Backgrounder: Atrazine: Banned in Europe, Common in Canada

Atrazine is a herbicide primarily used against broad-leaf weeds and some grasses in Canadian corn fields, but also for sorghum, sugar cane and on lawns elsewhere.[1] Atrazine inhibits photosynthesis, but corn (and other monocot plants) can metabolize and excrete it rapidly, allowing for selective eradication of weeds in fields, even after seedlings emerge.[1-3]

Atrazine: Declining Usage but Lingering Danger

Atrazine is commonly used in over 80 countries.[1] Its popularity is attributable to its effectiveness as a herbicide, and low cost.[4] However, except in Asia, its use is steeply declining around the world.[5] First, glyphosate surpassed global atrazine sales in 2001.[6] Then, following the lead of early players such as Italy and Germany, atrazine was removed from the list of authorized plant protection products by the European Union as of 2003, due to its potential to contaminate groundwater.[7, 8] Owing to its past popularity and persistence in the environment, atrazine was still found in surface waters and in the urine of pregnant women three years after its elimination in Europe.[9]

In Québec, atrazine sales dropped by 72% from 1992 to 2014 (Figure 1),[10, 11] but 145,542 kilograms (kg) of active ingredients were still used. Treated surfaces decreased by three times from 1992-2011, when they reached 130,000 hectares.[12] Among pesticides sold in Québec, atrazine remains the top ranked active ingredient for environmental risk (contributing to 11.9% of global pesticide uses risk) and second in rank for health risks (11.7%).[11] In British Columbia, its use dropped by 99% between 2003 and 2010 (i.e., from 11,535 kg to 43 kg). This drop has been attributed to changes in the registration labels of the Pest Management Regulatory Agency (PMRA)[13] which now prohibits the use of seven of the 13 formulations still registered in Canada.[14] Local authorities fear that registration of novel formulations submitted to PMRA could lead to an eventual rise in sales in the near future.[13]

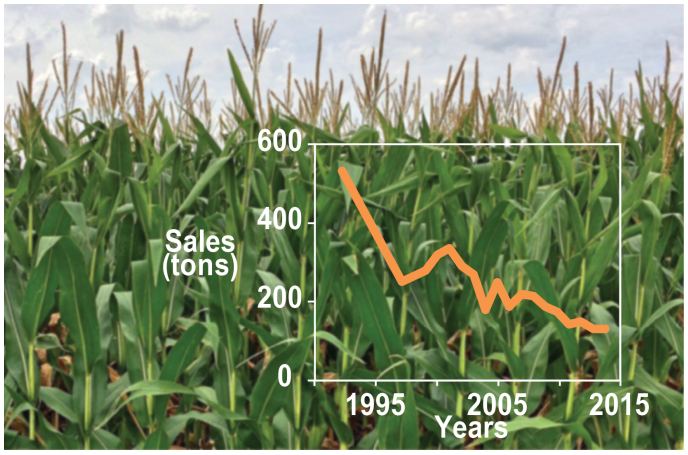

Figure 1: Atrazine sales in Québec.

Frequent and Troubling Surface Water Contamination

Atrazine is moderately soluble in water (Figure 2). It is resistant to breakdown by water (hydrolysis) and light (photolysis). Breakdown by microorganisms is relatively slow under aerobic conditions, and even slower in anaerobic conditions.[1] Because atrazine does not bind strongly to soil particles, its leaching potential is high.[1]

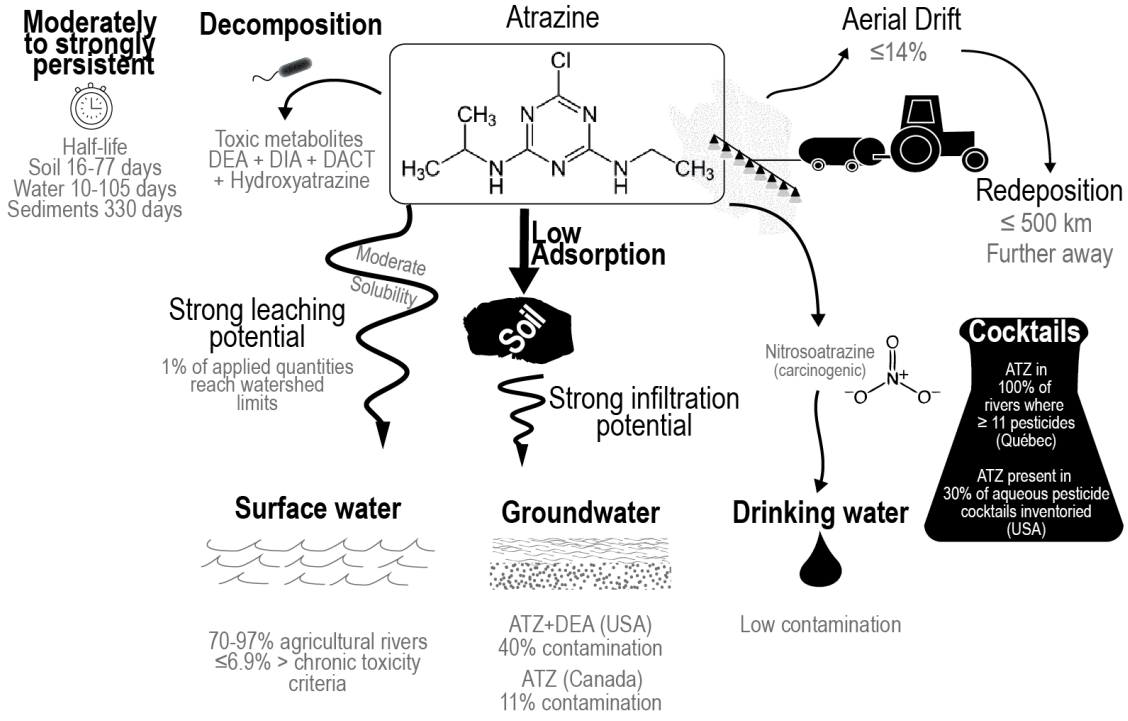

Figure 2: Atrazine movement and environmental persistence.

