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CAPERN – 012M  
C.G. – Examiner les  
impacts des pesticides  
sur la santé publique  
et l'environnement  
VERSION RÉVISÉE

**OBJET : Mémoire portant sur l'impact des pesticides sur la santé publique et l'environnement rédigé pour la Commission publique de l'Assemblée Nationale**

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Monsieur Garant,

Je vous écris cette lettre au nom d'Autisme Montréal, afin de vous soumettre un mémoire pour la Commission de l'agriculture, des pêcheries, de l'énergie et des ressources naturelles (CAPERN) examinant l'impact des pesticides sur la santé publique et l'environnement qui aura lieu en septembre 2019.

Cet enjeu est une préoccupation importante pour Autisme Montréal, étant donné la multitude d'études qui ont été, et continuent d'être publiées portant sur le lien entre l'exposition aux pesticides et le risque accru pour un fœtus/enfant de développer l'autisme. L'augmentation flagrante et continue de la prévalence de l'autisme nous oblige à regarder de plus près ce lien. Actuellement, la prévalence au Québec se situe à 1 enfant sur 64. À titre d'information, le *Centers for Disease Control* (CDC) affirme que l'autisme est devenu «un problème urgent de santé publique». Le gouvernement se doit de tenir compte de toutes les variables pouvant compromettre la santé prénatale et le développement neurologique d'un fœtus/enfant. Les risques générés par les pesticides ne peuvent être ignorés.

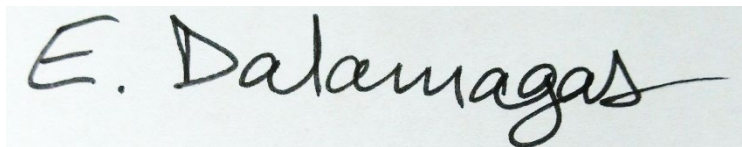
Je tiens à mentionner que le but derrière ce mémoire était de souligner l'impact des pesticides sur la santé et le neurodéveloppement d'un fœtus/enfant avant, durant et après la grossesse. Ce rapport n'est en aucun cas censé banaliser, dénigrer ou manquer de respect envers les personnes autistes, qui sont des citoyens à part entière et méritent que leur inclusion sociale soit promue et soutenue.

Le mémoire qu'Autisme Montréal soumet aujourd'hui pour la Commission publique a été rédigé en collaboration avec la *Fondation David Suzuki*, *l'Alliance contre les pesticides systémiques*, Dre Isabelle Pitrou, MD, épidémiologiste et d'autres professionnels partageant cette même préoccupation.

Le mémoire est composé de 2 documents : 1) un sommaire exécutif résumant les conclusions d'une revue de littérature et 2) une revue de la littérature scientifique présentant le lien entre les pesticides et le risque de développer l'autisme. Le sommaire exécutif a été traduit en français. Pour la revue de littérature, le travail de traduction est en cours. Nous vous la soumettrons durant le mois d'août. Conséquemment, nous vous demandons de ne pas rendre publique ce mémoire tant que la traduction et la mise en page ne seront pas finalisées.

De plus, je souhaite également réitérer mon souhait d'être entendu en audition publique lors de la Commission. Afin de mieux guider les députés dans leurs travaux, je crois qu'il serait nécessaire de pouvoir exposer les préoccupations issues de ce mémoire décrivant l'impact des pesticides sur la santé prénatale et le développement neurologique.

Veuillez agréer, Monsieur Garant, mes sentiments distingués.

A handwritten signature in black ink on a light grey background. The signature reads "E. Dalamagas" in a cursive, flowing script.

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## Auteurs du mémoire



Établie en 1990, la Fondation David Suzuki a pour mission de protéger l'environnement et notre qualité de vie, maintenant et pour l'avenir. À travers la science, la sensibilisation et l'engagement du public, et des partenariats avec les entreprises, les gouvernements et les acteurs de la société civile, la Fondation œuvre à définir et à déployer des solutions permettant de vivre en équilibre avec la nature. La Fondation compte sur l'appui de 300 000 sympathisants à travers le Canada, dont près de 100 000 au Québec.

**Louise Hénault-Ethier** est chef des projets scientifiques pour la Fondation David Suzuki à Montréal. Ses recherches touchent la protection des milieux naturels, les pesticides, le recyclage, la gestion des matières organiques et les technologies inspirées des insectes et des plantes. Elle siège au Comité de suivi et au comité conseil sur les justifications agronomiques et les prescriptions de pesticides mis sur pied par le gouvernement québécois en 2018.

Sa thèse de doctorat, achevée en 2016, porte sur l'efficacité des bandes riveraines végétalisées à limiter le ruissellement de la pollution diffuse de source agricole, incluant les fertilisants et les herbicides à base de glyphosate. Son examen doctoral portait sur les controverses entourant l'évaluation de la toxicité et l'homologation des pesticides.

Elle a fait plusieurs revues de littérature sur divers ingrédients actifs pesticides, notamment une sur les pyréthrinoïdes pour le compte d'Équiterre en 2016. Louise a aussi rédigé de nombreux mémoires à l'attention du gouvernement fédéral et provincial concernant l'homologation et l'encadrement de divers ingrédients actifs, notamment les néonicotinoïdes, ainsi que pour la refonte du Règlement sur les permis et les certificats pour la vente et l'utilisation des pesticides et du Code de gestion des pesticides. Elle a aussi contribué à plusieurs ouvrages vulgarisés concernant les risques liés à l'utilisation des pesticides, dont une série pour l'Association canadienne des médecins pour l'environnement. Elle est un membre cofondateur du Collectif de recherche écosanté sur les pesticides, les politiques publiques et les alternatives (CREPPA).

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**Dre Isabelle Pitrou, MD** est médecin de santé publique et épidémiologiste. Depuis l'obtention de son doctorat en 2012 à l'Université Paris Descartes, Isabelle Pitrou a exercé comme épidémiologiste dans plusieurs structures (fondations de recherche et universités) à Paris, FR et à Londres, GB. Elle occupe aujourd'hui le poste de professionnelle de recherche à l'Université de Sherbrooke. Sa mission principale est de conduire des travaux de recherche sur la santé mentale des personnes âgées dans la communauté. Isabelle Pitrou a également un intérêt fort pour l'écologie et les enjeux environnementaux actuels.

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**L'Alliance pour l'interdiction des pesticides systémiques (AIPS)** est un regroupement de citoyens et d'organismes constitué en décembre 2014 autour des objectifs suivants:

- Le bannissement des pesticides systémiques et particulièrement les néonicotinoïdes
- La promotion d'un système agricole biologique et durable
- La sensibilisation des citoyen-ne-s, des élu-e-s et professionnel-le-s du milieu agricole du Québec aux dangers des pesticides systémiques pour la biodiversité et la santé humaine.

**Pascal Priori** est diplômé en sciences politiques de l'Institut d'Étude Politiques d'Aix-en-Provence et détenteur d'une maîtrise en science en Environnement et développement durable à l'Université de Montréal. Pascal Priori est aujourd'hui chercheur indépendant et consultant spécialisé sur les enjeux environnementaux, dont les pesticides et les politiques publiques. Depuis 2014, il est porte-parole de l'Alliance pour l'interdiction des pesticides systémiques et occupe le poste de vice-président du conseil d'administration de Vigilance OGM.



**Autisme Montréal** est un organisme à but non lucratif qui cherche à améliorer les conditions de vie des personnes présentant un trouble du spectre de l'autisme (TSA) ainsi que celles de tous les membres de leur famille. Œuvrant à Montréal depuis 1981, Autisme Montréal tâche, notamment, de sensibiliser l'ensemble de la population aux différents enjeux reliés au TSA et à la diversité de ces individus, de contribuer à la recherche et au développement des compétences dans ce domaine, ainsi que de soutenir les actions entreprises pour assurer la défense des droits individuels et collectifs. L'organisme offre également une large gamme de services et d'activités.

**Electra Dalamagas** a obtenu une maîtrise en service social de l'Université McGill en 2002. Elle travaille dans le milieu de l'autisme depuis plus de 20 ans et à Autisme Montréal depuis 2004. Elle s'est spécialisée en défense de droit des personnes autistes et leurs familles, et demeure à l'affut des plus récentes recherches sur la santé liées à l'autisme. Ayant un intérêt particulier pour la santé prénatale, Madame Dalamagas a lu durant les dernières deux années toutes les études scientifiques portant sur le lien entre les pesticides et les troubles neurodéveloppementaux. Madame Dalamagas occupe le poste de Responsable de l'intervention familiale et la majorité de son travail est axé sur les situations psychosociales complexes ou de crise.

# ALARMING INCREASE IN AUTISM: SHOULD WE WORRY ABOUT PESTICIDES?

Literature review



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# Disclaimer

The following report is not intended to trivialize, denigrate or disrespect people with autism, who have equal merit as citizens in society, and whose social inclusion must be promoted and supported. This report's objective is to bring to light the impact that pesticide use can have on health and neurodevelopment prior to conception, *in utero* and during early childhood.

## List of acronyms

**ADHD** Attention deficit hyperactivity disorder  
**ASD** Autism spectrum disorders  
**CDC** Center for disease control and prevention  
**DDE** Dichlorodiphenyldichloroethylene  
**DDT** Dichlorodiphenyltrichloroethane  
**DNA** Deoxyribonucleic acid  
**EDC** Endocrine disrupting chemical  
**EPA** Environmental Protection Agency  
**GABA** Gamma aminobutyric acid  
**GSH** Gluthathione  
**IRPeQ** : Pesticide environmental risk Indicator for Québec  
**PGE2** Prostaglandin E<sub>2</sub>  
**ROS** Reactive oxygen species

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# 1.A worrying increase in cases of autism

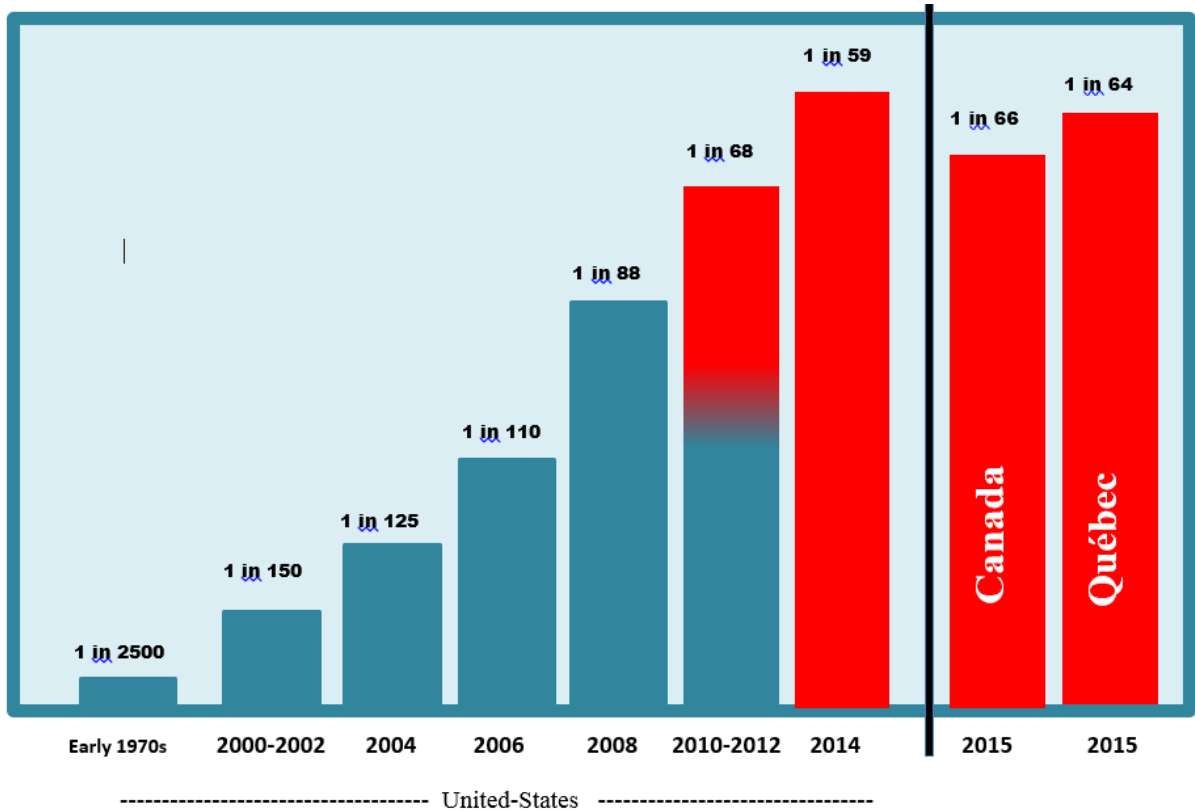
Autism<sup>1</sup> is a complex neurodevelopmental disorder affecting 1 in 66 children in Canada and 1 in 64 children in the province of Quebec [1] (Figure 1). Between 2001 and 2017, the number of students with autism enrolled in public schools of Quebec increased by 808% {Ministère de l'Éducation et de l'Enseignement supérieur, 2001-2002 to 2017-2018 #499} (Figure 2). Autism is equally increasing at an alarming rate worldwide [2]. According to the Center for Disease Control (CDC), autism has become '*an urgent public health concern*' [3] due to its rapidly increasing prevalence, which stands at 1 in 59 children in the United-States.

