufficient to yield concentrations potentially toxic to benthic organisms (low ppb range).[17] Since pyrethroids tend to bind strongly to particles, their toxicity in sediments might be more important than that expressed by the dissolved water concentrations.[17,93, 95-97]

Pyrethroids are not commonly detected in Quebec surface water bordering corn and soy fields,[98] but have been detected in surface water in regions of vegetable production (Lambda-cyhalothrin, Permethrin and Cypermethrin)[38] and orchards or potato growing.[99] Sometimes, the concentrations of insecticides in Quebec's surface water are greater than the chronic criteria for aquatic life.[38] For the pyrethroids, specifically, Quebec's chronic toxic criteria for aquatic life of Permethrin is 0.004 μg/l (and the acute toxicity criteria is 0.044μg/l, for short-term exposure). This criterion has been surpassed in 14-33% of samples from streams in orchards and potato growing regions, with the maximal peak concentration exceeding the acute toxicity criteria by 32 times and consequently the aquatic chronic toxicity criteria by 350 times. Deltamethrin is more rarely detected, and the chronic toxicity criterion (0.0004 μg/l) is lower than the analytical capabilities of governmental laboratories (no acute toxicity criteria exists for this molecule), meaning that in any sample where Deltamethrin can be detected, it is already in concentrations exceeding the chronic toxicity criteria, a baseline established to protect crustaceans which are the most sensitive organisms in the aquatic environment. Concentrations measured in streams in three orchard and potato growing regions range from 0.04 μg/l to 0.07 μg/l, which is 100-175 times in excess of the chronic toxicity criteria for aquatic life. Finally, a 2005 report does not mention ground water contamination with pyrethroids in Quebec agricultural regions, though this may be due to the absence of analysis for pyrethroids directly, since provincial surface water reports from those years did not survey for pyrethroids either.[100] A 2015 report on groundwaters showed that Permethrin had been detected in 6% of groundwater samples obtained from the lower Saint-François region, with concentrations ranging from 0.035-0.048 μg/l.[101] While this appears above the Quebec's chronic toxic criteria for aquatic life and in the range of the acute toxicity criteria, the original study focuses on detection (i.e. not quantification of precise concentrations). Piperonyl Butoxide, commonly associated to pyrethroids, was also detected in 24% of the samples with concentrations ranging from 0.009-0.028 μg/l.[101]

In the US, the first pyrethroid detected in surface water was Bifenthrin in 1996 (in San Francisco Bay, California).[93] Only Permethrin is monitored in the US National Water Quality Assessment (NAWQA) program of surface and ground water due to budgetary and analytical constraints.[102] Permethrin is considered a high-use pesticide by the US Geological Survey, and it is tracked in the surface and ground water quality monitoring program with an analytical detection limit of 0.003µg/l in water (GCMS) and 5 µg/kg dry weight in sediments.[102] In California, several pyrethroids have been measured, often in high concentrations, in agricultural streams sediments, and at even higher concentrations in urban streams.[93] Recent research by the US Geological Survey shows that pyrethroids commonly occur in urban streams sediments (45%) across the country, and that they may be contributing to sediment toxicity. Varying types and concentrations of pyrethroids were detected in metropolitan areas, suggesting regional differences in their use and environmental fate.[93] Nearly half (45%) of the surveyed stream sediment beds contained detectable concentrations of one or more pyrethroids (out of 14 measured pyrethroids, 5 were detected in the study, namely Bifenthrin, Cyhalothrin, Cypermethrin, Permethrin and Resmethrin). Bifenthrin was the most commonly detected pyrethroid.

Degradation and persistence

The effect and persistence of pyrethroids is influenced by abiotic conditions, for instance, natural Pyrethrins and synthetic pyrethroids are known to be more efficient insecticides at lower temperatures, and this temperature effect may also affect non-target organisms.[103] Pyrethroids are known to degrade relatively rapidly in the environment by one or more biotic or abiotic processes, though adsorption to sediments may render them unavailable to degraders.[104] Plants, animal and microbial degradation or photodegradation have all been demonstrated.[104] The rate of soil degradation varies for the different pyrethroids and is influenced by the nature of the soil, the climate and the abundance and diversity of microbes present. Different bacterial genus, such as *Pseudomonas*, *Enterobacter*, *Stenotrophomonas*, *Aeromonas*, *Erwinia*, *Bacillus*, *Achromobacter*, *Serratia* and *Yersinia* have been found to degrade different pyrethroids, some even being able to use the insecticide as a sole carbon source (see review in [104]). In direct sunlight, Cypermethrin is considered relatively stable with a half-life as long as eight weeks, and may persist three months after indoor domestic treatments, or travel to untreated rooms via the air.[105] Hydrolysis and photolysis are known to be considerably slower indoors, with a rapid degradation occurring within a few days, followed by much slower rates of degradation over a period of two years.[106] In areas where sunlight and air circulation is limited, for instance in grain elevators or subway tunnels, most of the applied pyrethroids (D-Phenothrin) remain after one year.[92] Cypermethrin may persist more than 50 days in normal environmental water conditions and photodegradation may require 100 days.[107] Permethrin is also one of the pyrethroids most stable to UV light. When bound (adsorbed) to soil particles, it may have a half-life of 43 days, and in formulations designed to kill termites (termiticides), can persist up to 5 years.[92] In general, pyrethroids are considered to have similar physico-chemical properties that affect their transport and fate in the environment, and the average half-life in soils in presence of air (aerobic) varies between 30 to 100 days.[17]