In Québec, median concentrations of atrazine declined from 1992 to 2004 in surface waters of agricultural watersheds where corn and soy are intensively farmed[12] possibly due to reduced use.[11] However, atrazine, or its metabolite DEA, was still detected in 97% and 70% of water samples collected between 2011 and 2014.[12] In Québec, atrazine is considered a problematic to aquatic life at concentrations as low as 1.8 micrograms/litre (µg/l).[12] Despite this, concentrations measured in 2014 were as high as 13 µg/l, and samples exceeded the criteria for the protection of aquatic life in 4.3% to 6.9% of samples, depending on the years (and by as much as 17.2% of the time for the Rivière des Hurons in 2012).[12]

Atrazine is a Common Groundwater Contaminant

At a national level, the PMRA estimates that 11% of subsurface-water samples contain as much as 2.32 µg/l of atrazine. Using hydrogeological models, it is estimated that groundwater could contain as much as 164 µg/l.[15] When Canadian and US data are considered together, it is estimated that 20% of groundwater is contaminated with atrazine with maximum concentrations as high as 18.8 µg/l.[15]

Atrazine is the most commonly detected pesticide in US ground water (±40% detection rate, including the DEA metabolite ; Figure 2).[16] Atrazine detection is expected to be geographically variable and correlated with corn production regions.[16] Indeed, detection rates in groundwater are generally lower in potato- growing regions of Québec (5% of wells, 1999-2001)[17] compared to areas such as Centre-du-Québec where corn is the dominant crop (24% of wells, 2014, 52-55 ng/l).[18]

Atrazine is an Evident Endocrine Disruptor

Regulatory agencies generally describe atrazine as moderately toxic.[1, 19-21] The governments of Québec,[22] Canada,[23] USA,[24] and Australia[19] classify atrazine as an evident endocrine disruptor, giving rise to concerns about impacts on reproduction and potential carcinogenicity (Figure 3).[19, 25] Atrazine has been implicated in reduced androgen[24, 26] (a male hormone) and increased estrogen[24, 27] (a female hormone) in a wide range of animal models (both in live vertebrates[28-31] and cultured human cell lines[31]). In animal models, atrazine appears to inhibit secretion of gonadotropin hormone, leading to early miscarriages and spontaneous abortion,[32, 33] though this mechanism has yet to be confirmed in humans.[19] Increased estrogen production has been implicated in the development of certain hormone-dependent breast cancers.[34]

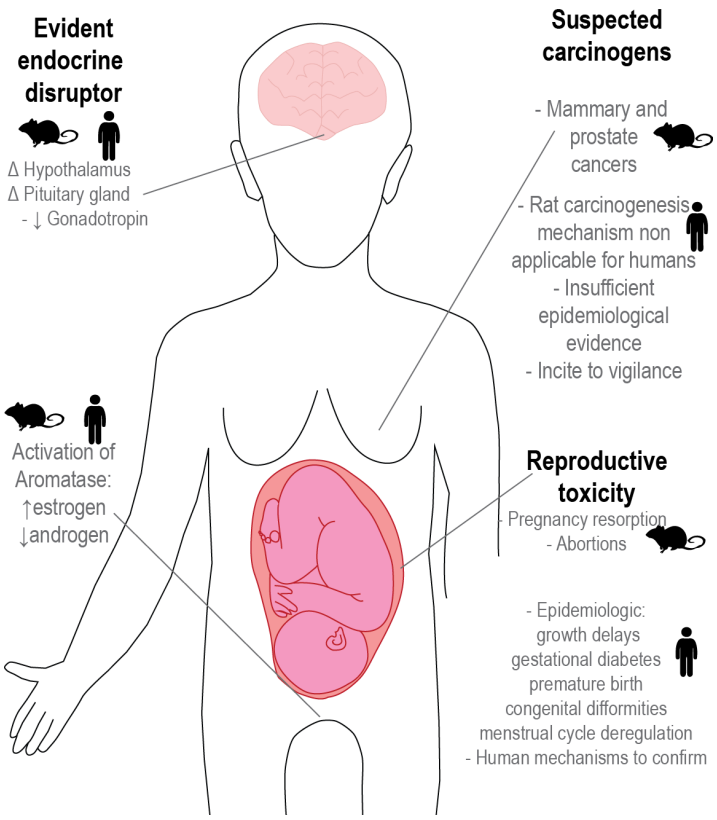

Figure 3: Toxic effects of atrazine on human and rat.