Leading scientific researchers, medical experts, epidemiologists, child developmentalists, and children's health advocates have raised the alarm that we are witnessing a '**pandemic of neurodevelopmental toxicity**' worldwide [4, 5]. Besides autism, developmental neurotoxicity may also be associated with Attention deficit hyperactivity disorder (ADHD) as well as other more subtle and insidious cognitive deficits affecting a larger number of undiagnosed children, a worrying effect sometimes referred to as a "chemical brain drain" [4].

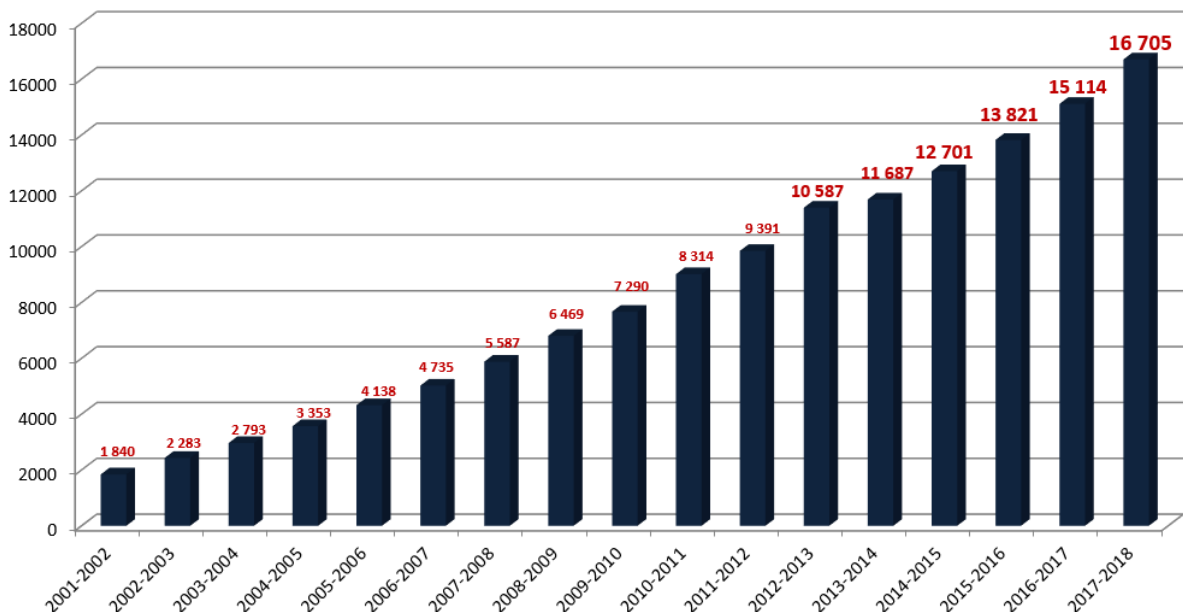
Autism impacts many areas of development of a child including communication, behaviour, social interaction, as well as sensory, motor and cognitive function. While each individual is unique and will have different needs, abilities and levels of intellectual functioning, many will however require significant support throughout their lives. Although persistent deficits in social communication and interaction; disrupted reciprocal social interactions; restricted and repetitive patterns of behaviour, interests or activities; inflexible adherence to routines; as well as hyper- or hypo-reactivity to sensory input; are the benchmarks of the disorder [6], many other variables commonly accompany the diagnosis and add to the complexity of the disorder. These include, but are not limited to, the presence of associated intellectual disability, being non-verbal, lacking awareness of physical or social danger, wandering behaviours, hyperactivity, self-injurious behaviours such as head-banging, hand biting or scratching, as well as aggressive behaviours. A number of health problems are equally known to be associated to autism such as gastrointestinal problems (i.e. constipation, digestive problems, reflux, restrictive eating), sleep disorders, epilepsy and allergies, but mental health conditions such as anxiety, depression, ADHD, and obsessive compulsive disorder can also be present [7].

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<sup>1</sup> For the purpose of making the following document easier to read, the word autism will be used to refer to all autism spectrum disorders (ASD) as well as to the previous terminology of "pervasive developmental disorder" [2] and Asperger's syndrome [8].



**Figure 1: Increase in the prevalence of autism over time in the United States and latest statistics for Canada and the province of Quebec.** Graphic compiled by authors based on statistics from CDC [9-11] and the Public Health Agency of Canada [12]. Statistics for Quebec and Canada are not available prior to 2015.



**Figure 2 : Increase in the number of students with autism diagnosis from 2001 to 2017 in Quebec.** Graphic compiled by authors based on statistics from the Ministry of Education of Quebec {Ministère de l'Éducation et de l'Enseignement supérieur, 2001-2002 to 2017-2018 #499}.

## 2. Genetic, environment and diagnosis contributions to the elevated prevalence rate of autism

While autism is characterized by large phenotypic heterogeneity, it is likely that a myriad of biochemical pathways and processes culminate in an autism diagnosis [2]. It is generally agreed that the etiology stems from a complex interaction between genetic predisposition and environmental factors. Research indicates that **environmental factors play a much more important role than initially suspected** and that genetic vulnerability alone cannot account for the current increase being observed worldwide [4, 5, 13-20].

- Because genes evolve slowly, genetic factors alone could not explain the rapid increase in cases of autism [17].
- While genetic vulnerabilities in autism do exist, there is no single unique gene involved in autism [13, 14].
- Only around 10% autism cases are related to other genetically based neurodevelopmental disorders [9, 14].
- Changes to diagnostic criteria or better awareness of autism can play a role, but neither can account for the current rapid growth being witnessed worldwide [17, 19]. These factors could only partly account for 20% [21] to 33% [19] of the increase in autism prevalence.

There is therefore a critical need to better understand the contribution of environmental factors.

## 3. Impact of environmental toxicants on neurodevelopment

**While there are many environmental factors that contribute to developing autism, no single environmental factor can independently fully explain the current autism epidemic** (see Annex 1). **However environmental toxicants are of particular concern** [2]. The association between exposure to environmental toxicants and autism is not new in research and it has been identified numerous times [2, 4, 5, 15-20, 22, 23]. The development of the central nervous system and the human brain is extraordinarily complex, and involves numerous time-sensitive events during gestation that are impacted by ongoing interactions between genetic and environmental factors [4, 17, 20]. There is a substantial body of research that indicates there are «complex interactions between genetic factors and certain environmental toxicants that act synergistically during critical periods of neurodevelopment in a manner that increases the likelihood of developing autism» [15, 24].

### 3.1 Developmental vulnerability during gestation

The developing human brain is uniquely vulnerable to toxic chemical exposures, and major **windows of developmental vulnerability** occur particularly *in utero* but also during infancy and childhood as well [4] (Figure 3). For instance, the blood-brain barrier and the placental barrier are not 100% effective at protecting the foetus against environmental toxicant exposure throughout pregnancy [17]. In addition, embryos, foetuses, newborns and children do not possess perfectly developed detoxification capacities, making them much more vulnerable to chemicals present in their environment [25, 26].

Trimester	First									Second			Third	
Gestational Weeks	1	2	3	4	5	6	7	8	9	16	20	22	28	38
<b>Brain Pathology</b>														
Neurogenesis <sup>1,3</sup>	Weeks 1-20													
Neuronal Migration <sup>1,4</sup>	Weeks 1-16													
Neuronal Maturation <sup>1,5</sup>	Weeks 1-24													
Cortical Layer Formation, Organization, and Neuronal Differentiation <sup>5</sup>	Weeks 1-30													
<b>Exposure</b>														
Freeway Proximity <sup>7</sup>	3 <sup>rd</sup> Trimester													
Traffic-related Air Pollution <sup>8</sup>	1 <sup>st</sup> , 2 <sup>nd</sup> , and 3 <sup>rd</sup> Trimester													
Pesticides <sup>9-11</sup>	Days 26-81													
Prenatal Vitamins <sup>12</sup>	1 <sup>st</sup> Month and 3 Months Before													
Folic Acid <sup>13,14</sup>	1 <sup>st</sup> Month <sup>a</sup>													
Rubella Infection <sup>15,16</sup>	Weeks 1-8													
Fever <sup>17,18</sup>	1 <sup>st</sup> and 2 <sup>nd</sup> Trimester													
Thalidomide <sup>19</sup>	Days 20-24													
Valproic Acid <sup>20,21</sup>	Days 22-28													
SSRI <sup>22, 23</sup>	1 <sup>st</sup> Trimester <sup>b</sup>													
Prenatal Stressors <sup>24</sup>	Weeks 25-28													

Figure 3: Critical periods of brain development and susceptibility to pesticides from Studies of Autism Spectrum Disorder [13]

Furthermore, the **human brain does not only develop** in the womb, but pursues its development into childhood, adolescence [27] and, some would argue even into adulthood [28]. Research has shown that the developing human brain, is extremely vulnerable to toxic chemical exposures, which can cause permanent brain damage at low levels of exposure that would have little or no adverse effect in an adult [4]. Consequently, children are at a high risk of developing neurodevelopmental disorders that affect the brain and the nervous system [5] as the developing brain is extremely vulnerable to environmental toxicants [18].

### 3.2 Biochemical pathways affected by toxicants

There is a growing consensus that autism has a clear biological basis and should not solely be defined on the basis of behavioural observations [29], as it is currently the case [6]. Biological markers associated with autism include inflammation, oxidative stress, mitochondrial dysfunction and endocrine disruption. These physiopathological alterations are

identified as important pathways in the development of autism [17, 25, 29]. In parallel, these same responses are also common consequences of exposure to environmental toxicants (see for instance inflammation [30], oxidative stress [31], mitochondrial dysfunction [32] and endocrine disruption [33]).

Endocrine disrupting chemicals (EDC) are known to contribute to cognitive deficits and neurodevelopmental disabilities [34]. A properly functioning thyroid hormone is particularly important for normal brain development [34]. Prenatal exposure to a variety of maternal thyroid hormone disrupting chemicals represents a plausible biological mechanism that can explain the current increase in neurodevelopmental disorders [17, 35] including autism and ADHD [34]. The central nervous system is uniquely vulnerable and sensitive to adverse effects of thyroid disrupting chemicals in the maternal and foetal environment during early development [4, 17, 20, 34, 35]. Maternal hypothyroidism increases the risk of autism 4-fold [36], so it is logical to examine associations between chemicals that affect signalling pathways of thyroid hormones and risk for autism in humans. While, the association between gestational exposure to EDC and autism reported in epidemiological studies are common in the literature, there are some exceptions [37].

Numerous toxicants have been associated with autism including pesticides, phthalates, polychlorinated biphenyls (PCBs), solvents, toxic waste sites, air pollutants and heavy metals [2, 15, 37]. In one specific literature review, 92% of studies – that is 34 out of 37 - reported an association between autism risk and environmental toxicant exposure [15]. In this same review, the strongest associations between environmental toxicants and autism were reported for air pollutants and pesticides [15]. Furthermore, biomarker studies measuring toxicant concentration in blood or urine, also reported an association between autism and levels of solvents, phthalates and again, pesticides [15].

## 4. Epidemiological evidence associating autism and pesticides

«Pesticides are designed to interfere with synaptic transmission in the central nervous system, however, neurotoxic properties of pesticides may have unintended consequences in the brain of developing children» [31]. In epidemiological studies of environmental toxicants, pesticide exposure frequently appears associated to the development of autism [2, 5, 15-19, 22, 23, 34, 35, 38]. Epidemiological studies examining pesticide exposure are either ecological in design (i.e. residential proximity to sites contaminated with pesticides) or biomarker-based (i.e. quantification of pesticides in body fluids), since voluntary testing of pesticides on pregnant women or babies would be considered unethical.

Epidemiological studies have identified that residential proximity to agricultural pesticides application prior to conception and during pregnancy increases risk of having a child with autism [18] as much as by 60% (OR = 2.0; 95% CI: 1.1-3.6) [16]. The first biomarker-based evidence linking pesticide exposure in early pregnancy to autism measured maternal serum

p,p'-DDE concentration (a metabolite of the insecticide DDT) [39]. Offspring born from mothers which were most exposed to p,p'-DDE (75<sup>th</sup> percentile exposure group) showed a 32% increase in the risk of autism (OR = 1.3; 95% CI: 1.0-1.7). Furthermore, the odds of having both autism and intellectual disability were increased by more than two-fold in this high exposure group (OR = 2.2; 95% CI=1.3-3.7)[39].

In both types of epidemiological studies, when considering estimated or measured exposure during the period of gestation, pesticides are amongst the toxicants with the highest association to autism [15, 16]. This is not surprising, since pregnancy is a period in which there is very rapid development of the central nervous system of a foetus. Some studies report a two- to five-fold increase in the odds ratio of autism with gestational exposure to pesticides [15]. Pesticides are of great concern, because research now indicates that exposure to pesticides, whether inside or outside the home, **even prior to becoming pregnant, can also affect the neurodevelopmental outcome of a future offspring that has not yet even been conceived** [5, 16]. More recent research even indicates that while prenatal pesticide exposure contributes the most to the risk of developing autism [10], pesticide exposure in early infancy increases by 50% the risk for a child with autism to have comorbid intellectual disability [40]. However, the evidence linking pesticide exposure to autism is stronger during the gestational period than for childhood exposure [15]. Studies also demonstrate a dose-response relationship: the greater the exposures, the more likely it is that there will be a more profound and detrimental impact on neurodevelopment [20, 22, 40, 41].