Non-targeted organisms

Terrestrial

Mammals may have long-term risks and secondary poisoning risks for some pyrethroids (i.e. Bifenthrin[108]). But generally, mammals are protected by poor dermal adsorption, rapid metabolism and rapid excretion of pyrethroids metabolites.[6]

In birds, Bioallethrin appears to be the most toxic (680 mg/kg body weight), while Permethrin appears as the least toxic (>13,500 mg/kg body weight).[104] Pyrethroids are generally considered moderately toxic to birds (LD_{50} >1000mg/kg), but the main threat to birds is the indirect impact on their food supply: insects.[92]

Insects, however, are 2,250 times more susceptible to pyrethroids than mammals because of the increased sensitivity of their sodium channels, smaller body size and lower body temperature.[6] Field risks have been identified for non-target arthropods for some pyrethroids, such as Bifenthrin.[108] This may be consequential for bees and biological agents (predators, parasitoids or parasites that are used against commercially damaging pest insects in lieu of insecticides). Predator-prey relationships may also be disturbed when, in some cases, predators are susceptible to lower doses than the targeted insect pest.[92]

Bees are notably lacking detoxification enzymes and may be particularly at risk from pyrethroid insecticides.[109] Bees have not been tested with all pyrethroids, but in studied instances, toxicity varies from toxic to highly toxic, except for Fluvalinate which appears non-toxic.[104] Bees are commonly exposed to various pesticides, and while some honey or wax may be uncontaminated, the pollen and the honeybees themselves may be contaminated.[110, 111] Very often, this exposure is composed of a cocktail (54% of the time apiaries contain between two and four pesticides)[110] and coincidentally occurring pesticides may reach a maximum of nine active substances.[111] Bees may be contaminated by pyrethroids via direct contact with spray, treated crops or adjacent flowers, contact with contaminated foliage or uptake of the chemical in the nectar or pollen.[112] Pyrethroids such as Tau-Fluvalinate may reach apiaries indirectly when they are used as insecticides, or be used directly in hives as acaricides, though it is not recommended anymore in French apiaries because of developed mite resistance. Tau-fluvalinate has been observed in 6.1% of pollen collected from French hives, with a mean concentration of 487.2 µg/kg and a maximum of 2020.0 µg/kg,[110] and other researchers observed a range of concentrations varying from 5 to 260 µg/kg,[43, 110] ranges higher than what would normally be lethal to bees (LD_{50} = 65.85).[110] But pollen is not the most commonly contaminated compartment for Tau-Fluvalinate: 52.2% of wax samples may be contaminated, with concentrations averaging 220.0 µg/kg[111]. Cypermethrin, also toxic at low concentrations (LD_{50} = 0.06 µg/kg)n has been observed in concentrations ranging from 70-1900 µg/kg ([113] in [110]) though it is not found in all studies.[110] Deltamethrin was also observed in bees (5.9% of samples), wax, honey and finally pollen, where the highest concentrations were quantified (39.0 µg/kg). However, not all pesticides are lethal at environmental concentrations, and small quantities which are harder to detect may affect behaviour. The quality and quantity of pollen consumed by bees in their first days of life affects the pesticide resistance for the rest of their lives.[110]

