A review of pesticide effects on sensitive receptors: children (draft)

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March 14, 2014

INTRODUCTION

Although pesticides are essential for eradicating pests in agriculture and for public health, they are toxic chemicals with lethal consequence if excessive exposure occurs. The widespread uses of pesticides can affect children's health in a variety of settings. In additional to dietary intake, children encounter pesticides at home, in parks and gardens, and on school ground daily. Children's behaviors, such as playing on the floor or ground/lawn where pesticides are commonly applied and putting objects/hands into their mouths, increase their chances of exposure to pesticides. Studies have shown that households with children are commonly found used and stored pesticide products. A survey on inventory pesticides in and around the home at California showed 95% of the households have stored at least one pesticide product [Guha N 2013]. Similarly, all 107 households with children in a non-agricultural community in Arizona [Bass JK 2001] and most (93%) of the 308 households with children in Minnesota [Adgate JL 2000] that stored pesticide products reported using the products during the time of survey. The use of pesticides at childcare facilities [Kim HH2013], athletic fields [Gilden R 2012], school ground [Alarcon WA 2005] could all presented potential exposures and health hazards to children.

Because children are still developing and maturing, their immunes may provide less protection and their enzymatic and metabolic systems may have less capability to detoxify and excrete pesticides than those of adults. Therefore, they are more vulnerable to pesticides. Epidemiological studies also support that pesticide exposure can have greater impact on children's health than adults [Sheets LP 2000, Faustman EM 2000]. Children expose to pesticide at homes or schools have experienced acute toxic effects on respiratory, gastrointestinal, nervous, endocrine systems, and other serious medical outcomes [Spann MF 2000, Landrigan PJ 1999, Alarcon WA 2005]. The concern of health effects associated with long-term low level exposure to pesticides in children is increasing in recent years, and leads to a substantial amount of epidemiological studies demonstrating the associations between pesticide exposures and childhood cancers [Zahm SH 1998, Infante-Rivard C 2007, Wigle DT 2009, Metayer C 2008, Turner MC 2010, Maele-Fabry 2011]. Prenatal and childhood pesticide exposure have also been linked to neurodevelopment and endocrine development disorders [Roberts JR 2012]. Nevertheless, most of the studies have focused on parental occupational exposure or agricultural exposure. There are a few reviews on residential pesticide exposure and childhood cancers, but the relationship was not clearly elucidated by including parental occupational exposures data in these reviews and

quantitative analysis or investigating multiple risk factors together which increasing chance findings due to multiple statistical testing [Metayer C 2008, Turner MC 2010, Maele-Fabry 2011]. There hasn't been any review reported on residential pesticide exposure on neurological development or asthma in children. In this review, we summarize currently available epidemiologic evidence on relationships between non-occupational/non-agricultural prenatal/maternal or childhood pesticide exposure and children's health, mainly on childhood cancer, and also on neurological development and asthma.

RESIDENTIAL PESTICIDE EXPOSURE ASSESSMENT IN CHILDREN

Residential pesticide use, both indoor and outdoor, could create a close source of exposure to children. Studies have shown that the prevalence and persistence of pesticide residues that are readily available for exposure once pesticides were used. In an earlier study, Lewis et al. (1994) found 23 of 30 target pesticides in indoor air, carpet dust, outdoor soil, or on the children's hands. The most frequently detected pesticides were chlordane, chlorpyrifos, dieldrin, hepatachlor, and pentachlorophenol. Gurunathan et al. (1998) showed that routine indoor application of pesticides could lead to continued accumulation in toys and other sorbent surfaces, e.g., pillows, with large sorbent reservoirs, which can become a long-term source of exposure to a child. They estimated that a 3-6-year-old child could receive a total non-dietary dose of 208 µg/kg/day in which dermal and nondietary oral doses from playing with toys contributed to 39 and 61% of the total dose, respectively. In another cross-sectional study with repeated measurements in children ages 2-5, Hore et al. (2005) showed that after the crack-and-crevice application, the average chlorpyrifos levels in the indoor air and surfaces were 26 (pretreatment)/120 (post-treatment) ng/m^3 and 0.48 (pretreatment)/2.8 (post-treatment) ng/cm^2, respectively, reaching peak levels between days 0 and 2; subsequently, concentrations decreased throughout the 2-week period. Chlorpyrifos in/on the plush toys ranged from 7.3 to 1,949 ng/toy post-application, with concentrations increasing throughout the 2-week period, demonstrating a cumulative adsorption/absorption process indoors. The daily amount of chlorpyrifos estimated to be absorbed by those children post-application ranged from 0.04 to 4.8 µg/kg/day.