Furthermore, many pesticides, particularly neurotoxic insecticides [16], have not been tested for their neurodevelopmental toxicity [4] and are known to be endocrine disrupting chemicals.

## 4.1 Specific pesticides associated with autism

Scientific literature reports that many pesticides are associated with autism, and this even at low level exposures considered to be below toxic range [42]. Insecticides that act on the nervous system are therefore obvious research targets for their potential roles in autism. Insecticide chemical families associated with autism include carbamates [16], organochlorines [20, 42], organophosphates [16, 20, 40, 43, 44], pyrethroids [16, 20, 40], neonicotinoids [45], organobromine [40] and macrocyclic lactone derivatives [40]. Organochlorines, organophosphates, and pyrethroid pesticides all have an effect on developing synapses (the connections between neurons) and this may explain associations with neurodevelopmental disorders [46]. Among the insecticides that have been identified to be associated to autism are DDT and its derivative DDE [39], chlorpyrifos [16, 40, 42, 43], diazinon [40, 42], malathion [40], avermectin [40], permethrin [40], cypermethrin [42], bifenthrin [43], imidacloprid [45], dicofol [17, 42], endosulfan [17, 42], and methyl bromide [40]. Beside insecticides, herbicides (glyphosate [40, 47], and ammonium glufosinate [48, 49]), fungicides (myclobutanil [40], phosphine [50], pyraclostrobin, trifloxystrobin, famoxadone and fenamidone [51]) and rodenticides (rotenone [51]) have also been listed in studies showing correlations with autism. Many of these pesticides are still registered for sale in Canada according to the Pest Management Regulatory Office of Health Canada (Table 1). For more details on the history of pesticides, epidemiological or mechanistic evidence linking specific pesticides to autism,

please refer to Annex 2. For more details on the type of epidemiological study and exposure assessments on various primary studies, please refer to Annex 3.

**Table 1: Various pesticides that have been mentioned in studies exploring associations with autism and their registration status in Canada.**

Pesticide category	Chemical family	Active ingredient	Reference	Products registered in Canada <sup>1</sup>
Insecticides	Carbamates		[16]	76
	Organochlorines		[20, 42]	
		DDT and DDE (metabolite)	[39]	0
		Dicofol	[17, 42]	2
		Endosulfan	[17, 42]	0
	Organophosphates		[16, 20, 43, 44]	12
		Chlorpyrifos	[16, 40, 42, 43]	24
		Diazinon	[40, 42]	9
		Malathion	[40]	32
	Pyrethroids		[16, 20]	
		Permethrin	[40]	345
		Cypermethrin	[42]	9
		Bifenthrin	[43]	3
	Neonicotinoids	Imidacloprid	[45]	65
	Organobromines	Methyl Bromide	[40]	5
Herbicides	Phosphonic acids/ organophosphorous	Glyphosate	[40, 47][21, 52-55]	448
		Glufosinate ammonium	[48, 49, 56]	60
Fungicides	Inorganics	Phosphine	[50]	27
	Strobilurines	Pyraclostrobin	[51]	5
		Trifloxystrobin	[51]	1
	Oxazolidinediones	Famoxadone	[51]	2
	Imidazolones	Fenamidone	[51]	1
	Triazoles	Myclobutanil	[40]	4
Rodenticides		Rotenone	[51]	4

Notes: <sup>1</sup> The number of products registered in Canada is based on a search on Health Canada's Pesticide Management Regulatory Agency pesticide labels database in June 2019.[57]

Furthermore, the succession of pesticides entering the market, and later restricted or completely banned, reveals the worrying process of regrettable substitutions [58, 59]. Exceptional authorizations granted for the use of otherwise banned pesticides are also worrying observers due to their high frequency [60]. This story is also marked by "legacy pesticides" that were banned, but remained present in the environment, in our food and water due to their high persistence over time (i.e. DDT, although banned since the early 1970's, remains in the environment for hundreds of years). The most worrying classes of pesticides associated with autism are insecticides, which are known to target the nervous system. Unfortunately, advanced neurodevelopmental testing in the mandatory registration testing of many pesticides is lacking [59]. As such, if an effect is not obvious through the mandatory acute testing, it may very well remain unstudied. This applies particularly to any long term

effects on human health associated with pesticide use in real life (as opposed to mandatory testing done in controlled environments before registration). This is likely the case with neurodevelopmental disorders such as autism. As society substituted organochlorines for organophosphates, then pyrethroids and more recently neonicotinoids, we left a legacy of health issues that can transcend generations and lead to yet unidentified consequences.

## 5. Routes of pesticide exposure in mothers and children

Other than overt exposure to pesticides when actually applied in one's indoor or outdoor environment, the general population is also exposed to pesticides or their metabolites through drinking water, food, air pollution, dust, insect repellent, and pet flea and tick treatments [18, 22, 44, 61-64]. For children, the primary route of exposure to many pesticides, for instance permethrin, is ingestion of contaminated food [65], while organic diets have been shown to decrease pesticide loads in children [66], both in rural and urban locations [67]. Domestic exposure to air and dust is equally important in homes where pesticides have been used or in homes of farmers [68]. A non-negligible alternate route of exposure for children and spouses of farmers may also be exposure through contact with clothes or surfaces [68, 69].

Exposure to pesticide is nearly ubiquitous. For example, most US households have measurable levels of insecticides (as detected in floor wipe samples); the most commonly detected is Permethrin (89%)[70]. Cypermethrin (46%) is also commonly detected [70, 71]. Low income populations are also greatly at risk : permethrin was detected in all (100%) urban public housing units surveyed in Boston (Mass., USA), while Cypermethrin had a prevalence of more than 90% [72]. Dust concentrations are a useful indicator for adult and children exposure to pesticides [68]. The ubiquity of pesticides in our environment unsurprisingly results in pesticides and metabolites detection in nearly all children. For example, a Quebec study from 2004 also showed that 98,7% of 442 urine samples taken from children aged 3 to 7 years old had presence of organophosphate pesticide residues [73]. Another study in California revealed that the majority of children (>72%) have pesticide metabolites in their urine, including residues of organophosphorous and pyrethroids insecticides [67] which are associated with autism. In China, 100% of children and adults tested in rural areas had imidacloprid residues in their urines, and this detection was of 95% in urban subjects [74]. A literature review of glyphosate concentrations in urine revealed frequencies above analytical limits of detection oscillating between 30 and 80% amongst seven studies, but dismissed potential health effects as reported concentrations were below the acceptable daily intake (ADI) or the acceptable operator exposure level (AOEL) [75] (even though advanced neurodevelopmental toxicity studies were never required, therefore not considered in glyphosate registration [76]). One of these studies included in the literature review was conducted in the USA with subjects specifically avoiding genetically modified food and pesticides. Glyphosate residues were still found in the maternal milk of 30% of the 10 subjects tested and in the urine of 37% of the 35 adults and children tested [77].

The fact that many pesticides and their breakdown products have a low rate of biodegradability may lead to accumulation in the environment [78]. This implies that the harm they are susceptible to cause to adults and children exposed may extend long after we cease their use.

## 6. Biological alterations caused by pesticides during neurodevelopment

### 6.1 Pesticides impact on child neurodevelopment

Many pesticides are well known for their endocrine disrupting capacity (such as thyroid function), as well as for their ability to disrupt critical neurodevelopmental signaling [17, 34]. Interference with normal hormonal signalling during brain development may have profound impacts on the unborn child. For example, during the first 10-12 weeks of gestation, a foetus is fully dependent on the functioning of his/her mother's thyroid gland [35]. Thyroid hormone is essential for normal brain development because «it influences during specific temporal windows, neurogenesis, neuronal migration, neuronal and glial cell differentiation, myelination and synaptogenesis» [35]. As such, adequate maternal **thyroid** function plays an essential role in foetal brain development and function [17, 34, 43]. Research indicates that maternal hypothyroidism increases autism risk 4-fold [34] and even moderate forms of maternal thyroid dysfunction may affect child cognitive development and increase neurodevelopmental disorders [35]. It is suspected that the development of autism begins in the 8-14<sup>th</sup> weeks of gestation period [14].

Studies directed at pregnant women found that those with higher levels of pesticides in the umbilical cord plasma or in serum samples, had a greater risk to bearing a child who would develop autism [13, 17, 37]. During gestation, the **blood brain barrier and the placental barrier** transport essential nutrients between the mother and foetus and into the central nervous system of the foetus [17]. However, certain pesticides are capable of crossing these barriers using certain transporters normally carrying other signalling molecules such as **lipid mediator prostaglandin E2 (PGE2)**[17]. Therefore, these pesticides can interfere with various biochemical signalling processes of the developing brain and body of the foetus [17]. Prenatal development of the brain requires highly specific signalling from key biological pathways that carefully regulate the expression of genes. These pathways can be turned on or off, or expressed in specific concentration gradients, during different stages of development [17].

Pesticides also influence neurodevelopment by disrupting endocrine function, such as **lipid mediator PGE2** signaling, which is essential in the development and functioning of the brain [17]. Pesticides can also cause mitochondrial dysfunction and disrupt neuronal signalling (acetylcholine, serotonin, GABA, sodium and calcium channels) [15, 16, 38, 43]. For example, acetylcholine is a neurotransmitter specifically targeted by a number of pesticides. It normally plays a critical role in learning, attention, and memory and its concentration is known to be reduced in frontal and parietal cortices of children with autism.

## 6.2 Metabolic and biochemical interferences of pesticides and autism

Pesticide exposure leads to numerous biochemical interferences including immune dysregulation, hormonal aberrations, nutrient deficiencies, epigenetic alterations and/or by inducing *de novo* DNA changes [14, 15]. Pesticides can also induce oxidative stress which leads to the production of reactive oxygen species (ROS) that can decrease mitochondrial function (involved in cellular respiration). The decreased mitochondrial function is a recurring trait in autism [17]. Indeed, some people with autism have physiological abnormalities involving oxidative stress and lower glutathione (GSH) levels [15]. Oxidative stress profoundly alters various biological structures, such as cellular membranes, lipids, proteins and nucleic acids, and it is involved in numerous malignancies [79]. Reduced GSH is one of the most important scavengers of ROS which protects the body against oxidative stress. Males, which are predominantly affected by autism (4:1 ratio), are known to have heightened oxidative stress and lower GSH levels and they are also more susceptible to the effects of various toxicants, including pesticides [15].

This raises the possibility that children with autism may be more vulnerable to synergistic actions on biochemical pathways that are simultaneously damaged by the toxicants and due to a reduced detoxification capacity. Indeed, studies have shown that the *PON1* gene, an environmental response gene critical for detoxification of pesticides, exhibits some polymorphism in people with autism [15]. Children with autism may have less active paroxanases, the enzyme responsible for organophosphate degradation, making them more sensitive to this family of insecticides [80]. Therefore, children with autism might metabolize toxicants differently and may experience toxicity to pollutants at a lower concentration compared with typically developing children [15, 38].

Some pesticides, including glyphosate, also interfere with the 'shikimate pathway' in human gut microbes, neurotransmitter production such as serotonin, and sulfate synthesis which increases a number of biomarkers (p-cresol, serum sulfate deficiency) that are related to autism [14].

Several studies have shown that imbalances of excitatory/inhibitory neurotransmitters resulting from neurodevelopmental impairments in glutamatergic and GABAergic system might be a common pathological mechanism for autism and ADHD [81]. GABA (gamma aminobutyric acid) is an inhibitory neurotransmitter essential and critical for proper development and functioning of brain [81]. Autism has been associated with alteration of GABAergic pathways either through genetic variations and neuronal interactions modulation that affect the excitatory-inhibitory ratio of the brain [15]. Numerous pesticides, such as pyrethroids, are equally known to interfere with GABA signalling [13].

DNA methylation, a process by which methyl groups are added to the **DNA** molecule, is a crucial epigenetic process which leads to different expression of the DNA genes. Methylation is a key element amongst the different control mechanisms that govern gene expression in

vertebrates [82]. DNA methylation may also play a role in the inheritance of certain traits [83]. Research indicates that pesticides professionally applied outside or inside homes could alter placental DNA methylation more than other factors [18]. Genetic mutations may thus simply be co-occurring secondary effects of mutagenic agents to which a developing foetus is exposed to during gestation[14].

## 7. Other health impacts of pesticides

Exposure to pesticides is known to cause a range of health and developmental concerns other than autism. Pesticide exposure is known to cause structural abnormalities of the brain, low head circumference, and persistent neurobehavioral deficits [4]. These include IQ loss and associated intellectual disability, ADHD, impaired cognition and motor function, reproductive problems for males and females, childhood and adult obesity, diabetes [34, 35, 84], as well as childhood leukemia [85]. Therefore, children, until they reach adulthood, are at an increased risk for many health consequences as a result of being exposed to pesticides. Furthermore, pesticide exposure of parents and grandparents can even be linked with health consequences in unexposed children or grandchildren. This is the case for grandparent exposure to the insecticide DDT which can lead to obesity of grandchildren, likely due to epigenetic factors such as DNA methylation [86]. Put more simply, since many pesticides are highly persistent in the environment [78], they can therefore impact health long after their application or their restriction.