Insect pollination, mostly by bees, is necessary for 75% of crops directly used as human food,[114, 115] with fruit crops most vulnerable. The annual economic value of insect pollination was estimated at 153 billion Euros in 2005, representing 9.5% of the total economic value of agriculture worldwide.[115, 116] Bees have been affected by massive colony losses in the US (59% from 1947 to 2005), the European Union (25% between 1985 and 2005, documented in France, Belgium and the UK) and elsewhere around the globe.[109, 111, 115] Growing concern for the fate of domesticated and wild pollinators led to the establishment of the special International Pollinator Initiative by the Convention on Biological Diversity of the United Nations.[115, 117] One of the issues leading to massive bee losses is a broadly defined problem termed the Colony Collapse Disorder (CCD) and is characterized by a rapid loss of adult workers, with a noticeable absence of dead workers in or around the hive, and a delayed invasion of the hive by pests and neighbouring bees.[109] Though research shows that CCD is not random geographically (with neighbouring hives more likely to be infected or exposed to a common detrimental environmental factor), no one can precisely pinpoint the most likely cause, among which appears pesticides levels and pathogen loads, as well as interaction between both.[109] The general pollinator decline may be linked to direct insecticide-related mortalities, direct application to agricultural sites, aerial drifting from semi-rural habitats to nesting and foraging sites, application of indirect herbicides and fertilizers (which induce shifts in the availability of floral resources), climate change and habitat loss.[115]

But honeybees are not the only important pollinators, and pesticide risk assessment for honeybees may not apply to bumblebees. For instance, early morning or evening application of pyrethroids to oilseed rape, to avoid honeybee foraging hours, may increase the chance of affecting bumblebees which are active at that time.[112] Applications of Dimethoate or alpha-Cypermethrin to oilseed rape, or application of lambda-Cyhalothrin to field beans has been linked with bumblebee losses in the UK.[112] But sub-lethal effects have also been evidenced in bumblebees exposed to pesticides.[112] Canadian, US and EU legislations require oral and acute tests on honeybees, but there is no obligation to study sub-lethal effects and no obligation to study bumblebees.[112]

Long-term risks have also been identified for earthworms (i.e., Bifenthrin[108]) which are important in organic matter cycling and indicators of soil health in several natural ecosystems.[118]

Reptiles are rarely considered in toxicity testing and risk assessment of pesticides, and in the case of pyrethroid, this is of concern.[119] Pyrethroids have long known to be more toxic at lower environmental temperatures[103] and this is particularly important in lizards whose metabolism (and detoxification capacity) is influenced by environmental temperatures and whose neurons are more sensitive to Pyrethrin stimulation at lower temperature. It appears incorrect to assess the toxicity of pyrethroids based on mammals and birds responses, without specifically considering reptiles.[119] Fish and frogs have also been shown to be increasingly affected by pyrethroids at lower temperatures (see references in document [120]).

Aquatic

Aquatic organisms are also at risk from pyrethroids. However, the registration eligibility decision of several pyrethroids lacks the critical toxicity tests that are normally minimally required by legislators. All pyrethroids that have been tested on fish for acute toxicity are at least toxic, with Cypermethrin and Tralomethrin being extremely toxic.[104] However, chronic toxicity data is lacking for reptiles, amphibians (terrestrial and aquatic phase), freshwater fish, freshwater crustaceans and mollusks for Allethrins, and

both chronic and acute toxicity data is lacking for marine and estuarine fish and crustaceans.[121] In the case of Cypermethrin, acute toxicity is better documented but data is lacking for chronic toxicity to freshwater invertebrates, benthic organisms and estuarine and marine fish.[122] Furthermore, the estimation of transport to surface water resulting from indoor and outdoor use of some pyrethroids (Allethrins) is not currently estimated since standard models used by the US EPA are designed to model agricultural runoffs, not urban runoffs. Hence products which are registered for applications in ''cracks and crevices'', outdoor applications or pet shampoos which can certainly result in environmental releases to surface waters are not currently quantified in registration eligibility decisions. Risks to aquatic organisms is considered minimal based on the calculation involving spill of whole cans or shampoo bottles content directly in surface water, but this does not represent any estimation of simultaneous releases originating from normal use from urban environments, and such estimates would not only be essential for each active substance, but also for all pyrethroids conjointly.[121]

Younger organisms (of daphnia, copepods, and carp) may be more sensitive than adults, and males may be more sensitive than females.[17] Nutritional status of aquatic species may also affect their likelihood of being affected by pyrethroids.[17] Aquatic organisms may suffer from reduced growth (mysid shrimp, bluegill sunfish); fish may suffer from altered behaviour like rapid erratic swimming, loss of equilibrium, jaw spasms, gulping respiration, lethargy and darkened pigmentation; and waterflea may exhibit immobilization or decreased movement to stimulation.[17] Reproduction in mysid shrimp, daphnia and fish may be impaired.[17] Immunity of fish and ability to resist infectious agents may also be challenged when exposed to pyrethroids.[17] Swimming performance tests, a direct measurement of how well a fish can move and feed in the wild, reveals that fish may be affected by pyrethroids even at levels generally considered to have no observable effects.[17]