Understanding behavioral patterns of young children is especially important as critical time windows in early development lead to higher vulnerability to the toxicity of pesticides. In addition, typical children's behaviors such as increased hand to mouth activity and crawling on floors/carpets and turf result in higher exposures. However, assessing children's exposures from residential, both indoor and outdoor, pesticide applications has

been a challenge because of the lack of detailed information on the manner and patterns of applications and exposure related behaviors. There are additional factors that have the potential to influence exposure, such as which rooms/areas are commonly treated coupled with how much time children spend in those rooms/areas will influence exposure. Additionally, activities following the application may modify exposures: opening windows to increase ventilation or cleaning surfaces after the treatment may decrease exposure, whereas allowing children to play in the treated area shortly after an application (when concentrations will be highest) may increase exposures. Those limitations reflect on the meager literatures in reporting children's exposures to residential pesticide uses and the adverse health effects. Regardless, there are several recent studies

A recent study (Wu et al. 2011) reported the residential insecticide usage and actual application details collected in a population-based sample of 477 households residing within 22 counties in northern California between January 2006 and August 2008. They collected information on residential use of insecticides, including outdoor sprays, indoor sprays, indoor foggers, professional applications, and pet flea/tick control during the previous year. Interviews also covered post-treatment behaviors, which influence post-application exposure levels. Altogether, 80% of the households applied some type of insecticide in the previous year, with half of this population using two or more application methods. Of the households using insecticides, half reported applying insecticides relatively infrequently (<4 times per year), whereas 11–13% reported high frequency of use (>24 times per year). In this study, Wu et al. (2011) showed that spot treatments appeared to be the most prevalent application pattern for sprays. For one out of three of the indoor applications, children played in the treated rooms on the day of the application, and for 40% of the outdoor applications, pets played in the treated area on the day of the application. These findings describing the intensity of insecticide use and accompanying behaviors in families with young children may inform future insecticide exposure modeling efforts, and ultimately, risk assessments. Babina et al. (2012) analyzed children living in urban, sub-urban, and rural areas in a cross-sectional study to demonstrate their pesticide exposures. They found widespread chronic exposure to organophosphate and pyrethroids, and exposure to more than one pesticide was common among those children. Approximately 92 and 97% of urine samples collected from those children living in urban and sub-urban areas, respectively, contained the urinary metabolite for a very common OP pesticide for uses in residential environment.

Very few studies specifically targeted at outdoor pesticide applications on turf, bushes, or trees in relate to children's exposure. Morgan et al. (2008) demonstrated that petting dogs to be an important exposure pathway for transporting pesticide residues into homes and onto its occupants (in particular young children) following residential lawn applications. They found the average pesticide loading on the fur clippings were at least 14 times higher on days 1, 2, 4, and 8 post-application than mean loadings (0.8+/-0.4 ng/cm^2) at pre-application. For transferable residues from dog fur, the mean loadings on the technician's cotton glove samples (surrogate to hands) were the lowest before application (0.04+/-0.08 ng/cm^2) and the highest on day 1 post-application (10.4+/-23.9 ng/cm^2) of pesticide to turf. Urinary metabolite concentrations for the participants ranged from <0.3 to 5.5 ng/mL before application and <0.3-12.5 ng/mL after application of pesticide on turf. Those results showed that the participants and their pet dogs were likely exposed to low levels of pesticide residues from several sources (i.e., air, dust, and soil), through several pathways and routes, after lawn applications at these residences. Lastly, the pet dog appears to be an important pathway for the transfer and translocation of pesticide residues inside the homes and likely exposed occupants through personal contacts (i.e., petting).