## 8. Society's role in protecting future generations

The long term adverse effects of pesticides have been described as a “silent pandemic” [87]. The resulting neurodevelopmental disabilities are at a cost that is far too high for the affected individuals, their families, their communities and society as a whole [2, 34]. These costs include the health care system, physicians fees, specialized educational programs, specialized residential services, welfare and employment support [2]. A 2014 Canadian report pertaining to the financial cost associated to supporting a person with autism, estimated that the lifespan value of caregiver time alone to support a severely affected individual with autism to be approximately \$5.5 million above the costs of a neurotypical individual. In cases where adolescents and adults with severe autism are placed into long-term care or other supported housing arrangements the annual cost of housing, which includes caregiver time, can be \$400 per day, amounting to approximately \$150,000 a year {Dudley, 2014 #500}. Statistics from 2011 pertaining to the United-States, reported that the total costs per year for children with autism in the United States were estimated to be between \$11.5 billion – \$60.9 billion. This significant economic burden represents a variety of direct and in-direct costs, from medical care to special education to lost parental productivity {Center for Diseases Control and Prevention, 2019 #501}[88]. Another report from the US pertaining to 2015 indicated that the cost of caring for Americans with autism had reached \$268 billion in 2015 and would rise to

\$461 billion by 2025 in the absence of more-effective interventions and support across the life span {Autism Speaks, 2019 #502}.

Families may suffer from a net income loss of approximately 14% as well as experience problems that affect their capacity to work [2]. Families and particularly parents experience additional stress and psychological challenges, related to the imperative to reorganize their entire daily functioning around their child's needs [2].

The need to protect future generations of children and families is critical. The evident question that begs to be asked is, what is being done to protect future foetuses and future mothers from pesticide exposure [18]?

Our society, our governing leaders and our public health agencies must take action to reduce widespread exposures to chemicals that interfere with foetal brain development [5]. Given that the literature reports an association between *in-utero* pesticide exposure and impaired child neurodevelopment, clinicians should educate parents about prevention of exposure, there is sufficient consistency across to warrant caution regarding exposure of pregnant women to pesticides due to the potential impacts on child neurodevelopment. Policy-makers should act accordingly [8].

Since non-genetic factors influence the underlying neurodevelopmental processes during the prenatal period, it is essential to act upon the modifiable preconception and/or prenatal factors that have been associated with autism [15]. By increasing awareness and knowledge about the potential adverse effects of pesticides on foetuses, children and future mothers, future generations stand to potentially have healthier brain development and overall health. Autism is one condition amongst a very large number of chronic conditions that have followed similar rates of increasing prevalence. This includes asthma, type 1 diabetes, metabolic syndrome, schizophrenia, sleep disorders, etc [2]. These conditions all have early life origins, can be connected to a grid of comorbidities and have environmental factors that remain to be precisely identified in future epidemiological research[2]. " An effective environmental risk reduction strategy for autism is likely to have a broader relevance that could encompass other developmentally based diseases. " [2]

While research indicates taking higher doses of folic acid supplements prior to conception and during early gestation mitigates the risk for a foetus developing autism when exposed to pesticides during pregnancy [13], it does not however completely eliminate the risk [23].

Therefore, the potential risk for foetuses and children, remains too elevated [5]. Thus, decreasing exposure to harmful chemicals such as pesticides is an essential step for society to take. Facing the current pandemic of neurodevelopmental toxicity, action can and must be taken without further delay to limit exposure to pesticides (35).

## 9. Policy recommendations

The responsibility to curtail neurodevelopmental toxicity depends on what collective actions will be taken [4]. To achieve such an endeavour, a coordinated and concerted action plan containing comprehensive and concrete strategies must be rapidly developed and implemented by provincial and federal governments in Canada, as well as internationally. Here are a few of these strategies that should guide this effort in Canada:

### 9.1 Federal jurisdiction

- Ban all known reproductive toxicants and endocrine disruptors, whether or not they have carcinogenic properties.
- Reform the *Canadian Environmental Protection Act* and *Pest Control Products Act*, particularly the registration and reassessment process of pesticides must be based on independent scientific studies rather than industry funded studies, and should include:
  - a thorough evaluation of complete formulation rather than mostly focusing on the active ingredients
  - assessment of long term effects on human health and environment
  - advanced neurodevelopmental studies for any pesticide that may interfere with neurotransmitters or endocrine signalling
  - cumulative and synergistic effects in their risk assessment according to the pesticide field uses and environmental co-occurrence of pesticides
- Health Canada must decrease the maximum 'safety residue limits' of pesticides allowed in food [44], water and air, to levels that are safe for vulnerable populations, such as pregnant women and children.
- Assess and identify alternatives to toxic substances and place the burden on industry to show that safer substitutes are not otherwise available.
- Mandatory integrated pest management and promotion of non-toxic or least toxic control methods to address pest problems for both residential and agricultural practices [44].
- Mandatory warning labels with easily recognizable symbols and colors placed on toxic products sold to the general public.
- Ban advertisement of pesticides on all media.
- Ban any form of discounts on pesticide products.
- Prohibit pesticide product placement in high circulation areas (store entrance or exit, near cash register, etc.).
- Do not allow pesticides to be sold in supermarkets or pharmacies
- Obligate companies that develop pesticides to provide funds for ongoing independent scientific research on the impact of pesticides on human health and the environment, using a governance structure that prevents any form of conflict of interest.

## 9.2 Provincial jurisdiction

- Restrict or completely ban the use of pesticides known as reproductive toxicants, neurodevelopmental toxicants or endocrine disruptors.
- Reform and update Pesticide Risk Indicator for Québec (IRPeQ) Health and Environment. This indicator must be based on independent and up to date science.
- Put in place an obligatory digital system for tracking and reporting all pesticide application, not only for the top ranked risk pesticides as is currently the case.
- Improve the obligatory reporting systems for retail and bulk sales to include a mandatory digital information transmission, enabling for reporting of regionalized maps of pesticide sales describing their exact nature and sales in volume. This information would equally aid in conducting epidemiological research to protect citizens and improve prevention.
- Organize a rapid prevention and sensitization campaign by public health establishments [35] to protect the health and the development of future generations from risks related to pesticides.
- Implement a comprehensive strategy to raise awareness and train health professionals including doctors, obstetricians, paediatricians, psychologists, developmentalists, child therapists as well as nurses, on the impact of environmental toxins such as pesticides on fetuses. Enlarge training if possible to all paramedical professionals as for example midwives as they have a mission for prevention and follow-up of pregnant women.
- Implement obligatory training to farmers, professional gardeners as well as exterminators, as to the impact of pesticides on health.
- Rapidly implement economic disincentives, such as an additional eco-tax, when purchasing or applying pesticides, especially for agricultural use. This eco-tax could be reinvested for the purpose of developing organic farming strategies.
- Provide further financial incentive to farmers to transform their farming practices into organic farming practices.
- In urban areas, further restrict the use of pesticides inside and outside residential homes and buildings, particularly in health care facilities, schools and daycares.
- In agricultural areas, restrict the use of pesticides near homes, buildings and public roads to a minimum distance of 2 km[16].
- Obligate the public announcement in advance of pesticide application on agricultural fields (also taking into consideration wind direction) in order to help minimize unnecessary exposure. Awareness campaigns should also include strategies to protect children and homes, such as closing windows and A/C systems, not allowing children to play outdoors during or after application, etc.
- Impose high fines to companies and individuals that contravene regulations/by-laws

### 9.3 Municipal jurisdiction

- Prohibit cosmetic pesticide uses outside of homes in municipalities that do not yet have such a bylaw.
- Prohibit pesticide sales in municipalities where bylaws restrict their use.
- To gain public support and frame pesticide reductions with a positive messaging, adhere to certification programs that promote biodiversity conservation and pesticide use reduction. See for example, the programme *Ville ami des monarches* from the David Suzuki Foundation.
- Conduct educational and sensitization campaigns which should [35] :
  - Discourage indoor pesticide uses by providing information to citizens and companies regarding the risks of pesticides to humans and the environment.
  - Improve basic insect knowledge - which can increase public tolerance to cohabitation with insects that do not pose health or structural issues to buildings – and therefore result in fewer indoor pesticide uses.
  - Promote behaviours and actions that strategically minimize the risks of home infestations such as preventing insect entry (sealing cracks or openings in homes), reduce attractiveness to insect pests (improve food and garbage storage), reduce available food and water sources for insect pests (improve house clean up and residents behaviours) and reduce the risk of actively transporting insects, such as bed bugs, inside homes (by inspecting furniture or plants before entry, and putting luggage in quarantine after a trip).

## 10. Conclusion

The ramifications of pesticide exposure are evidently quite severe to unborn foetuses, and very young children with a large range of neurodevelopmental associated risks, raising pesticides as a current public health challenge. While pesticides are one of the many environmental toxicants associated with the development of autism, it is one that can and must be collectively acted upon to protect early brain development [40]. Society can no longer afford to turn a blind eye on this issue. The risks and the costs involved are just too elevated. The motivations for approving the use of pesticides must not and cannot be to the detriment of public health and safety. Collective and proactive efforts must be undertaken to limit pesticide exposure to humans, particularly to vulnerable individuals such as pregnant women and children. Raising awareness on the impact of pesticide exposure should be implemented through dissemination of information and prevention strategies involving multiple health professionals and government bodies.

# Annex

## Annex 1: A non-exhaustive list of environmental risk factors involved in the development of autism other than pesticides

<b>Risk factors</b>	<b>Comments</b>	<b>Reference</b>
Maternal immune activation	Maternal infections, allergies, asthma, stress, fever and inflammation during pregnancy are associated with the risk and severity of autism. Bacterial infections, like Streptococcus could activate the materno-foetal immune system, triggering autistic-like phenotypes.	[89-95]
Complications during pregnancy or at birth	Prenatal and perinatal factors (i.e. preeclampsia, polyhydramnios, oligoamnios, placenta praevia, umbilical cord knot, gestational diabetes, lack of oxygen) are associated with the severity of autism symptoms. There is a very high risk for developing autism in extremely preterm born children.	[96-100]
Maternal hormonal imbalances	A prenatal sex steroid theory of autism was formulated on the basis of associations between maternal hormonal imbalances and autism in offspring. Elevated levels of many hormones (androgens, progesterone, cortisol) in the amniotic fluid are associated with autism. Conditions that may elevate androgen, for instance polycystic ovary syndrome, are associated with a higher rate of autistic traits in mothers and also in their offspring.	[101]
Use of acetaminophen (Tylenol) during pregnancy and early childhood	Acetaminophen during pregnancy is associated with hyperactivity, ADHD, and autism (the latter with a stronger association for men). Babies and young children exhibit an even greater association between acetaminophen and autism, likely due to lower detoxification capacities. Suggests women, babies and young children should limit acetaminophen intake.	[25, 102-104]
Depression during pregnancy or use of antidepressant before and during pregnancy	Depression during pregnancy is associated with an increased risk of having a child with autism, regardless of antidepressant use. However, there is also an association between maternal antidepressant use and risk of autism in offspring, which is particularly important even before conception.	[105-107]
Use of other medication during pregnancy	Thalidomide and valproic acid during pregnancy induces abnormal neuron development which may be involved in the development of autism in the offspring	[108]
Nutritional deficiency during pregnancy	Maternal intake of folic acid and multivitamins before and during pregnancy is significantly	[13, 23, 109-116]

	<p>associated with a decreased risk of autism in the offspring, particularly in high-risk families. Lower uptake of essential elements like manganese and zinc is also observed in offspring with autism. Dysregulation of metal metabolism (including the zinc-copper cycles) are common in children with autism. Vitamin D deficiency during pregnancy is associated with an increased risk of autism, and is readily preventable with supplementation. Folic acid intake may mitigate the risk of pesticides exposures and autism.</p>	
<p>Maternal and grandmother smoking during pregnancy</p>	<p>Maternal smoking during pregnancy is associated to increased risk of autism and ADHD in children in some studies, but not all. Grandmother smoking during pregnancy is associated with an elevated risk of autism in grandchildren. This may be due to exposure of the developing ovaries to cigarette toxicants, or to mutations in the mitochondrial DNA, which lead to an effect in the second generation.</p>	<p>[117, 118]</p>
<p>Advanced parental age</p>	<p>The risk of autism increases with both maternal and paternal age, independently, and this has implications for public health planning and the investigation of the aetiology of autism.</p>	<p>[119-121]</p>
<p>Environmental toxicants, endocrine disrupting compounds, plastic derived chemicals, heavy metal, air pollutants, consumer products and pesticides</p>	<p>Higher levels of some organochlorine compounds during pregnancy (PCBs, organochlorine pesticides) are associated with autism. Prenatal exposure to arsenic or manganese, and postnatal exposure to lead, are associated with lower IQ and neurodevelopmental disorders. Children with autism may exhibit a higher uptake of the neurotoxin lead. Air pollution during pregnancy may be associated with an elevated risk of autism in children, and this may be an interaction between the air pollutants and offspring genes. Air pollutants of concern mentioned in autism studies include: particulate matter, heavy metals, styrene, chromium, PAHs and methylene chloride or other pollutants originating from highways. Some symptoms of autism (including emotional reactivity, aggressive behaviour, inattention symptoms, cognitive, motor or language disabilities) may be associated with plastic derived chemicals such as bisphenols or phthalates (but not in all studies). Several endocrine disruptors affect the thyroid signalling and may play a role in the development of autism.</p>	<p>[13, 15, 17, 35, 37, 111, 117, 122-125]</p>