The risks to aquatic vertebrates may lead to the conclusion that the use of some pyrethroids is unacceptable.[108] Bioaccumulation in fish has been documented (488X for Cypermethrin)[122] but uncertainty remains for other instances (e.g., Bifenthrin).[108] Fish may be 100 times less sensitive than crustaceans[122, 123] but up to 1000 times more sensitive than mammals and birds.[120] The aquatic amphipod, *Hyalella azteca*, exhibited increased mortality when exposed to environmental sediments collected from different regions of the US, and Bifenthrin was a likely contributor of this toxicity.[93] Environmental concentrations observed in water is generally below lethal concentrations for many fish,[120] though the environmental concentrations value that killed half of a study population (LC_{50}) values of targeted mosquito or blackfly larvae is similar to that for bluegill sunfish and lake trout (<1ppb).[92] However, sub-lethal concentrations of Cypermethrin akin to environmental water concentrations, were shown to negatively affect reproduction in salmons. This occurs because Cypermethrin exposure decreased or inhibited the olfactory response of male salmons to female prostaglandins, which are important priming pheromones released in the females' urine at the time of spawning.[120] Similar reduced reproductive output has been shown in other species of fish such as the Australian crimson-spotted rainbowfish (*Melanotaenia fluciatilis*) and the bluegill sunfish (*Lepomis macrochirus*).[120]

Although plants are not targeted by the primary mode of action of pyrethroid insecticides (neurotoxicity), there is insufficient data to ascertain that secondary modes of action do not threaten plant populations (e.g., Bifenthrin,[108] Allethrins[121] and Cypermethrin[122]).

Mixtures and synergism

Cumulative risk assessment

In the US, cumulative risk assessments have been required since the Food Quality Protection Act of 1996[124] and was also present in the 2002 Canadian Pest Control Act.[125] Authors strongly tied with the industry have argued that a cumulative risk assessment for various pyrethroids or for pyrethroids and other pesticides combined is inadvisable as effects on target sites are not cumulative, and sometimes antagonistic.[25] For instance, the relationship between pyrethroids and decreased sperm quality appear statistically stronger when compared to individual metabolite concentrations, then when compared to the sum of all metabolites, possibly indicating non-cumulative effects.[16] Furthermore, a better understanding of pyrethroid mode of action, for instance on calcium channels, is required in order to correctly assess cumulative risk assessments.[69] However, the USGS assumes that the toxicity of pyrethroids is additive and thus sums toxic units to assess toxicity of pyrethroid mixtures.[93] During a cumulative risk assessment of Pyrethrins and pyrethroids in 2011, the US EPA considered that these insecticides do not pose risk concerns for children or adults, and supported the registration of additional uses of these pesticides.[8] Though legally required, these cumulative risk assessments still require improvement.

Pyrethroids are known to co-occur in US sediments samples, with two-thirds of the samples analyzed containing two types of pyrethroids simultaneously; the most common mixtures were Bifenthrin with either Cyhalothrin or Permethrin.[93] In aquatic ecosystems, mixtures of pyrethroids and organophosphorus insecticides can affect fish, possibly because organophosphorus insecticides affect the detoxicifation potential of fish.[102] The synergistic effect could increase the toxicity by 140-170 times. Furthermore, pyrethroids have simultaneously been detected with neonicotinoids (another class of potent insecticides undergoing bans and restrictions in several regions of the world) in Quebec surface waters.[99] Previous studies have shown that neonicotinoids and pyrethroids can have synergistic effects in terrestrial insects such as bees, but that these effects may not be detected with the current short-term (96h for Acute exposure) laboratory guidelines.[126]

Co-occurrence of pesticides such as pyrethroids and organophosphorus insecticides is also common in households, with 100% of urban housing having more than two analytes in vacuum dust, and more than three analytes in kitchen floor dust. More complex mixtures reaching more than 5 analytes occurred in 49% of vacuum dust and 56% of living room floor wipe samples, while more than 6 analytes co-occurred in more than 64% of kitchen floor wipe samples.[30] It is known that organophosphorus insecticides can increase a target's sensitivity to pyrethroids, and so joint applications of pyrethroids and organophosphorus insecticides are common, especially in the case of resistance to pyrethroids.[127] An epidemiological study suggests lower sperm counts in men exposed to organophosphorus and pyrethroids, highlighting that more research attention is required for these types of mixtures.[127]

Pesticide mixtures do not only threaten humans, since significant concurrent detection of pyrethroids and other pesticides is also observed in bees, for example Tau-Fluvalinate with Imidacloprid or Lindane and Deltamethrin with 6-chloro-nicotinic acid or Coumaphos.[111] It has been shown that some pesticides mixtures may enhance the sensitivity of bees, for example, with Coupaphos increasing the susceptibility to Tau-Fluvalinate.[128]