The Feminization of Frogs and Other Adverse Impacts on Animals

The role of atrazine in worldwide amphibian population declines has been evoked (Figure 4).[35] Reproductive toxicity (including hermaphrodism, demasculinization, feminization),[27, 29] was first observed in frogs, but has now been reported in other vertebrates, including fish, reptiles and mammals). *In utero* exposure may induce spontaneous abortions in rodents,[32, 33] and lead to observable toxicological symptoms in adult male[36] and female[37, 38] rats or their descendents.[37] For example, low doses could alter the development of mammary glands,[39] while high doses could lead to reduced birth weight or delays in vaginal opening.[40] Atrazine exposure in adult rats also appears to affect testes morphology.[41]

Atrazine exposure has also been linked to neuronal toxicity[42] and immuno-toxicity[5, 43] in rodents. In bees, atrazine exposure results in reduced β-carotene synthesis, a vitamin A precursor essential for growth and vision.[44] A 2015 literature review by Quebec's Ministère du Développement durable, Environnement et Lutte contre les changements climatiques (MDDELCC) summarizes a number of scientific studies indicating liver and kidney toxicity in fish, gill toxicity in bivalves, and a reduced growth rate in amphibians exposed to atrazine concentrations commonly measured in surface waters.[12]

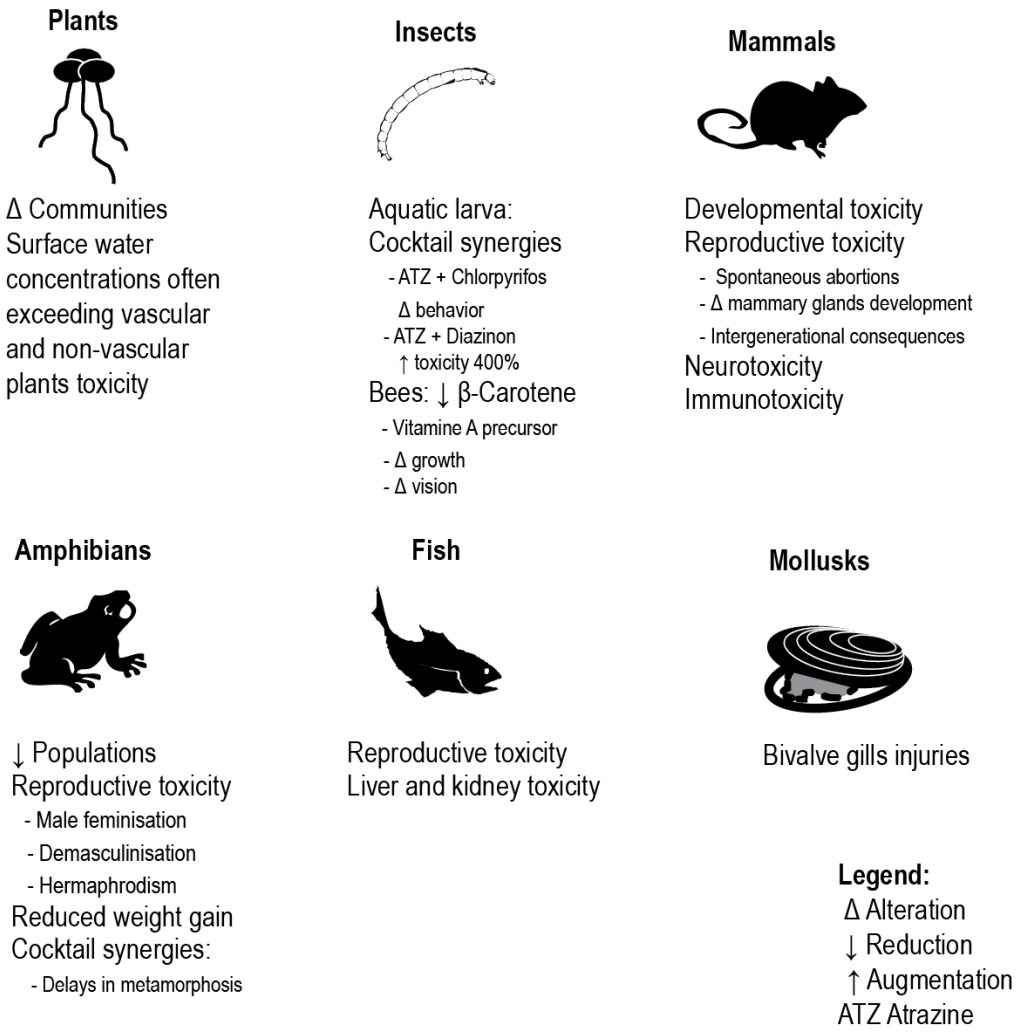

Figure 4: Atrazine ecotoxicity.