## Annex 2 : History of pesticides and their epidemiological or mechanistic evidence linking them to autism

### Insecticides

**Organochlorines** – Originally used to control mosquito borne Malaria, organochlorines such as DDT were banned in the United States of America in 1972 [126]. Beside DDT, examples of organochlorines include endosulfan and dicofol [17]. Organochlorines can cross the intestine, the skin and the blood brain barrier [127]. Being particularly persistent, they remain in circulation in the environment long after their application and continue to pose a risk to human health [128, 129]. However, when comparing the increasing trend of autism with the generally decreasing trend of organochlorine pesticide use would not make this family of pesticide a lone suspect to explain epidemiologic trends [21]. Nevertheless, there is an association between organochlorine exposure in the first trimester and autism for people living near agricultural fields {Roberts, 2007 #326}. Critical periods of vulnerability to organochlorine insecticides which have been linked with autism range from one month prior to conception to five months after conception and approximately two to eight months after birth [130]. While one study failed to find a linear dose-response association between organochlorine pesticides prenatal exposure and autism, further studies based on non-linear trends with decile analyses are warranted (i.e. epidemiologic study in Southern California quantifying trans-Nonachlor and p,p'-DDE in maternal mid-pregnancy serum samples [37]). Beside associations with autism, maternal exposure to DDT and DDE is associated with premature birth and small gestational age status [39]. The DDT metabolite (DDE) has also been implicated in reduction in cognitive, verbal, memory and neurodevelopmental scores [131] and other neurodevelopmental deficits such as decreased reflex response, psychomotor and mental effects, attention problems, hyperactivity disorder and pervasive developmental disorder, the former term for ASD [8]. One of the proposed mechanisms of action is through modulation of male hormonal signalling. DDE is a known androgen receptor binding inhibitor, androgen transcriptional activity inducer and androgen action modulator [132]. Lowered dehydroepiandrosterone (DHEA) levels have been observed in adult individuals with autism [133].

**Organophosphates** – Originally manufactured to replace the more toxic organochlorines, organophosphates unfortunately also pose a risk to human health [17]. They have short to moderate environmental persistence (half-life of 11 to 180 days in aerobic soils) but have been used in large volumes in farms and in homes. Examples of organophosphates include chlorpyrifos, dichlorvos and malathion [17]. Despite domestic use ban in 2001 by the US EPA, they are still used in agriculture. Organophosphates kill pest insects by inhibiting acetylcholinesterase and by causing nerve damage [134].

A systematic literature review found an association between higher organophosphates exposure and altered neurodevelopment (in 26 out of 27 studies) [22]. This response was dose-dependent in all but one of the 12 studies that assessed organophosphorus exposure [22]. Longitudinal studies that assessed prenatal exposure to organophosphorus revealed cognitive deficits (working memory) at 7 years of age, behavioural (attention) deficits in toddlers and motor deficits (abnormal reflexes) in newborns [22]. At any moment in pregnancy, exposure to agriculturally used organophosphates is associated with elevated risks of autism [41]. In a 2019 study, risk of autism spectrum disorder was associated with prenatal

exposure to three organophosphates, namely chlorpyrifos (OR = 1.13, 95% CI: 1.1-1.2), diazinon (OR = 1.1, 95% CI: 1.0-1.2) and malathion (OR = 1.1, 95% CI: 1.0-1.2)[40]. For autism spectrum disorder with comorbid intellectual disability, estimated odds ratios were higher (by about 30%) for prenatal exposure chlorpyrifos (OR = 1.3, 95% CI: 1.0-1.6) and diazinon (OR = 1.41, 95% CI: 1.2-1.7)[40].

Symptoms of pervasive developmental disorder, the former term for ASD, were associated with higher organophosphates metabolites in the urine [135] or chlorpyrifos in umbilical cord blood plasma [136] in two different studies. Organophosphates have been shown to interfere with thyroid hormone, either in animal models and in humans [137], and this may be a plausible biological mechanism for autism. Organophosphate may also induce other behavioral and cognitive deficits [138, 139] as well as differences in brain volume [140]. Organophosphate exposure have also been associated with loss of IQ points and intellectual disability which has incurred costs ranging between €46.8 to €194 billion per year in Europe [34].

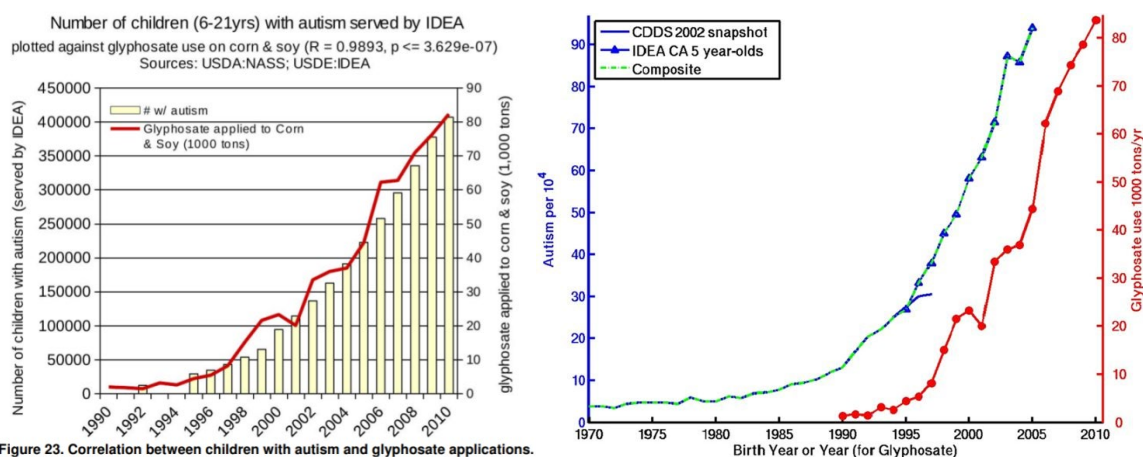
Chlorpyrifos is the most widely used organophosphate in the United States and in Europe [34]. It is also one of the top 5 most hazardous pesticides in Quebec both for the environment and for human health [141]. There is strong evidence that it is an endocrine disrupting chemical, inhibiting acetyl-cholinesterase, but it can also induce neurodevelopmental toxicity through other mechanisms such as interference with thyroid hormone signalling [34]. Higher concentrations of chlorpyrifos in the umbilical cord plasma has been associated to heightened risks of pervasive developmental disorders the former term for ASD, in 3-year-old children [142]. Children with higher concentrations of chlorpyrifos have structural changes in the brain regions that are linked to attention, social cognition and receptive language processing [143]. Organophosphates can induce oxidative stress, mitochondrial dysfunction and cytotoxicity to neurons and liver cells [144, 145].

**Pyrethroids** – Pyrethrins are naturally derived insecticides from the chrysanthemum flowers. Pyrethroids are their chemically synthesized relatives that are more persistent in the environment. Examples include permethrin and cyfluthrin. Just as organophosphates replaced organochlorines when the latter were found toxic and banned, pyrethroids heavily replaced organophosphates when these were in turn found toxic and banned. Once again, pyrethroids are not devoid of toxicity. They have been shown to influence neurodevelopment through a variety of mechanisms including interference with serotonergic systems, altered GABA function, oxidative stress, mitochondrial dysfunction, endocrine disruption and alteration in calcium signalling [13, 17]. In a 2019 study, the risk of autism was associated with prenatal exposure to the pyrethroid permethrin (OR = 1.10, 95% CI: 1.0, 1.2)[40]. For autism with comorbid intellectual disability, estimated odds ratios were higher (by about 30%) for prenatal exposure to permethrin (OR = 1.5, 95% CI: 1.2 to 1.8)[40].

Despite warnings against the use of pesticides during pregnancy, 88% of American pregnant women surveyed between 2000 and 2008 reported using pesticides at some point (mostly pyrethroids after the restrictions on organophosphates)[146]. Moreover, up to 75% of American children and adults, and up to 80% of teenagers, had urinary metabolites of pyrethroids [147]. Because pyrethroid metabolites are normally short-lived in the body, this high frequency of detection in the urine suggests that we are constantly exposed to pyrethroids in our daily living.

## Herbicides

**Glyphosate** – The link between glyphosate and autism is a topic of intense research and debate in the scientific literature. As a proof, searching Google Scholar for the terms glyphosate and autism yields 1300 results. But through those numerous references, only a few contained theories on the modes of action, many of which are considered speculative. But the authors warrant further scientific studies to clarify the potential role of exposure to glyphosate in triggering autism. First, correlations between the increase in use of glyphosate and the rise of autism have already been exposed. When comparing the rising trend of autism with the exposure trends to the top 10 toxic compounds encountered in the United States between 1980 to 2005, only three chemicals – including glyphosate - show a positive correlation (co-rising trends) [21]. Co-occurring rising trends have strikingly high correlations values in another study ( $R = 0.989$  [52]). Of course, even a near perfect correlation does not imply causation. But because glyphosate is the most widely sold pesticide on the planet, a strong correlation between the alarming rise of a serious health disorder and a toxic chemical cannot be simply dismissed without further studies [53]. Parallel to the ecological studies linking glyphosate and autism, other studies observed an excess of ADHD amongst children born to glyphosate applicators in South America [149] as well as glyphosate use and ADHD diagnosis in the United States [150]. In 2019, a new epidemiological study reported that autism was associated with prenatal exposure to glyphosate (OR = 1.2; 95% CI: 1.1-1.3), and that comorbid autism with intellectual disability were 30% higher for prenatal exposure to glyphosate (OR = 1.33, 95% CI: 1.1-1.7)[40].



**Figure 4: Increasing trends of autism and glyphosate use in the United States. Image sources: Left, using glyphosate applied to GMO corn and soy [52] and right, using all glyphosate applications [21].**

Mechanistic pathways that could explain the observed correlation were proposed by the researchers Samsell and Seneff. One proposition involved glyphosate's mimicry of the amino acid glycine that could disrupt calcium inflow in immature neurons [54]. Another hypothesis is the manganese chelation capacity of glyphosate which could lead to impaired mitochondrial function and impaired ability to detoxify glutamate, which are both linked to autism [55]. Finally, Beecham and colleagues proposed that by chelating metals (a known characteristic of glyphosate), this active ingredient could hamper the functioning of a manganese-dependent

enzyme leading to reduction in Thyroid-Stimulating Hormone (TSH), a condition itself correlated with increased autism risk in mid-pregnancy mothers [53]. The authors of this report warrant focused research effort to clarify this. Indeed, we need further research on the potential links between glyphosate and autism. Some have argued that some of the mechanisms proposed by the team of Samsell and Seneff are speculative [151]. Even severe critiques of these theories nevertheless advocate for better scientific studies to enlighten this debate [152] and that studies supporting glyphosate's safety are generally funded by the agrochemical industry, whereas those suggesting toxicity below the set safety limit generally come from independent researchers [151]. Another important theory potentially implying glyphosate – a patented antibiotic - and autism involves action on the gut microbiota {Samsel, 2013 #128}. Indeed, the potential role of antibiotics and alteration of the gut microbiota and its putative role in autism is increasing in popularity in the scientific community [153]. At the same time, the effect of glyphosate on gut bacteria is not required in registration testing and symptoms in test animals including diarrhea and loose stools are often dismissed as non-specific [154]. At the very least, this theory too deserves further study.

**Ammonium Glufosinate** – As weed resistance to glyphosate is increasing, a rising alternative herbicide is a close chemical relative called ammonium glufosinate. As for most pesticides, studies on potential adverse effects related to developmental neurotoxicity are lacking. Recently, a study on mice revealed that *in utero* exposure led to offspring that displayed symptoms strikingly similar to animal models of Autistic Spectrum Disorders, including early reflex development, pup communication, affiliative behaviours, and preference for social olfactory cues[48]. These behavioural traits were also concomitant to biological changes implying impaired neurogenesis and neuroblast migration through cytoskeleton destabilization [49]. This is the first evidence of the link between early life exposure to the herbicide and molecular and cellular consequences and the onset of ASD-like phenotype later in life. Neural stem cells of the subventricular zone of the developing brain can be affected both by ammonium glufosinate and its main metabolite 4-methylphosphinico-2-oxobutanoic acid through different modes of action [56]. Finally, ammonium glufosinate also leads to neurotoxicity and altered behaviour in reptiles, and this effect is exacerbated in males compared to females [155].