Best practices

Registrations and bans

Pyrethroids appeared on the market almost 50 years ago. Hence, several molecules have already been the subject of periodic reregistration reviews in the US and Canada. The latest round of review in the United States was completed by the EPA in 2008 for Pyrethrins, Allethrins, Cypermethrin, Tau-Fluvalinate, Permethrin, Resmethrin, Sumithrin (D-Phenothrin), Tetramethrin as well as the synergists MGK-264 (also known as N-octyl bicycloheptene dicarboximide) and piperonyl butoxide. However, because pyrethroids have common modes of action and are often used as substitutes for one another, the EPA thought it made sense to review all Pyrethrins and pyrethroids to manage their risk within a similar timeframe. The registration review of different products was thus initiated from 2010 to 2012:[8]

- in 2010 (Cyphenothrin, Esfenvalerate, Allethrins stereoisomers, Deltamethrin, Tralomethrin, Bifenthrin, Fenpropathrin and Cyfluthrin),
- in 2011 (gamma-Cyalothrin, lambda-Cyhalothrin, Tau-Fluvalinate, Permethrin, Imiprothrin and the synergist piperonyl butoxide). and
- in 2012 (Pyrethrins and derivatives, Sumithrin (Phenothrin), Tetramethin, Cypermethrin, Prallethrin, Resmethrin, Metofluthrin, Tefluthrin and the synergist MGK-264).

In Canada, only ten pyrethroids, Pyrethrins and synergists are to be considered together in a common review initiated in 2011 to be completed in 2016[129]: Allethrins (*d*-cis, *trans*- and *d-trans*- isomers), Cyfluthrin, Cypermethrion, Deltamethrin, D-Phenothrin (Sumithrin), Lambda-cyhalothrin, Permethrin, Pyrethrins, Resmethrin, Tetramethrin and the sygergists piperonyl butoxide and MGK-264. Canadian and US pesticide reviews are often coordinated since they share common markets and borders.

In Canada, the PMRA office integrated within the Health Canada Department is responsible for registration oversight, and federal laws supersede any others. In the Province of Quebec, supplementary legal and regulatory frameworks exist under environmental ministry responsibility (*Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques*). The two main laws are the Pesticides Act and the Environmental Quality Act. Under the Pesticide Act, is a regulation on licences and certificates to sell and use pesticides. One of its main objectives is to keep track of pesticide sales and make sure applicators are properly trained through the delivery of authorization certificates. A classification system ranges from restricted use pesticides (Class 1) down to domestic use pesticides (Class 4 or 5 depending on the regulated level of environmental and human health risk). Note that domestic pyrethroids generally fall in Class 5 (http://www.mddelcc.gouv.qc.ca/pesticides/Classification-Pesticides.pdf).

There is also the Pesticides Management Code (Code de Gestion des Pesticides), in effect since 2003 designed to reduce the health and environmental impacts of pesticides use by setting guidelines for certified distributors or applicators (stores, farmers, technicians, etc.) but also for the attention of the general public for domestic use pesticides. In the case of daycares, elementary and high schools pyrethroids are not to be used (http://www.mddelcc.gouv.qc.ca/pesticides/permis/code-gestion/index.htm). The Canadian Environmental Protection Act contains legislation on impact assessment, issuing certificates of authorization for any activities which may impact the environment like pyrethroid applications, drinking water regulations monitoring several pesticides concentrations in

drinking water (pyrethroids are not targeted) and pesticide waste management. Details on these laws, regulations and codes are available via the Quebec environmental ministry web site (http://www.mddelcc.gouv.qc.ca/pesticides/cadrelegal.htm#loi).

Furthermore, some 131 Quebec municipalities have adopted regulations concerning pesticides uses in their jurisdiction. The regulations cannot supersede federal (e.g., registration of active substances) and provincial (e.g., certificates delivery) authority but may bring further restrictions, for example, on the use of pesticides for aesthetic purposes (http://www.mddelcc.gouv.qc.ca/pesticides/Liste-municipalites.pdf). For instance, the City of Montreal banned pesticide use outdoors, except for low impact pesticides which do not comprise the pyrethroids or when a temporary licence is granted for an infestation.[130] Offenders may be subjected to a fine. However, this regulation does not control indoor use of pesticides such as the pyrethroids.