Atrazine may be Harmful to Human Reproduction

In epidemiological studies, associations between atrazine exposure and intrauterine growth retardation,[9, 45, 46] gestational diabetes,[47] premature births,[48, 49] abdominal wall defects,[50, 51] nasal cavity defects,[52] genital malformations in boys,[53] and menstrual cycle deregulation in women[54] have all been

reported (Figure 3). But a recent meta-analysis of epidemiologic studies concluded that poor data quality precludes firm conclusions on the causal relationship between atrazine exposure and reproductive problems in humans.[55]

No Consensus on Atrazine's Cancer-Causing Potential

There is no consensus on atrazine carcinogenicity.[56-58] Mammary and prostate cancers observed in rats[1, 59-61] could originate from endocrine disruption of a pathway not pertinent for humans (Figure 3).[1, 60, 61] One epidemiological study suggested possible links between atrazine and breast cancer, but this association was not found in subsequent studies.[62-64] Increasing prevalence of various cancers,[65-67] are deemed insufficient to confirm atrazine's carcinogenic potential, but suggest the need for greater monitoring and vigilance.[1]

Atrazine in drinking water

Drinking water standards for atrazine are set at 5 µg/l by Health Canada and 3.5 µg/l by the province of Québec. In Québec, between 2005 and 2009, the maximum concentration of atrazine found in tap water was 1.0 µg/l. However, 66% of upstream water treatment plants samples tested positive, with raw (input) and treated (output) waters containing up to 4.45 and 2.26 µg/l of atrazine, respectively.[68] Atrazine and metolachlor (another common corn field herbicide) are the two most frequently detected pesticides in raw and treated waters.[68] But because only municipality water systems serving more than 5000 residents have mandatory testing for atrazine and other organic chemicals, exposure from drinking water in other systems in largely unknown. Drinking water is the principal route of exposure for humans since atrazine is seldom found in food and there is little opportunity for inhalation.[69, 70]

Atrazine in Pesticides Mixtures

Atrazine is often found in combination with other chemicals. In Québec, atrazine was detected in 98% of surface water samples from corn-growing regions, often along with 20 other herbicides.[12] According to this provincial study, atrazine was present in 100% of the samples for almost half of the rivers where 11 pesticides were also present (Figure 2).[12] A study of US agricultural watersheds found that atrazine was present in 30% of pesticide mixtures, and that it often exceeded ecotoxicological standards.[16]

Mixtures containing atrazine may reduce immunity in fish and amphibians;[71] synergize behavioural changes on aquatic invertebrates when combined with the insecticide chlorpyrifos.[16] Atrazine may increase the toxicity of the insecticide diazinon to aquatic invertebrates by as much as 400%;[16] and when combined with the herbicide, S-metolachlor, retard the growth and development of frogs.[25] The presence of atrazine and nitrates in drinking water has been associated with a 2.5–fold increase in the risks of developing non-Hodgkin's lymphoma,[72] as well as delay intrauterine growth in humans.[73]

Legal action in the United States

In the United States, an action taken in 1999 by environmental, health and consumer advocacy groups to obtain enhanced protection of populations and ecosystems, concluded with an out-of-court settlement four years later.[74] In 2011, 50,000 letters and a 10,000-signature petition requesting an

immediate ban on atrazine was sent to the EPA.[75, 76] Allegations of scientific fraud, wilful blindness, and excessive lobbying were made.[8, 71, 77] In 2012, a class action by 2,000 communities in the US Corn Belt–to recover additional costs for removing atrazine from drinking water–was resolved through a $105 million settlement.[78] In 2015, a threatened prosecution by the Center for Biological Diversity was settled out of court through an agreement under which the EPA would evaluate atrazine's impact on 1,500 threatened plant and animal species in the USA before 2020.[79]

In Canada, atrazine was re-registered by the Pest Control Management Agency in 2007. In 2012, Équiterre and the David Suzuki Foundation requested a special review of the registration of some pesticides – including atrazine – on the basis of their banning by other OECD members for environmental or health concerns. After a first refusal by the PMRA, Équiterre and the David Suzuki Foundation, represented by Ecojustice, filed a lawsuit in 2013, after which PMRA committed to do these reviews. The review of atrazine was announced in 2015.[80] The scope of the special review of atrazine was restricted to earlier motives expressed by Europeans, which were the high leaching potential in runoff and groundwater. In its proposed decision, the PMRA recommended maintaining registration on the basis that atrazine does not present an unacceptable risk for human or environmental health, despite recognizing its leaching potential to groundwater.[15] In its proposed re-evaluation note, the PMRA did not conduct a complete risk evaluation, but focused solely on groundwater, even though groundwater only represents a drinking water source for a restricted subset of the Canadian population. In Québec, most municipal water systems use surface water.[68]

Viable alternatives to atrazine

Atrazine manufacturers have argued that corn farmers would lose 1.4% to 9.5% of their crop yields if atrazine were banned in the US.[81] US government estimates put the loss at 1.2%.[82] Predictions of yield reductions may not be accurate: following atrazine's elimination in Europe, corn yield actually increased.[83] Several potential replacement herbicides are registered in Canada, several of which may be more profitable to them,[84] but as is the case for all pesticides, they may pose a risk to human and environmental health. Atrazine being the registered substance with the highest environmental risk and the second with regard for the health risk, it is easy to find less toxic alternatives on SAgE Pesticides website (in French: www.sagepesticides.qc.ca). Using integrated pest management (IPM), favouring more competitive varieties of crops, cover crops, early screening, and crop rotation could decrease the use of herbicides and maintain healthy yields. Mechanical weeding and other mechanical weed control techniques are becoming increasingly effective, thanks to technological advancements such as precision cropping systems (GPS-based technologies).[85]

Conclusion

Atrazine is ubiquitous in our environment, often at concentrations exceeding the criteria for the protection of aquatic life, but fortunately within drinking water criteria. Available research strongly suggests that atrazine presents serious hazards for both humans and the environment. If atrazine's carcinogenic potential is not clearly established, its potential to disrupt the endocrine system is clear. Atrazine use is rapidly declining in Canada because several formulations are already restricted in

Western Canada, replacement products are available on the market, and it was banned in Europe without yield losses. However, it is imperative to finally ban the use of this pesticide in our country to fully protect human populations and ecosystems.