## Annex 3 : Pesticide families associated with autism in various epidemiological studies

This table was reproduced from a systematic literature review {Schmidt, 2014 #339}

Pesticides				
<i>Organophosphates (OP)</i>				
Rauh et al., 2006 New York, USA	Prospective cohort (n=228; <5% PDD cases)	Measures of chlorpyrifos in plasma (cord or maternal)	Highest chlorpyrifos exposure group had greater risk for PDD as defined by scores on Child Behavior Checklist (CBCL)	Four studies using different methods consistently show elevated risk. Exposure measurements or other information all pertain to the prenatal period. Outcomes not based on clinical assessment in majority of studies. Studies suggest potential association between an organophosphate pesticide and ASD or related symptoms. However, use of one or two isolated measurements may not provide valid surrogates for overall prenatal or infant exposures. Further research with
Environmental Factor and Study Reference, Location, and Name	Study Design	Exposure Assessment	Results	State of the Evidence
Eskenazi et al., 2007 California, USA (CHAMACOS)	Prospective cohort (n=355; 51 PDD cases)	Prenatal & child OP (organophosphate) urinary metabolite levels	Prenatal and postnatal dialkylphosphate (DAP) metabolites associated with more than two-fold higher risk for PDD as defined by scores on Child Behavior Checklist	confirmation of diagnoses using gold standard protocols and better measures of individual-level exposures over time is needed.
Roberts E., et al., 2007 California, USA	Case-control (n=465 cases and 6,975 matched controls)	Proximity to agricultural applications of organophosphates	ASD community diagnosis modestly associated with organophosphate applications within 250m, during gestation	
Shelton J.F., et al., 2014 California, USA (CHARGE)	Case-control (486 ASD cases; 316 typically developing population controls)	Proximity to agricultural applications of organophosphates	Clinically confirmed ASD diagnosis associated with organophosphate applications within 1.5 km during pregnancy, particularly chlorpyrifos during 2 <sup>nd</sup> trimester	
<i>Other Pesticides</i>				
Roberts E., et al., 2007 California, USA	Case-control (n=465 cases and 6,975 matched controls)	Proximity to agricultural applications of organo-chlorine insecticides, or pyrethroid insecticides	ASD community diagnosis strongly associated with residential proximity to organochlorine applications during 1 <sup>st</sup> trimester, and moderately for the pyrethroid, bifenthrin, during the overall gestation	Analyses from one report suggesting a strong association of ASD with organochlorines and a moderate one with a pyrethroid require confirmation in independent samples, preferably with gold standard diagnoses. Results on imidacloprid potentially related to differences in reporting accuracy between cases and controls.
Keil et al., 2014 California, USA (CHARGE)	Population-based case-control (n=407 ASD, and 262 typically developing controls)	Maternal report of common flea or tick treatment for pets (imidacloprid)	Using Bayesian methods, no overall association. Higher risk in those with frequent use. Sensitivity analyses to address misclassification yielded inconclusive results	

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# HAUSSE INQUIÉTANTE DE LA PRÉVALENCE DE L'AUTISME: DEVRIIONS-NOUS NOUS INQUIÉTER DES PESTICIDES?

Sommaire exécutif de la revue de littérature



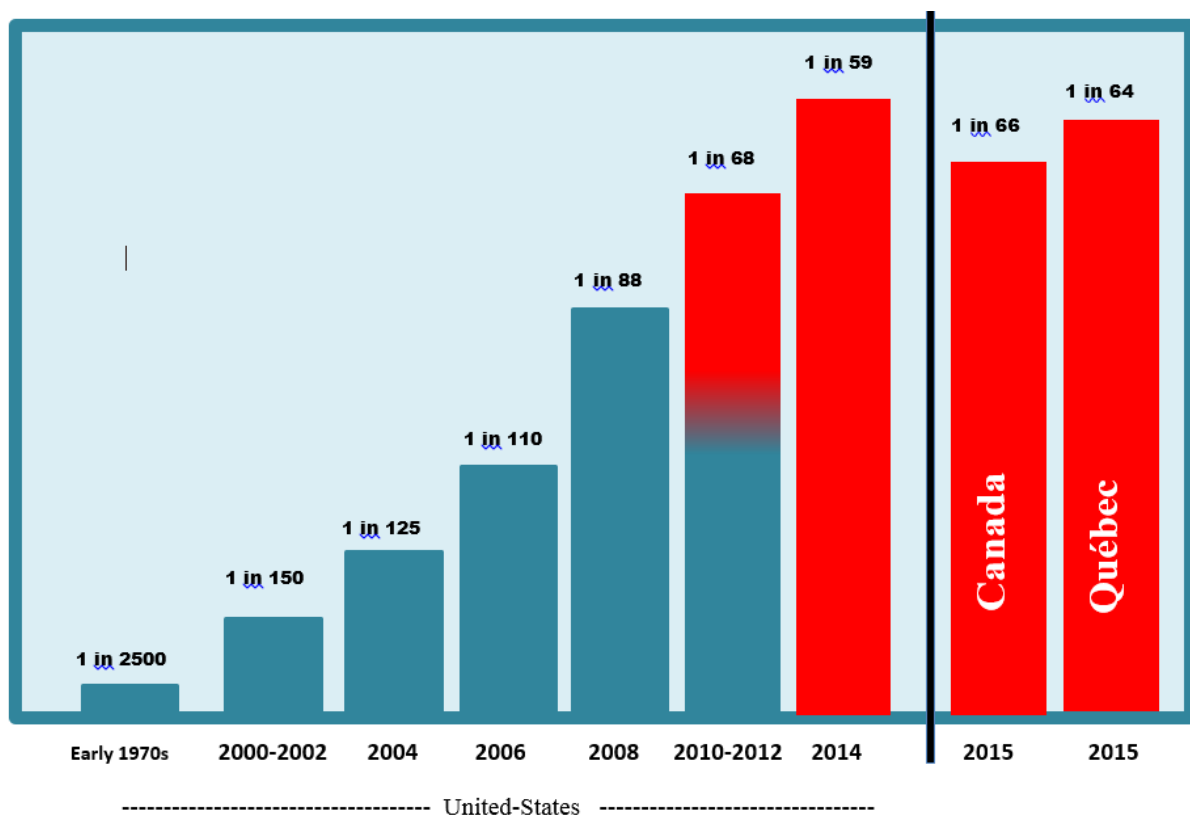
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## 1- Hausse inquiétante de la prévalence de l'autisme

L'autisme est un trouble neurodéveloppemental complexe qui touche 1 enfant sur 66 au Canada et 1 enfant sur 64 au Québec [1]. Or, il se propage à une vitesse alarmante à l'échelle mondiale [2]. Selon les Centers for Disease Control and Prevention (CDC), l'autisme est maintenant un « *problème urgent de santé publique* » [3] compte tenu de l'augmentation rapide de sa prévalence, qui s'élève à 1 enfant sur 59 aux États-Unis (figure 1). Des chercheurs et des experts médicaux renommés en sont venus à sonner l'alarme et croient que nous sommes aux prises avec une « **pandémie d'effets toxiques sur le développement neurologique** » [4, 5].



**Figure 1 : Hausse de la prévalence de l'autisme au fil des années aux États-Unis et plus récentes statistiques pour le Canada et le Québec.** Les auteurs ont produit ce graphique en compilant les statistiques des CDC [6-8] et de l'Agence de la santé publique du Canada [9]. Il n'existe pas de statistiques pour le Québec et le Canada avant 2015.

Les troubles du spectre de l'autisme (TSA) affectent plusieurs facettes du développement d'un enfant, dont la communication, le comportement, les interactions sociales ainsi que les fonctions cognitives, motrices et sensorielles [10, 11]. Bien que chaque individu soit unique et n'ait pas les mêmes besoins, capacités et degrés de fonctionnement intellectuel qu'un autre, bon nombre d'entre eux nécessiteront une aide soutenue tout au long de leur vie.

Pour faciliter la lecture de ce document, le mot « autisme » sera utilisé en référence à tous les troubles du spectre de l'autisme ainsi qu'à l'appellation antérieure « troubles envahissants du développement » [2] et au syndrome d'Asperger [12].

## **2- La prévalence accrue de l'autisme s'explique-t-elle par des facteurs génétiques ou environnementaux, ou bien simplement par un taux de dépistage plus élevé?**

S'il est vrai que l'autisme est caractérisé par une forte hétérogénéité phénotypique, il est aussi probable qu'une myriade de voies et de processus biochimiques puissent mener à un diagnostic d'autisme [2]. Il est généralement admis que les causes de ce désordre sont attribuables à une interaction complexe entre une prédisposition génétique et des facteurs environnementaux. Les études indiquent que les **facteurs environnementaux jouent un rôle bien plus important qu'on le croyait auparavant** et que la vulnérabilité génétique ne peut à elle seule rendre compte de l'augmentation actuelle de la prévalence de l'autisme dans le monde [4, 5, 13-20].

- Étant donné que les gènes évoluent lentement, ils ne peuvent être les seuls responsables de la hausse rapide des cas d'autisme [17].
- Ce désordre est bel et bien caractérisée par des vulnérabilités génétiques, mais on ne peut l'attribuer à un seul gène [13, 14].
- Seulement quelque 10 % des cas d'autisme sont liés à d'autres troubles neurodéveloppementaux d'origine génétique [6, 14].
- Par ailleurs, ni la révision des critères de diagnostic ni une connaissance plus répandue de ce désordre peuvent expliquer la hausse rapide des cas d'autisme, qui est observée en ce moment à l'échelle mondiale [17, 19]. Ces facteurs pourraient compter pour aussi peu que 20 % [21] à 33 % [19] de la prévalence accrue de l'autisme.

## **3- Les substances toxiques qu'on trouve dans l'environnement peuvent-elles nuire au développement du cerveau?**

Le développement du cerveau et du système nerveux central d'un être humain est extraordinairement complexe et suit une séquence de nombreux événements qui surviennent à des moments bien précis durant la grossesse et qui sont sensibles à l'interaction continue des facteurs génétiques et environnementaux [4, 17, 20]. Pendant ces périodes cruciales du développement du système nerveux central, les facteurs génétiques et certaines substances toxiques présentes dans l'environnement interagissent de façon complexe et d'une manière qui peut accroître le risque d'autisme [15, 22]. Le développement du cerveau humain est très sensible à l'exposition aux substances toxiques. D'importantes **fenêtres de vulnérabilité pour le développement** sont ouvertes à certains moments, en particulier *in utero*, mais aussi en bas âge et pendant l'enfance [4]. En outre, les capacités de détoxification des embryons, des fœtus, des nouveau-nés et des enfants ne sont pas encore pleinement fonctionnelles, ce qui rend ceux-ci bien plus vulnérables aux substances chimiques qui se trouvent dans leur

environnement [23, 24]. Au cours de ces étapes critiques de la vie, les substances chimiques, même si elles sont présentes à une concentration qui n'aurait pas ou peu d'effets chez un adulte, peuvent causer des lésions cérébrales permanentes [4].

De nombreux facteurs environnementaux contribuent à l'apparition de l'autisme, mais on ne peut attribuer l'épidémie actuelle de cas de ce désordre à un seul d'entre eux [2]. Néanmoins, les substances toxiques présentes dans l'environnement sont particulièrement préoccupantes [2, 4, 5, 15-20, 25, 26]. De nombreuses études, dont certaines portaient même sur la mesure des concentrations toxiques dans le sang et l'urine, ont démontré que parmi toutes les substances liées à l'autisme, les pesticides présentaient la plus forte association avec ce désordre lorsque l'exposition avait lieu pendant la grossesse [2, 15, 27].

Un consensus se forge de plus en plus quant au fait que l'autisme a un fondement biologique évident et qu'il ne devrait pas seulement être défini sur la base des observations comportementales [28], comme c'est le cas actuellement. Les marqueurs biologiques qui interviennent dans l'autisme comprennent l'inflammation, le stress oxydatif, une dysfonction mitochondriale et une perturbation endocrinienne [23, 28].

Par ailleurs, les perturbateurs endocriniens, dont les pesticides, causent non seulement un déséquilibre hormonal, mais contribuent aussi à un déficit cognitif et à des troubles du développement neural [29]. Or, l'intégrité des hormones thyroïdiennes est particulièrement importante pour le développement normal du cerveau [29]. Le système nerveux central est très vulnérable et sensible aux effets nocifs des substances qui perturbent ces hormones chez la mère et le fœtus pendant les premières phases du développement de l'enfant [4, 17, 20, 29, 30]. Les études indiquent que l'hypothyroïdisme maternel est associé à un risque d'autisme quatre fois plus élevé [29] et que même une dysfonction thyroïdienne modérée peut nuire au développement cognitif de l'enfant et accroître l'occurrence de troubles neurodéveloppementaux [30].

#### **4- Quel est le lien entre l'autisme et les pesticides ?**

Les pesticides figurent parmi les substances toxiques qui sont présentes dans l'environnement et qui sont fréquemment citées dans les études portant sur l'apparition de l'autisme à la suite d'une exposition pendant la grossesse [2, 5, 15-19, 25, 26, 29-31], une période pendant laquelle le développement du système nerveux central de l'embryon et du fœtus est très rapide. L'évaluation de la toxicité de nombreux pesticides pour le développement, en particulier les insecticides, qui sont des substances neurotoxiques [16], n'a pas été considéré comme obligatoire en vue de l'homologation des pesticides [4]. Beaucoup d'entre eux sont également des perturbateurs endocriniens. Les pesticides représentent une grande source d'inquiétude, parce que la recherche indique maintenant que l'exposition – que ce soit à l'intérieur ou à l'extérieur des maisons – même avant la grossesse peut aussi affecter le neurodéveloppement d'une progéniture qui n'a pas encore été engendrée.