Bifenthrin was banned in the Netherlands in 2001, then throughout Europe in 2009 (2009/887/EC).[108] The opinion of experts on pyrethroid toxicity followed the precautionary principle (necessity to prove absence of harm) to determine the acceptability of a pesticide.[53]

Risk and benefits should be balanced in legislating on pyrethroids since developed countries may have relatively benign pests to handle and could chose precaution, while other countries, such as those in Africa, are plagued with malaria, which kills millions of people annually.[53, 131]

Managing resistance

In developing countries (e.g., (Gambia, Ghana and Kenya), insecticide-treated nets can decrease childhood malaria morbidity by 50% and decrease overall mortality by 20-30%. Pyrethroids are the insecticide of choice because of their high efficacy, rapid rate of knock-down, strong mosquito repellent properties, low mammalian toxicity and cost-effective ratio (leading to high community acceptance).[132] Pyrethroids may eventually lead to pest population resistance, much like the situation for DDT today, highlighting the need for careful and localized use of pyrethroids if we want it to remain an effective tool in the fight against malaria.[133] That is why the WHO co-ordinates its efforts to minimize the widespread mosquito resistance to pyrethroids.[132] If nothing is done to control resistance, the public health consequences would be devastating, according to the WHO. Nevertheless, use of pyrethroids in cotton-growing and urban areas selects for pyrethroid resistance among the mosquito population, with the rainy season increasing selection pressure even further.[133] To control for the spread of the West Nile virus in Quebec, several types of insecticides are used to target the larvae and adult populations. Pyrethroids such as Resmethrin and Permethrin are used to control the adult stages of the mosquito, alongside the organophosphorus Malathion, while the control of larvae maybe via the synthetic hormonal mimic insecticide Methoprene or the selective biopesticides *Bacillus thurigiensis* var. *israelensis*, or *Bacillus sphaericus*.[134]

The resistance of mites to pyrethroids appeared as early as the 1990's in the scientific literature,[44, 128, 135] despite the use of alternate substances (coumaphos, amitraz) to try to minimize the appearance of this resistance. Today, no chemical treatment against mites which are parasites of bees is 100% effective. However, natural substances, such as Thymol and oxalic acid, which have been around for hundreds of years, exhibit no evolved resistance,[128] suggesting possible alternatives to synthetic pyrethroids.

Alternatives to pyrethroids

When insect pests are not life-threatening, and when potential economic losses or personal comfort health and comfort are at stake, several alternatives to pyrethroids exist. Alternative means of controlling pest insects include physical options, biological treatments, low impact pesticides or essential oils and finally behavioral changes.

Physical means of controlling insects exist. They include heat treatments (effective against bed bugs and head lice) and cold treatments (freezing potentially contaminated objects or food, against bed bugs, head lice or cockroaches). [136-141] Behavioral changes such as early and frequent monitoring, reducing hospitability of your homes or preventing the arrival of the pests are all appropriate methods. Some professional exterminators are now trained and offer physical control of home dwelling insects.

Biological insect control has been proven efficient against a wide variety of agricultural pests without any reliance on synthetic pesticides. Integrated pest management practices may occasionally rely on chemical pesticides when pest populations reach a potential economic damage threshold, but favour prophylaxis, safer chemical alternatives (low-impact pesticides), and more spatially and temporally targeted applications. The discovery of apparently less toxic synthetic pesticides, for instance the newly US- registered flupyradifurone is expected to have a lower toxicity to honeybees than certain pyrethroids, neonicotinoids, organophosphates and avermectin insecticides.[142] Even at home, several safer alternatives to pyrethroids exist to successfully eradicate head lice and cockroaches.[137-139]

For instance, combing is an acceptable alternative treatment against head lice because it is easy, inexpensive, self-sufficient, non-toxic to the patient and for the environment, and serves both to diagnose and treat head lice.[34] Combing clean, wet hair with ordinary hair conditioner applied on days 1, 5, 9 and 13 proved to be four times more efficient than a double Phenothrin lotion treatment (1 week apart) in a UK randomized trial.[34] Obviously, the recommended combing protocols are not followed correctly, this treatment is ineffective. Making the head an inhospitable environment to head louse (using gels or shaving), unattractive or repellant (lavender, citronella or anise oils), or using compounds that interfere with gas exchanges (oils) are alternative that merit further exploration to reduce our dependency on pyrethroids.[34] Logically, combing methods should be prioritized over chemical treatments, but care should also be taken to avoid misinformation and gimmicky treatments which are not licensed and have no clinical evidence to support their efficacy or assess their safety.[34] Recommendations found on home remedy sites and popular online forums to use dog flea shampoo to treat children with head lice are particularly worrisome.