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References

1. EPA, Decision Documents for Atrazine In Office of Prevention, Pesticides and Toxic Substances. In 2006; p 323.
2. Shimabukuro, R. H.; Swanson, H. R., Atrazine metabolism, selectivity, and mode of action. *J Agr Food Chem* **1969,** *17*, (2), 199-205.
3. Solomon, K. R.; Giesy, J. P.; LaPoint, T. W.; Giddings, J. M.; Richards, R. P., Ecological risk assessment of atrazine in North American surface waters. *Env Toxicol Chem* **1996,** *32*, (1), 10-11.
4. Coursey, D. *Illinois Without Atrazine: Who Pays? Economic Implications of an Atrazine Ban in the State of Illinois*; Chicago, 2007-02-27, 2007; p 32.
5. Chen, J. Y.; Song, Y.; Zhang, L. S., Immunotoxicity of atrazine in Balb/c mice. *J Env Sc & Health, Part B* **2013,** *48*, (8), 637-645.
6. Hayes, T. B.; Collins, A.; Lee, M.; Mendoza, M.; Noriega, N.; Stuart, A. A.; Vonk, A., Hermaphroditic, demasculinized frogs after exposure to the herbicide atrazine at low ecologically relevant doses. *PNAS* **2002,** *99*, (8), 5476-5480.
7. EC (European Comission) Review report for the active substance atrazine, Health & Consumer Protection Directorate-General. http://ec.europa.eu/food/plant/protection/evaluation/existactive/list_atrazine.pdf (2014-12-30)
8. Sass, J. B.; Colangelo, A., European Union bans atrazine, while the United States negotiates continued use. *International journal of occupational and environmental health* **2006,** *12*, (3), 260-267.
9. Chevrier, C.; Limon, G.; Monfort, C.; Rouget, F.; Garlantézec, R.; Petit, C.; Durand, G.; Cordier, S., Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort. *Environmental health perspectives* **2011,** *119*, (7), 1034-41.
10. MDDELCC Bilan des ventes de pesticides au Québec 2014. http://www.mddelcc.gouv.qc.ca/pesticides/bilan/ (2016-05-18)
11. Gorse, I.; Balg, C., Bilan des ventes de pesticides au Québec pour l'année 2011 *In* Ministère du Développement durable de l'Environnement et des Parcs - Direction des politiques agricoles et des pesticides. Gouvernement du Québec. 60p.: 2014; p 60.
12. Giroux, I. Présence de pesticides dans l'eau au Québec - Portrait et tendances dans les zones de maïs et de soya 2011 à 2014. http://www.mddelcc.gouv.qc.ca/eau/flrivlac/pesticides.htm (2015-09-12)
13. Wins-Purdy, A. *2010 Pesticide Sales in British Columbia*; Victoria, BC, 2013; p 40.
14. Health Canada Pesticides & Pest Management - Search product label. http://pr-rp.hc-sc.gc.ca/ls-re/index-eng.php (2016-01-29),
15. Health Canada. *Examen spécial de l'atrazine: projet de décision aux fins de consultation. REV2015-11. Agence de règlementation de la lutte antiparasitaire.*; Ottawa, Ontario, 2015; p 19.
16. Gilliom, R. J.; Barbash, J. E.; Crawford, C. G.; Hamilton, P. A.; Martin, J. D.; Nakagaki, N.; Nowell, L. H.; Scott, J. C.; Stackelberg, P. E.; Thelin, G. P.; Wolock, D. M. *The Quality of Our Nation's Waters - Pesticides in the Nation's Streams and Ground Water*; 2006; p 172.
17. Giroux, I., Contamination de l'eau souterraine par les pesticides et les nitrates dans les régions en culture de pommes de terre. Campagne d'échantilonnage de 1999-2000-