De surcroît, des études indiquent que plus un fœtus est exposé à des pesticides, plus il risque de subir des effets néfastes profonds sur son neurodéveloppement [20, 25, 32, 33]. L'exposition aux pesticides pendant la grossesse est celle qui présente la plus forte association avec l'autisme lorsqu'on la compare à l'exposition aux autres substances toxiques [15, 16]. Certains chercheurs signalent même que les risques peuvent être multipliés par deux à cinq [15]. Des études épidémiologiques ont révélé que la proximité du domicile de la mère avec une zone agricole d'application de pesticides avant qu'elle ne devienne enceinte et durant sa grossesse augmentait le risque d'autisme chez l'enfant [18] jusqu'à 60 % [16]. Des concentrations sériques élevées d'un sous-produit (le métabolite p,p'-DDE) découlant de la dégradation du DDT, un insecticide bien connu, chez des femmes enceintes ont été associées à une hausse de 32 % du risque d'autisme chez les enfants. De plus, les risques d'être atteint à la fois d'autisme et d'une déficience intellectuelle étaient plus que doublés dans ce groupe fortement exposé au produit [34]. Une étude plus récente indique même que l'exposition aux pesticides en bas âge accroît de 50 % le risque qu'un enfant autiste ait également une déficience intellectuelle [33].

## **5- Quels pesticides sont associés aux troubles du spectre de l'autisme?**

Selon la littérature scientifique, de nombreux pesticides ont un lien avec l'autisme, même à de faibles niveaux d'exposition jugés inférieurs à la plage de toxicité [35]. Les insecticides qui agissent sur le système nerveux font évidemment l'objet d'études compte tenu du rôle qu'ils pourraient jouer dans l'apparition de l'autisme. Parmi les familles de pesticides qui ont déjà été associées à l'autisme, mentionnons les carbamates [16], les composés organochlorés [20, 35], les composés organophosphorés [16, 20, 36, 37], les pyrèthriinoïdes [16, 20], les composés organobromés [33] et les dérivés des lactones macrocycliques [33]. Quant aux ingrédients actifs des insecticides associés à l'autisme, on trouve le DDT et son dérivé (le DDE) [34], le chlorpyrifos [16, 33, 35, 36], le diazinon ([33, 35]), le malathion [33], l'ivermectine [33], la perméthrine [33], la cyperméthrine [35], la bifenthrine [36], le dicofol et l'endosulfan [17, 35], ainsi que le bromométhane [33]. Outre les insecticides, des herbicides (glyphosate [33, 38] et glufosinate-ammonium [39, 40]), des fongicides (myclobutanil [33], phosphine [41], pyraclostrobine, trifloxystrobine, famoxadone et fénamidone [42]) et des rodenticides (roténone [42]) ont aussi été répertoriés dans les études montrant une corrélation avec l'autisme.

La succession de pesticides qui ont été commercialisés, et dont l'usage a ensuite été restreint, puis complètement interdit met en relief l'épée de Damoclès que représentent les substitutions malencontreuses. Tout cela sans compter certains pesticides du passé, comme le DDT, qui ont cessé d'être utilisés à plusieurs endroits, mais qui demeurent présents dans l'environnement, les aliments et l'eau en raison de leur persistance pendant des décennies après leur application.

## **6- Comment les mères et les enfants y sont-ils exposés?**

En plus d'être exposée librement aux pesticides durant leur application à l'intérieur ou à l'extérieur, la population générale est également exposée aux pesticides et à leurs métabolites par l'entremise de l'eau potable, des aliments, de la pollution atmosphérique, de la poussière, des insectifuges ainsi que des traitements contre les poux et les tiques chez les animaux domestiques [18, 25, 37, 43-46]. Dans le cas des enfants, la principale voie d'exposition semble être les aliments ingérés, bien que l'exposition soit aussi importante lorsque des pesticides sont utilisés à la maison. De plus, une étude réalisée au Québec en 2004 a montré que 99 % des 442 échantillons d'urine prélevés chez des enfants de 3 à 7 ans contenaient des résidus de pesticides organophosphorés [47]. Les enfants et les conjoint(e)s d'agriculteurs(trices) pourraient aussi être indirectement exposés aux pesticides par le contact avec des surfaces ou des vêtements contaminés.

## **7- Mécanismes biologiques des effets des pesticides sur le neurodéveloppement d'un fœtus**

La capacité de perturbation endocrinienne des pesticides est bien connue, tout comme leur tendance à perturber les signaux essentiels pour le neurodéveloppement [17, 29]. Les pesticides peuvent traverser la barrière hématoencéphalique et affecter plusieurs signaux biochimiques intervenant dans le développement du cerveau et du corps du fœtus [17]. Les pesticides peuvent également perturber les signaux véhiculés au moyen des neurotransmetteurs, des hormones ainsi que du sodium ou du calcium, et causer un déséquilibre dans les niveaux d'énergie cellulaire (dysfonction mitochondriale) [15, 16, 31, 36]. Par exemple, l'acétylcholine est un neurotransmetteur ciblé spécifiquement par plusieurs pesticides. Elle joue normalement un rôle essentiel dans l'apprentissage, l'attention et la mémoire. Or, on sait maintenant que sa concentration est réduite dans les lobes frontal et pariétal des enfants atteints d'autisme. Plusieurs études ont montré que la perturbation de l'équilibre fragile entre les neurotransmetteurs qui activent ou inhibent les influx nerveux peut mener à des troubles du neurodéveloppement, comme l'autisme et le trouble déficitaire de l'attention avec hyperactivité (TDAH) [48]. Qui plus est, les pyréthriinoïdes perturbent les neurotransmetteurs en raison de leur action sur la voie de signalisation du GABA [13].

L'exposition aux pesticides peut aussi causer de nombreuses interférences sur le plan biochimique dans notre corps, notamment un déséquilibre touchant les systèmes immunitaire et hormonal, une carence en nutriments et des modifications au sein même de l'ADN (mutations) ou dans son expression (altérations épigénétiques) [14, 15]. Par ailleurs, les pesticides peuvent provoquer un stress oxydatif dans les cellules par l'entremise de la production de dérivés réactifs de l'oxygène pouvant réduire la respiration cellulaire (fonction mitochondriale). Une diminution de la fonction mitochondriale est un trait récurrent de l'autisme [17]. Il est maintenant établi que les hommes, qui sont atteints d'autisme dans une proportion beaucoup plus importante que les femmes (ratio de 4:1), présentent un stress oxydatif plus élevé et des niveaux de glutathion (GSH) plus faibles

(suggérant une capacité de détoxification inférieure), et sont donc également plus sensibles aux effets de diverses substances toxiques, dont les pesticides [15]. Les enfants présentant l'autisme sont donc plus vulnérables aux actions synergiques sur les voies biochimiques, lesquelles sont en même temps perturbées par les substances toxiques, d'autant plus que la capacité de détoxification est réduite. Par conséquent, il est possible qu'ils métabolisent les substances toxiques d'une façon différente et qu'ils subissent les effets toxiques des polluants à une plus faible concentration en comparaison des enfants dont le développement est normal [15, 31].

### **8- Quels autres effets les pesticides peuvent-ils avoir sur la santé?**

Outre l'autisme, l'exposition aux pesticides cause une panoplie de problèmes sur le plan de la santé et du développement. Elle provoque des anomalies structurelles au cerveau, une microcéphalie et des déficits persistants sur le plan neurocomportemental [4], notamment une baisse du quotient intellectuel (QI) ou une déficience intellectuelle associée, un TDAH, ainsi qu'une perturbation des fonctions cognitives et motrices. Elle est également associée à des problèmes de fécondité, à l'obésité infantile et adulte, au diabète [29, 30, 49] et la leucémie infantile [50]. Pour cette raison, les enfants sont plus susceptibles, jusqu'à l'âge adulte, d'être atteints d'un des nombreux troubles de santé découlant d'une exposition aux pesticides. De plus, l'exposition des parents et des grands-parents peut être liée à des problèmes de santé chez les enfants ou les petits-enfants, même si ceux-ci n'y ont pas été exposés. C'est une observation que l'on a faite, par exemple, pour certains cas d'obésité chez des enfants dont les grands-parents ont été exposés à l'insecticide DDT. Ce phénomène est probablement dû à des facteurs épigénétiques, comme la méthylation de l'ADN [51]. Plus simplement, étant donné que de nombreux pesticides sont très persistants dans l'environnement [52], ils peuvent avoir une incidence sur la santé bien après leur application ou la restriction de leur utilisation.

### **9- Que pouvons-nous faire pour protéger les prochaines générations?**

Les effets néfastes à long terme des pesticides ont été qualifiés de « pandémie silencieuse » [53]. Les troubles neurodéveloppementaux qui en découlent représentant une charge financière bien trop lourde pour les personnes atteintes, leur famille et la société en général [29]. Selon un rapport rédigé en 2014 sur les coûts associés au soutien d'une personne autiste au Canada, la facture pour la prestation de soins à une personne atteinte d'une forme grave d'autisme tout au long de sa vie est plus élevée que celle pour une personne neurotypique d'environ 5,5 millions de dollars, et cela ne comprend que le temps consacré aux soins. Lorsqu'un adolescent ou un adulte qui présente une forme grave d'autisme nécessite des services résidentiels, le coût annuel d'hébergement, qui comprend le temps consacré aux soins prodigués par des intervenants, peut s'élever à 400 dollars par jour, soit environ 150 000 dollars par année [54]. Selon les statistiques de 2011 ayant trait aux États-Unis, le coût annuel total pour les soins aux enfants autistes se situerait entre 11,5 et 60,9 milliards de dollars. Ce fardeau économique important se décline en une variété de coûts directs et indirects, par exemple les soins médicaux,

l'adaptation scolaire incluant les écoles spécialisés et une plus faible productivité des parents au travail [55, 56]. Un autre rapport aux États-Unis montre que le coût des soins pour les Américains présentant l'autisme a atteint 268 milliards de dollars en 2015 et s'élèvera à 461 milliards de dollars en 2025 si des interventions et des soins plus efficaces ne sont pas mis en place pour s'occuper d'eux tout au long de leur vie [57].

Il est essentiel de protéger les enfants des prochaines générations et leur famille. La question qui s'impose est la suivante : Que fait-on pour protéger les futures mères et leurs fœtus de l'exposition aux pesticides?

Puisque des facteurs non génétiques ont une incidence sur les processus qui interviennent dans le neurodéveloppement pendant la période prénatale ou les perturbent, notre société, nos dirigeants et nos organismes de santé publique doivent prendre des mesures pour réduire l'exposition généralisée aux substances chimiques, en particulier les pesticides [5]. L'autisme constitue l'une des très nombreuses maladies chroniques dont la prévalence a connu une hausse marquée : asthme, diabète de type 1, syndrome métabolique, schizophrénie, troubles du sommeil, etc [2]. Ces maladies ont toutes une origine précoce, peuvent présenter plusieurs comorbidités et être associées à des facteurs environnementaux qui n'ont pas encore été décrits de façon précise [2]. « Une stratégie efficace de réduction des risques environnementaux pour l'une de ces affections ou maladies aura sans doute des effets qui pourraient s'étendre à d'autres désordres touchant le développement. » [2]

## **10- Quelles mesures doivent ou devraient être prises?**

La responsabilité de réduire la toxicité pour le neurodéveloppement dépend des mesures collectives qui seront prises [4]. Pour relever un tel défi, un plan d'action concerté comprenant des stratégies concrètes et exhaustives doit rapidement être élaboré et mis en application non seulement par les gouvernements fédéral et provinciaux au Canada, mais aussi à l'échelle internationale. Voici quelques-unes des stratégies qui devraient encadrer ces efforts au Canada :

### **10.1 Administration fédérale**

- Interdire toutes les substances toxiques pour la reproduction et tous les perturbateurs endocriniens, indépendamment de leurs propriétés cancérigènes.
- Réformer la *Loi canadienne sur la protection de l'environnement* et la *Loi sur les produits antiparasitaires*, notamment en faisant reposer les processus d'enregistrement et de réévaluation des pesticides sur des études scientifiques indépendantes plutôt que sur des études financées par l'industrie. Ces études devraient comprendre les volets suivants :
  - une évaluation approfondie de la formulation complète du pesticide plutôt que de ses ingrédients actifs seulement;

- une évaluation des effets à long terme sur la santé humaine et l'environnement;
- un examen approfondi dans le cas de tout pesticide pouvant affecter les neurotransmetteurs ou les signaux endocriniens afin de déterminer les effets sur le développement;
- la détermination des effets cumulatifs et synergiques dans le cadre de l'évaluation des risques en fonction des types d'utilisation des pesticides sur le terrain et de l'utilisation combinée d'autres pesticides dans l'environnement.
- Santé Canada doit réduire les « limites maximales de résidus » pour pesticides qui sont permis dans les aliments [37], l'eau et l'air à des niveaux qui sont sûrs pour les populations vulnérables, notamment les femmes enceintes et les enfants.
- Trouver et évaluer des solutions de rechange aux substances toxiques, et obliger l'industrie à démontrer qu'il n'existe pas de substituts plus sûrs.
- Rendre obligatoires la lutte intégrée et la promotion de méthodes de lutte non toxiques ou minimalement toxiques pour régler les problèmes que posent les organismes nuisibles en milieu résidentiel et agricole [37].
- Rendre obligatoire l'apposition d'étiquettes de mise en garde avec des symboles ou des couleurs faciles à reconnaître sur les produits toxiques vendus au grand public.
- Interdire les annonces publicitaires sur les pesticides dans tous les médias.
- Interdire toute forme de rabais pour les pesticides.
- Interdire le placement de produits pesticides dans les zones où la circulation est élevée dans les commerces (entrée ou sortie d'un magasin, emplacement à proximité d'une caisse enregistreuse, etc.).
- Ne pas autoriser la vente de pesticides dans les supermarchés ou les pharmacies.
- Obliger les entreprises qui fabriquent des pesticides à financer la recherche scientifique indépendante en cours qui porte sur les effets des pesticides sur la santé humaine et l'environnement en utilisant une structure de gouvernance qui prévient toute forme de conflit d'intérêts.