Various types of essential oils are effective against a wide variety of insects,[143] including some essential oils that have repelling or feeding deterrent, or even lethal properties against cockroaches.[143, 144] Contrary to common claims, there is a strong body of evidence for their effectiveness, though they are not currently commonly used as alternatives to pyrethroid treatment of domestic insect pests.[143] Because they are commonly used in culinary preparations, essential oils may not need the stringent testing requirements of other chemical pesticides (they are generally recognized as safe (GRAS) by the US Food and Drug Administration), and furthermore, several essential oils have proven beneficial to human health.[3, 143] For example, a commercialized mixture of essential oils (EcoSMART Technologies Inc,.) to treat pests led to no rat mortality at the highest US EPA required testing dose (2 g/kg).[143] Furthermore, the rainbow trout (*Oncorhynchus mykiss*) may be 1500 times less sensitive to eugenol (a monoterpene contained in several plants, including cinnamon, nutmeg, cloves and basil) compared to botanical

pyrethrum (96 h LC_{50}) and these compounds are not persistent in soil or water environments.[143]

Despite the fact that most families (84%) in a US urban public housing study on pyrethroids and organophosphates had used pesticides in the year preceding the study, the vast majority (92%) also manifested interest in non-pesticidal alternative treatments.[30] Also, considering that pyrethroid alternatives, even plant-based natural extracts, are not completely devoid of potential health and environmental side effects, and considering that alternate treatments may be considered as gimmicks if they are not backed by the scientific literature, further study of safer alternatives to pyrethroids appears to be essential since many people long for change.

Conclusion

Pyrethroids are one of the most important types of pesticide sold, and the most important class easily available to the general consumer market. However, their toxicity assessment is complex and several critical data gaps exist. The current US and Canadian pesticide registration review for a group of pyrethroids may bring answers to lesser characterized aspects of the environmental occurrence and persistence of these pesticides, exposure and toxicological risks for fauna and humans. Of particular interest is the review of the neurobehavioral toxicity of pyrethroids in children, for which animal, epidemiological and mechanistic studies suggest an impact coupled to insufficient regulatory testing. Another aspect of concern is the potential deleterious impact on human reproduction, via interference with the endocrine system. Finally, carcinogenicity re-evaluation may also bring a novel perspective on the putative relative safety of these products. Because of their extensive use on food and easy, unsupervised access by the general population, we may be facing higher risks than currently acknowledged. The precautionary principle should guide our action to prevent undesirable consequences of extensive pyrethroid uses. Further research on alternatives to synthetic pyrethroids critically needs supports from our governments and industries.

Policy Recommendations based on new knowledge, data gaps and international benchmarking

- Related to research and registration
    - Further research on neuronal death, neuronal toxicity and bioactivation, with more precise modern protocols, is necessary to ensure that older regulatory assessments of pyrethroids did not overlook subtle effects of repeated low-dose exposure, which is common in our environment. [26]
    - Further studies on the implications of varying meteorological and climatologic conditions on pyrethroids efficiency and toxicity should be conducted, especially in the face of global warming, since pyrethroids are known to be less efficient at higher temperatures.[103] Better knowledge of minimal time between application and forecasted rain is also important to improve risk management measures. [97]
    - Many waters in the US have been designated as impaired in accordance with the US Clean Water Act (they do not meet the total maximum daily loads water quality standards) by pesticides *a priori* authorized by the US EPA. Pyrethroid insecticides are of particular concern since they have been shown to cause toxicity to urban surface water sediment-dwelling organisms in California. Better assessment of the potential risks to surface waters by the US EPA at the time of registration could alleviate the financially demanding *a posteriori* evaluations that are required to restore contaminated waters from regional water boards (e.g., San Francisco Bay Region Water Quality Control Board). [145] In Canada (Quebec), insecticide concentrations may exceed chronic criteria for aquatic life; this was the case between 14-33% of the surveyed samples from agricultural regions for Permethrin. The acute toxicity criteria and chronic toxicity criteria were exceeded by 32 and 350 times in most concentrated samples analyzed.[38] Deltamethrin exceeded chronic toxicity criteria 100-175 times in the most concentrated samples taken from streams in orchard and potato growing areas of Quebec.[38]
    - Due to the widespread use of pyrethroids and the widespread contamination of humans (assessed via metabolite studies), a routine follow up of ground waters and drinking water testing is recommended for Quebec.
    - Critical data gaps concerning environmental fate and aquatic toxicity data should be filled. In some instances (e.g., Allethrins); none of the minimally required data sets are available for registration eligibility decisions, and at best, only a few studies are available. Data is lacking for: chronic aquatic toxicity for fresh, salt waters, and sediments; environmental fate of urban runoffs for active substances including all isomers and degradates and data to support modeling of urban runoffs.[97]
    - Better environmental monitoring of pyrethroids in Quebec surface water is recommended as currently, only few intensive agricultural regions are monitored (corn and soy, [98] orchards and potato growing regions[99]) and urban surface waters monitoring or general ground water monitoring is lacking (through Permethrin and Piperonyl Butoxique have been detected in Quebec groundwater)[101]. Furthermore, considering that few water treatment plants are