2001. Ministère de l'environnement. Gouvernement du Québec. 2003; p 34.
18. Larocque, M.; Gagné, S.; Barnetche, D.; Meyzonnat, G.; Graveline, M.-H.; Ouellet, M.-A. *Projet de connaissance des eaux souterraines de la zone Nicolet et de la partie basse de la zone Saint-François RAPPORT FINAL. Rapport déposé au Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques*; Université du Québec à Montréal. Département des sciences de la Terre et de l'atmosphère: Montréal, Canada, 2015; p 258 p.
19. Government of Australia *Atrazine toxicity: Analysis of potential modes of action*; Canberra, 2010-01, 2010; p 49.
20. WHO (World Health Organisation), Guidelines for Drinking-water Quality. In 4rd ed.; GEMS/Food Codex Committee on Pesticide Residues. Programme on Food Safety and Food Aid: 2011; Vol. Chapter 8 - Chemical aspects, p 541.
21. WHO (World Health Organisation) and FAO (Food and Agriculture Organization) *Pesticide residues in food - 2007 - Evaluations - Part II - Toxicological*; Geneva, 2007; p 544.
22. Québec, SAgE pesticides Fiche Toxicologie de la matière active: atrazine. In Ministère de l'Agriculture, des Pêcheries et de l'Alimentation, Ministère du Développement Durable, de l'Environnement et des Parcs, Institut national de santé publique: 2016.
23. Health Canada, Re-evaluation decision: Atrazine. Pest Management Regulatory Agency.(RRD2004-12). **2004**.
24. EPA *EDSP: Weight of evidence analysis of potential interaction with the estrogen, androgen or thyroid pathways chemical: Atrazine. - Office of pesticide programs, Office of science coordination and policy*; USA, 2015; p 167.
25. Hayes, T. B.; Case, P.; Chui, S.; Chung, D.; Haeffele, C.; Haston, K.; Lee, M.; Mai, V. P.; Marjuoa, Y.; Parker, J.; Tsui, M., Pesticide Mixtures, Endocrine Disruption, and Amphibian Declines: Are We Underestimating the Impact? *Env Health Persp* **2006,** *114*, (S-1).
26. Tavera-Mendoza, L.; Ruby, S.; Brousseau, P.; Fournier, M.; Cyr, D.; Marcogliese, D., Response of the amphibian tadpole (Xenopus laevis) to atrazine during sexual differentiation of the testis. *Env Toxicol & Chem* **2002,** *21*, (3), 527-531.
27. Hayes, T. B.; Anderson, L. L.; Beasley, V. R.; de Solla, S. R.; Iguchi, T.; Ingraham, H.; Kestemont, P.; Kniewald, J.; Kniewald, Z.; Langlois, V. S., Demasculinization and feminization of male gonads by atrazine: consistent effects across vertebrate classes. *J Steroid Biochem & Mol Biol* **2011,** *127*, (1), 64-73.
28. Crain, D. A.; Guillette, L. J., Reptiles as models of contaminant-induced endocrine disruption. *Animal Reprod Sc* **1997,** *53*, (1), 77-86.
29. Hayes, T.; Haston, K.; Tsui, M.; Hoang, A.; Haeffele, C.; Vonk, A., Atrazine-induced hermaphroditism at 0.1 ppb in American leopard frogs (*Rana pipiens*): laboratory and field evidence. *Env Health Persp* **2003,** *111*, (4), 568.
30. Sanderson, J. T.; Letcher, R. J.; Heneweer, M.; Giesy, J. P.; van den Berg, M., Effects of chloro-s-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. *Environ Health Perspect* **2001,** *109*, (10), 1027-31.
31. Sanderson, J. T.; Seinen, W.; Giesy, J. P.; van den Berg, M., 2-Chloro-s-triazine herbicides induce aromatase (CYP19) activity in H295R human adrenocortical carcinoma cells: a novel mechanism for estrogenicity? *Toxicol Sci* **2000,** *54*, (1), 121-7.
32. Narotsky, M. G.; Best, D. S.; Guidici, D. L.; Cooper, R. L., Strain comparisons of atrazine-induced pregnancy loss in the rat. *Reprod Toxicol* **2000,** *15*, (1), 61-69.
33. Cummings, A. M.; Rhodes, B. E.; Cooper, R. L., Effect of Atrazine on Implantation and Early Pregnancy in 4 Strains of Rats. *Toxicological Sciences* **2000,** *58*, (1), 135-143.
34. Fan, W.; Yanase, T.; Morinaga, H.; Gondo, S.; Okabe, T.; Nomura, M.; Komatsu, T.; Morohashi, K.-I.; Hayes, T. B.; Takayanagi, R., Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine

disruption in wildlife and reproductive cancers in humans. *Env Health Persp* **2007,** *115*, (5), 720.
35. Renner, R., Conflict brewing over herbicide's link to frog deformities. *Science* **2002,** *298*, (5595), 938-939.
36. Rayner, J. L.; Enoch, R. R.; Wolf, D. C.; Fenton, S. E., Atrazine-induced reproductive tract alterations after transplacental and/or lactational exposure in male Long-Evans rats. *Toxicol & Appl Pharmacol* **2007,** *218*, (3), 238-248.
37. Rayner, J. L.; Wood, C.; Fenton, S. E., Exposure parameters necessary for delayed puberty and mammary gland development in Long-Evans rats exposed in utero to atrazine. *Toxicol & Appl Pharmacol* **2004,** *195*, (1), 23-34.
38. Rayner, J. L.; Enoch, R. R.; Fenton, S. E., Adverse Effects of Prenatal Exposure to Atrazine During a Critical Period of Mammary Gland Growth. *Toxicological Sciences* **2005,** *87*, (1), 255-266.
39. Enoch, R. R.; Stanko, J. P.; Greiner, S. N.; Youngblood, G. L.; Rayner, J. L.; Fenton, S. E., Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. *Environmental health perspectives* **2007**, 541-547.
40. Davis, L. K.; Murr, A. S.; Best, D. S.; Fraites, M. J.; Zorrilla, L. M.; Narotsky, M. G.; Stoker, T. E.; Goldman, J. M.; Cooper, R. L., The effects of prenatal exposure to atrazine on pubertal and postnatal reproductive indices in the female rat. *Reproductive Toxicology* **2011,** *32*, (1), 43-51.
41. Victor-Costa, A. B.; Bandeira, S. M. C.; Oliveira, A. G.; Mahecha, G. A. B.; Oliveira, C. A., Changes in testicular morphology and steroidogenesis in adult rats exposed to Atrazine. *Reproductive Toxicology* **2010,** *29*, (3), 323-331.
42. Coban, A.; Filipov, N. M., Dopaminergic toxicity associated with oral exposure to the herbicide atrazine in juvenile male C57BL/6 mice. *J Neurochem* **2007,** *100*, (5), 1177-1187.
43. Rowe, A. M.; Brundage, K. M.; Barnett, J. B., Developmental immunotoxicity of atrazine in rodents. *Basic & clinical pharmacology & toxicology* **2008,** *102*, (2), 139-145.
44. Helmer, S. H.; Kerbaol, A.; Aras, P.; Jumarie, C.; Boily, M., Effects of realistic doses of atrazine, metolachlor, and glyphosate on lipid peroxidation and diet-derived antioxidants in caged honey bees (Apis mellifera). *Environmental Science and Pollution Research* **2015,** *22*, (11), 8010-8021.
45. Munger, R.; Isacson, P.; Hu, S.; Burns, T.; Hanson, J.; Lynch, C. F.; Cherryholmes, K.; Van Dorpe, P.; Hausler Jr, W. J., Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. *Environmental Health Perspectives* **1997,** *105*, (3), 308.
46. Ochoa-Acuña, H.; Frankenberger, J.; Hahn, L.; Carbajo, C., Drinking-water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery. *Environmental Health Perspectives* **2009,** *117*, (10), 1619.
47. Saldana, T. M.; Basso, O.; Hoppin, J. A.; Baird, D. D.; Knott, C.; Blair, A.; Alavanja, M. C.; Sandler, D. P., Pesticide exposure and self-reported gestational diabetes mellitus in the Agricultural Health Study. *Diabetes Care* **2007,** *30*, (3), 529-534.
48. Savitz, D. A.; Arbuckle, T.; Kaczor, D.; Curtis, K. M., Male pesticide exposure and pregnancy outcome. *American Journal of Epidemiology* **1997,** *146*, (12), 1025-1036.
49. Rinsky, J. L.; Hopenhayn, C.; Golla, V.; Browning, S.; Bush, H. M., Atrazine exposure in public drinking water and preterm birth. *Public health reports* **2012**, 72-80.
50. Mattix, K. D.; Winchester, P. D., Incidence of abdominal wall defects is related to surface water atrazine and nitrate levels. *Journal of pediatric surgery* **2007,** *42*, (6), 947-949.
51. Agopian, A.; Langlois, P. H.; Cai, Y.; Canfield, M. A.; Lupo, P. J., Maternal residential atrazine exposure and gastroschisis by maternal age. *Maternal and child health journal* **2013,** *17*, (10), 1768-1775.
52. Agopian, A. J.; Cai, Y.; Langlois, P. H.; Canfield, M. A.; Lupo, P. J., Maternal residential atrazine exposure and risk for choanal atresia and

stenosis in offspring. *The Journal of pediatrics* **2013,** *162*, (3), 581-586.
53. Agopian, A.; Lupo, P. J.; Canfield, M. A.; Langlois, P. H., Case–control study of maternal residential atrazine exposure and male genital malformations. *American journal of medical genetics Part A* **2013,** *161*, (5), 977-982.
54. Cragin, L. A.; Kesner, J. S.; Bachand, A. M.; Barr, D. B.; Meadows, J. W.; Krieg, E. F.; Reif, J. S., Menstrual cycle characteristics and reproductive hormone levels in women exposed to atrazine in drinking water. *Environmental research* **2011,** *111*, (8), 1293-1301.
55. Goodman, M.; Mandel, J. S.; DeSesso, J. M.; Scialli, A. R., Atrazine and pregnancy outcomes: a systematic review of epidemiologic evidence. *Birth Defects Research Part B: Developmental and Reproductive Toxicology* **2014,** *101*, (3), 215-236.
56. Jowa, L.; Howd, R., Should Atrazine and Related Chlorotriazines Be Considered Carcinogenic for Human Health Risk Assessment? *J Env Sc & Health, Part C* **2011,** *29*, (2), 91-144.
57. Boffetta, P.; Adami, H. O.; Berry, S. C.; Mandel, J. S., Atrazine and cancer: a review of the epidemiologic evidence. *Eur J Cancer Prev* **2013,** *22*, (2), 169-80.
58. Sathiakumar, N.; Delzell, E., A review of epidemiologic studies of triazine herbicides and cancer. *Critical Reviews in Toxicology* **1997,** *27*, (6), 599-612.
59. Wetzel, L. T.; Luempert, L. G.; Breckenridge, C. B.; Tisdel, M. O.; Stevens, J. T.; Thakur, A. K.; Extrom, P. J.; Eldridge, J. C., Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fischer 344 rats. *J Toxicol & Env Health* **1994,** *43*, (2), 169-182.
60. Stevens, J. T., A Risk Characterization for Atrazine: Oncogenicity Profile. *Journal of Toxicology and Environmental Health, Part A* **1999,** *56*, (2), 69-109.
61. IARC (International Agency for Research on Cancer), Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances - Atrazine. *IARC Monogr Eval Carcinogen Risk Hum* **1999,** *73*, 59-113.
62. Hopenhayn-Rich, C.; Stump, M.; Browning, S. R., Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Archives of Environmental Contamination and Toxicology* **2002,** *42*, (1), 127-136.
63. Kettles, M. K.; Browning, S. R.; Prince, T. S.; Horstman, S. W., Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. *Env Health Persp* **1997,** *105*, (11), 1222.
64. Mcelroy, J. A.; Gangnon, R. E.; Newcomb, P. A.; Kanarek, M. S.; Anderson, H. A.; Brook, J. V.; Trentham-Dietz, A.; Remington, P. L., Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. *Journal of Exposure Science and Environmental Epidemiology* **2007,** *17*, (2), 207-214.
65. Rusiecki, J. A.; Roos, A. D.; Lee, W. J.; Dosemeci, M.; Lubin, J. H.; Hoppin, J. A.; Blair, A.; Alavanja, M. C. R., Cancer Incidence Among Pesticide Applicators Exposed to Atrazine in the Agricultural Health Study. *J Nat Cancer Inst* **2004,** *96*, (18), 1375-1382.
66. Beane Freeman, L. E.; Rusiecki, J. A.; Hoppin, J. A.; Lubin, J. H.; Koutros, S.; Andreotti, G.; Zahm, S. H.; Hines, C. J.; Coble, J. B.; Barone-Adesi, F.; Sloan, J.; Sandler, D. P.; Blair, A.; Alavanja, M. C. R., Atrazine and Cancer Incidence Among Pesticide Applicators in the Agricultural Health Study (1994–2007). *Env Health Persp* **2011,** *119*, (9), 1253-1259.
67. Mills, P. K., Correlation analysis of pesticide use data and cancer incidence rates in California counties. *Archives of Environmental Health: An International Journal* **1998,** *53*, (6), 410-413.
68. Robert, C.; Bolduc, A., Bilan de la qualité de l'eau potable au Québec 2005-2009. Direction des politiques de l'eau. Ministère du Développement durable, de l'Environnement et des Parcs. *In* Gouvernement du Québec.: 2012; p 71.
69. INSPQ, Fiche Atrazine - Atrazine et ses métabolites. *In* Institut national de santé publique du Québec, Ed. 2003; p 10.