## **10.2 Administration provinciale**

- Restreindre ou interdire complètement l'utilisation de pesticides qui sont toxiques pour la reproduction et le neurodéveloppement, ainsi que les perturbateurs endocriniens.
- Améliorer et mettre à jour l'Indicateur de risque des pesticides du Québec (IRPeQ) – Santé et environnement. Cet indicateur doit reposer sur des données scientifiques indépendantes et à jour.
- Mettre en place un système numérique obligatoire pour suivre et déclarer toutes les applications de pesticides, pas seulement les applications des pesticides ayant le plus haut niveau de risque comme c'est le cas actuellement.
- Améliorer les systèmes de déclaration obligatoire pour les ventes au détail ou en gros de façon à ce qu'ils comprennent un outil numérique de transmission de l'information, ce qui permettra de produire des cartes régionales indiquant la

nature exacte des pesticides et le volume de leurs ventes. Ces renseignements aideront également à réaliser des études épidémiologiques pour protéger les citoyens et améliorer la prévention.

- Organiser une campagne accélérée de prévention et de sensibilisation qui sera menée par les établissements de santé publique [30] dans le but de protéger la santé et le développement des enfants des prochaines générations et de les prémunir contre les risques liés aux pesticides.
- Adopter une stratégie exhaustive de sensibilisation et de formation à l'intention des professionnels de la santé, notamment les médecins, les obstétriciens, les pédiatres, les psychologues, les spécialistes du développement, les thérapeutes pour enfants et les infirmières, sur les effets que les produits toxiques dans l'environnement, comme les pesticides, peuvent avoir sur les fœtus. Étendre si possible la formation à tous les professionnels paramédicaux, par exemple les sages-femmes, qui ont une mission de prévention et de suivi auprès des femmes enceintes.
- Mettre en place une formation obligatoire pour les agriculteurs, les jardiniers professionnels et les exterminateurs sur les effets des pesticides sur la santé.
- Mettre rapidement en œuvre des mesures économiques de dissuasion, comme une écotaxe additionnelle, au moment de l'achat ou de l'application de pesticides, surtout dans le cas d'une utilisation agricole. Les recettes de cette écotaxe pourraient être réinvesties dans l'élaboration de stratégies d'agriculture biologique.
- Offrir une incitation financière bonifiée aux agriculteurs pour qu'ils passent à l'agriculture biologique.
- Dans les zones urbaines, restreindre davantage l'utilisation des pesticides à l'intérieur et à l'extérieur des résidences et des bâtiments, notamment les établissements de santé, les écoles et les garderies.
- Dans les zones agricoles, restreindre l'utilisation des pesticides dans une zone d'au moins 2 km autour des maisons, des bâtiments et le long des routes publiques [16].
- Obliger les agriculteurs à annoncer publiquement à l'avance les applications de pesticides dans les champs (en tenant aussi compte de la direction du vent) pour réduire au minimum toute exposition inutile. Les campagnes de sensibilisation devraient aussi comporter des stratégies de protection des enfants et des maisons, comme fermer les fenêtres, éteindre les systèmes de climatisation et empêcher les enfants de jouer à l'extérieur pendant et après l'application, etc.
- Imposer des amendes salées aux entreprises et aux individus qui contreviennent aux divers règlements.

### **10.3 Administrations municipales**

- Interdire l'utilisation des pesticides cosmétiques à l'extérieur des maisons dans les municipalités qui n'ont pas encore un règlement à cet égard.
- Interdire la vente de pesticides dans les municipalités dont les règlements en restreignent l'utilisation.

- Pour favoriser l'adhésion du public et donner un ton positif aux réductions des pesticides, adhérer à des programmes de certification qui font la promotion de la biodiversité et de la réduction de l'utilisation des pesticides. Par exemple, voir le programme *Ville amie des monarches* de la Fondation David Suzuki.
- Mener des campagnes d'information et de sensibilisation qui visent à atteindre les objectifs suivants [30] :
  - Décourager l'utilisation de pesticides à l'intérieur en expliquant aux citoyens et aux entreprises les risques que posent les pesticides pour la santé humaine et l'environnement.
  - Approfondir les connaissances de base sur les insectes, ce qui peut accroître la tolérance du public à la cohabitation avec les insectes qui ne présentent pas de problèmes pour la santé ou l'intégrité des bâtiments, et ainsi réduire l'utilisation des pesticides à l'intérieur.
  - Encourager les comportements et les mesures qui permettent de réduire de façon marquée et stratégique les risques d'infestations résidentielles, comme prévenir la pénétration des insectes (en scellant les fissures et les ouvertures dans les murs des maisons), réduire l'attrait pour les insectes nuisibles (en améliorant le rangement des aliments et des déchets), réduire la nourriture et les sources d'eau disponibles pour les insectes nuisibles (en améliorant le nettoyage des maisons et les comportements des résidents) et limiter le risque de transport actif des insectes, notamment les punaises de lit, à l'intérieur des maisons (en inspectant les meubles et les plantes avant de les rentrer à l'intérieur et en mettant les bagages en quarantaine au retour d'un voyage).

## **Conclusion**

Les ramifications de l'exposition aux pesticides sont de toute évidence multiples pour les fœtus et les très jeunes enfants. Elles se traduisent par une panoplie de risques associés au neurodéveloppement, si bien que les pesticides constituent maintenant un enjeu de santé publique. Bien que ceux-ci fassent partie des nombreuses substances chimiques liées à l'apparition de l'autisme, ils peuvent et doivent faire l'objet de mesures collectives pour protéger le développement précoce du cerveau [33]. La société ne peut plus se permettre de fermer les yeux sur ce problème. Les risques et les coûts sont simplement trop élevés. Les motivations qui sous-tendent l'approbation de l'utilisation des pesticides ne doivent pas aller à l'encontre de la santé et de la sécurité du public. Il faut collectivement prendre les devants pour limiter l'exposition des citoyens aux pesticides, en particulier les personnes vulnérables, notamment les femmes enceintes et les enfants. Un programme de sensibilisation aux effets de l'exposition aux pesticides doit être mené et être articulé autour d'une campagne d'information et des stratégies de prévention auxquelles devra participer tout un éventail de professionnels de la santé et d'organismes gouvernementaux.

## **Annexe – Insecticides et herbicides bien connus associés à l'autisme selon diverses études**

**Composés organochlorés** – Initialement utilisés pour lutter contre la malaria transmise par les moustiques, les composés organochlorés, comme le DDT, ont été interdits aux États-Unis en 1972 [58]. Compte tenu du fait qu'ils sont très persistants, ils sont encore présents dans l'environnement et continuent de représenter un risque pour la santé humaine [59, 60]. Outre son lien avec l'autisme, l'exposition maternelle au DDT et à son métabolite, le DDE, est associée à des accouchements prématurés et à un faible âge gestationnel à la naissance [34]. Le DDE contribuerait également à une réduction des scores cognitifs, verbaux, de mémoire et neurodéveloppementaux [61] ainsi qu'à d'autres problèmes liés au neurodéveloppement, comme un réflexe automatique plus faible, des effets sur le plan psychomoteur et mental, des problèmes d'attention, l'hyperactivité et des troubles envahissants du développement [12].

**Composés organophosphorés** – Initialement mis au point pour remplacer les composés organochlorés, dont la toxicité est plus élevée, les composés organophosphorés posent malheureusement eux aussi un risque pour la santé humaine [17]. Même s'ils se dégradent plus rapidement dans l'environnement, ils ont été utilisés à profusion en milieu agricole et résidentiel. Le chlorpyrifos est le composé organophosphoré le plus utilisé aux États-Unis et en Europe [17, 29]. Il constitue aussi l'un des cinq pesticides les plus dangereux au Québec tant sur le plan de l'environnement que du point de vue de la santé humaine [62]. Malgré leur interdiction en milieu résidentiel en 2001 par le Environmental Protection Agency (EPA) des États-Unis, ces composés continuent d'être utilisés en milieu agricole, et ce type d'usage est associé à un risque élevé d'autisme, quel que soit le moment où a eu lieu l'exposition pendant la grossesse [32]. Deux études distinctes ont montré un lien entre les troubles envahissants du développement et la présence accrue de métabolites organophosphorés du chlorpyrifos dans l'urine [63] ou le plasma sanguin de cordon ombilical [64]. En Europe, l'exposition aux composés organophosphorés a été associée à un plus faible score sur l'échelle de QI et à une déficience intellectuelle [29]. Les concentrations accrues de chlorpyrifos dans le plasma de cordon ombilical ont été associées à un risque plus élevé de troubles envahissants du développement chez les enfants de 3 ans [65]. Par ailleurs, les enfants chez qui les concentrations de chlorpyrifos sont plus élevées que la normale présentent des modifications structurelles dans les régions du cerveau liées à l'attention, à la cognition sociale et au traitement du versant réceptif du langage [66].

**Pyréthroïdes** – Les pyréthrine sont des insecticides naturels extraits des fleurs de chrysanthème. Les pyréthroïdes sont leur version synthétisée chimiquement et sont plus persistants dans l'environnement. Tout comme les composés organophosphorés ont remplacé les composés organochlorés lorsque ceux-ci ont été interdits en raison de la découverte de leur toxicité, les pyréthroïdes ont à leur tour remplacé les composés organophosphorés à grande échelle pour la même raison. Il a été démontré que les pyréthroïdes avaient une incidence sur le neurodéveloppement par l'entremise de divers

mécanismes, dont l'interférence avec les neurotransmetteurs que sont la sérotonine et l'acide gamma-aminobutyrique (GABA), le stress oxydatif, la dysfonction mitochondriale, la perturbation endocrinienne et une altération des signaux calciques [13, 17]. Jusqu'à 75 % des enfants et des adultes et jusqu'à 80 % des adolescents aux États-Unis présentent des métabolites des pyréthroides dans leur urine [67].

**Glyphosate** – Le glyphosate est un herbicide organophosphoré. Le lien entre le glyphosate et l'autisme fait l'objet de nombreuses études et suscite un débat dans la littérature scientifique. D'abord, une corrélation entre l'utilisation accrue du glyphosate et une augmentation des cas d'autisme a été mise en lumière. Bien sûr, une corrélation ne signifie pas une relation de cause à effet. Mais comme le glyphosate est le pesticide le plus vendu dans le monde, une forte corrélation entre une hausse alarmante d'un grave trouble de la santé et une substance chimique ne peut être simplement mise de côté sans réaliser d'autres études [68]. Ensuite, plusieurs hypothèses sur les processus biologiques par lesquels le glyphosate pourrait mener à l'autisme ont été publiées (certaines sur la perturbation du flux calcique dans les neurones immatures [69], sur les propriétés de chélation du glyphosate et son effet sur la respiration cellulaire et la capacité de détoxification [70] ou bien sur la perturbation endocrinienne de la thyroïde [68]), mais comme aucune ne permet d'établir un mode d'action avec certitude, d'autres études sont nécessaires. Même si le glyphosate est un antibiotique breveté, son effet sur la flore intestinale n'est pas soumis aux analyses obligatoires menant à l'enregistrement d'un pesticide. Par conséquent, les symptômes de troubles gastro-intestinaux, comme la diarrhée et les selles molles, chez les animaux de laboratoire étudiés sont souvent rejetés pour des motifs de non-spécificité [71]. Toutefois, le rôle potentiel des antibiotiques et de la modification de la flore intestinale dans l'autisme suscite de plus en plus l'intérêt dans le milieu scientifique [72]. Il est donc urgent de mener des études scientifiques exhaustives pour faire la lumière sur ce lien potentiel.

**Glufosinate-ammonium** – Puisque la résistance des mauvaises herbes au glyphosate est en croissance, un nouvel herbicide qui lui est très apparenté, le glufosinate-ammonium, a fait son apparition. Comme c'est le cas pour la plupart des pesticides, les études réglementaires sur les effets néfastes potentiels liés à la neurotoxicité pour le développement font défaut. Récemment, une étude a révélé que la progéniture de souris exposées *in utero* à cette substance présentait des symptômes étonnamment semblables à ceux des modèles animaux sur les troubles du spectre de l'autisme [39].

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