equipped to remove pesticides from surface and groundwater, Quebec regulations on drinking water[54] should include monitoring a few common pyrethroids, such as Permethrin.
    - Further research is needed on safe and effective pyrethroid alternatives for agricultural and domestic uses.[143, 144]
- Sensitive populations
    - Pesticides should always be stored out of the reach of children, and in their original labelled containers, to prevent accidental poisoning.[2]
    - Because of the risk to the unborn child, pregnant women should avoid contact with pesticides.[28]
    - Labels of unrestricted pyrethroids (over-the-counter products) should warn sensitive sub-populations (like allergic or asthmatic people or those suffering from multiple chemical sensitivity) to avoid exposure.[29]
    - Everyone, and in particular children, should wash their hands before eating to minimize undesired ingestion of pyrethroids.[7]
- General population
    - To avoid pyrethroid exposure, it is advisable for people to remain indoors while the neighbourhood is sprayed with pyrethroids to control mosquito populations.[2]
    - To reduce dietary exposure, all fruits and vegetables should thoroughly be washed before being eaten.[7]
- User specific
    - If pyrethroids are chosen to solve a house pest or health issue, instructions should be carefully followed to ensure proper use and it is inadvisable to use more than the recommended quantity.[2]
    - Labels of unrestricted pyrethroids (over-the-counter) should better define what ventilating a treated area means, and increase the recommended re-entry delay period to better protect sensitive sub-populations.[2, 29] Professional pesticide applicators should initiate mechanical ventilation of treated homes instead of instructing occupants to enter and open windows.[29]
    - Cleaning surfaces with commercial cleaning products may considerably reduce the concentration of pyrethroids in house dust on surfaces, but not significantly in indoor air.[106] Care should be taken to completely eradicate insect pests in homes prior to cleaning to avoid reinfestation following subsequent hatching of eggs, for example, or development of resistance in individuals exposed to lower concentrations.[106]
- Education
    - Governmental agencies and health departments should educate applicators and consumers about the importance of reading and following all directions on pesticide labels, and educate asthma and allergy sufferers on the potential risk of pyrethroids. [29]
    - Pyrethroid labels (e.g., Allethrins) should clearly state the danger of increased runoffs to aquatic environment within the first few hours after application and all labels should clearly recommend a minimum time (as it is the case for Cypermethrin), a time which should be more in-line with the current state of scientific knowledge (i.e. 24 to 48 hours, not 8 hours).[97]
    - The use of symbols to communicate water quality stewardship concepts on pesticide labels, as used for other toxicants, may also help illustrate concepts for the target audience of pesticide users.[97]

- Alternatives
    - Efforts should be made to promote and institutionalize safer alternatives to pyrethroid treatments in multiple or low-income housing which are commonly contaminated with pyrethroid residues, with 100% kitchen floors contaminated with Permethrin.[30]
    - Placebo studies using no insecticide at all revealed that this was an effective treatment for head lice in 46% of the cases. Perhaps pediculicides showing less than 50% efficiency should simply be removed from the market, albeit on a local basis and not a nationwide one, since resistance is known to vary regionally.[34] This would require a local and periodic reporting protocol.
- Health professionals and reporting
    - Health professionals should be aware of the respiratory risks of pyrethroids and associated solvents in aerosols, and should report suspected and confirmed cases of exposure to a centralized reporting system.[29]
    - Reporting systems should keep track of regional specificities in pyrethroid poisoning since occurrence and severity of poisoning has been shown to vary in different regions.[29] Geographic based information systems may improve toxicosurveillance, allowing the better identification of high risk regions and the development of preventive interventions accordingly.[14]
    - Family physicians should advise parents to minimize children's exposure to indoor, home and garden pesticides, since home exposure to pyrethroids is common and preventable.[33]
- Strong political goals to minimize pesticide impacts
    - Several agricultural practices are recommended to reduce the impact of pesticides on surface and ground water. A Quebec study prioritized five interventions to reduce surface water contamination with agricultural pesticides: (1) No-till practices; (2) Minimum-till practices; (3) Crop rotations; (4) Use of low-impact pesticides and (5) Use of reduced pesticide doses. According to this research, vegetated buffer strips, crop rotations and low-impact pesticides could completely eliminate the presence of pesticides in agricultural watersheds. Additional governmental actions such as pesticide taxation, banning of the most toxic pesticides, eco-conditional subsidies, ecological labels and financial incentives should be explored. Despite efforts to reduce health and environmental impacts, current provincial and federal laws, regulations, programs and stakeholder actions have failed to reduce the use of pesticides, and this phytosanitary solution is still gaining in popularity.[55]

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