70. Gammon, D. W.; Aldous, C. N.; Carr, W. C.; Sanborn, J. R.; Pfeifer, K. F., A risk assessment of atrazine use in California: human health and ecological aspects. *Pest management science* **2005,** *61*, (4), 331-355.
71. Rohr, J. R.; McCoy, K. A., A qualitative meta-analysis reveals consistent effects of atrazine on freshwater fish and amphibians. *Env Health Persp* **2010,** *118*, (1), 20.
72. Rhoades, M. G.; Meza, J. L.; Beseler, C. L.; Shea, P. J.; Kahle, A.; Vose, J. M.; Eskridge, K. M.; Spalding, R. F., Atrazine and nitrate in public Drinking Water supplies and non-Hodgkin Lymphoma in nebraska, USA. *Env Health Insights* **2013,** *7*, 15.
73. Migeot, V.; Albouy-Llaty, M.; Carles, C.; Limousi, F.; Strezlec, S.; Dupuis, A.; Rabouan, S., Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: a historic cohort study. *Environmental research* **2013,** *122*, 58-64.
74. Natural Resources Defense Council *v.* Whitman, Case Number C -99-3701 CAL. *In* N.D. California: 2002.
75. SAVE THE FROGS!, Submission to the US Environmental Protection Agency. In *Petition to Ban Atrazine, Supportng & Related Material document issued by the Environmental Protection Agency (EPA)*, Kriger, K., Ed. EPA on Regulations.gov: 2011; p 413.
76. EPA, Response to Save the Frogs May 6, 20 I I Petition Requesting a Federal Ban on the Use and Production of Atrazine. In Office of Chemical Safety and Pollution Prevention. In regulations.gov: 2011; p 3.
77. Hayes, T., Chapter 10 - Atrazine Has Been Used Safely for 50 Years? In *Wildlife Ecotoxicology - Forensic Approaches*, Elliot, J. E.; Bishop, C. A.; Morrissey, C. A., Eds. Springer: Oak Ridge, TN, USA, 2011; p 476.
78. City of Greenville *vs* Syngenta Crop Protection Inc. Settlement Agreement Case No.: 3:10-cv-00188-JPG-PMF. In US District Court for the Southern District of Illinois: 2012; p 107.
79. EPA San Francisco Bay Area Endangered Species Litigation - Center for Biological Diversity *v.* EPA. http://www.epa.gov/endangered-species/san-francisco-bay-area-endangered-species-litigation-center-biological-diversity (2016-02-05)
80. Ecojustice Environmental groups force Ottawa to review approval of hundreds of pesticide products http://www.ecojustice.ca/media-centre/press-releases/environmental-groups-force-ottawa-to-review-approval-of-hundreds-of-pesticide-products (Accessed on: 2014-04-06)
81. Mitchell, P. D., Market-Level Assessment of the Economic Benefits of Atrazine in the United States. *Pest Man Sc* **2013**, DOI: 10.1002/ps.3703.
82. Ribaudo, M. O.; Bouzaher, A. *Atrazine: Environmental Characteristics and Economics of Management, Report number 699*; Washington, DC, 1994; p 22.
83. Ackerman, F., The economics of atrazine. *International Journal of Occupational and Environmental Health* **2007,** *13*, (4), 437-445.
84. Ackerman, F.; Whited, M.; Knight, P. *Atrazine: Consider the Alternatives*; 2013.
85. Vincent, C.; Panneton, B.; Fleurat-Lessard, F., *Physical control methods in plant protection*. Springer Science & Business Media: 2013.