LITERATURE SEARCH

We conducted the literature search in PubMed for papers published prior to Jan 2014. We used the combinations of the following key words to identify relevant papers: residential OR urban OR indoor OR house OR home OR household OR school, AND pesticide OR residential insecticide OR herbicide OR fungicide, AND children OR childhood OR youth OR toddler OR prenatal OR postnatal OR maternal. The searches were limited in human studies and written in English, and yielded to 7,360 articles.

Selection criteria

We included original epidemiological studies focusing on assessing non-occupational pesticides exposure on children's health. We used the following criteria to exclude papers from this review and the meta-analysis. We excluded: 1) review articles, ecologic studies, case reports, or cluster investigations; 2) toxicological studies; 3) studies conducted on occupational settings, hazardous waste sites, farms, or proximity to agricultural pesticides; 4) studies involving adults; 5) studies involving pesticides in general (no pesticide groups) or not just pesticides but a list of chemicals; and 6) studies without reporting health related outcomes. We also excluded studies related to insecticides-treated mosquito nets (or similar methods) for malaria control in children.

Based on the abstracts of those 7,360 articles from the initial PubMed search, we selected 88 papers after applying the inclusion/exclusion criteria. The complete articles were obtained in order to determine their eligibility based on the inclusion/exclusion criteria, which yielded to 22 articles, 16 on cancer outcome, 4 on neurological development and 2 on asthma. Among those 16 articles on cancer outcome, we further excluded one study because part of the study population was from a region with high agricultural pesticide use. Finally, we have identified 21 studies totally and 15 relevant studies on cancer outcome.

Data extraction

From each study in cancer outcome, we extracted information about the study design, population characteristics, exposure assessment methods, the most relevant estimators odd ratio (OR), and the 95% confidence intervals (CIs). All the data/information were organized and showed in the following tables.

LITERATURE REVIEW

Among the 21 studies identified, 16 are case-control studies, 5 are cohort studies and one is correlation study. Based on these studies identified, pesticide exposure and health effects in children are reviewed in three endpoints: cancer, neurological development, and asthma.

Cancer

Fifteen case-controlled studies on the association of pesticides exposure and childhood cancer are included in this review. Among them, 7 studies were associated with leukemia and 5 with childhood brain tumor (CBT). The remaining 3 studies involved cases of Wilms tumor, neuroblastoma and childhood cancer in general. The characteristics of these studies are summarized in table 1.

Leukemia

Leukemia is the most common cancer in children and adolescents in the U.S., and about 3 out of 4 childhood leukemias are acute lymphocytic leukemia (ALL) [Ma h 2013; Smith MA 1999, Howlander N 2013a,b]. There are approximately 2,900 children and adolescents younger than 20 years diagnosed with ALL each year in the US [Smith MA 1999, Dores GM 2012]. Over the last three decades, the incidence of childhood ALL has been increasing from the annual rate of 27 case per million people during 1973-1998 to 35 cases per million people during 2006 -2010, and the number of children under 14 years old diagnosed with ALL increased more than 25% [Xie Y, 2003, Ma HQ 2013, Howlander N 2013a, b].

Six studies evaluated the relationship between household pesticide exposures and childhood leukemia in this review reported relatively consistent findings. They demonstrated the association between indoor insecticides use during pregnancy and childhood and the increased risk of childhood leukemia [Infante-Rivard 1999, Ma X 2002, Meinet R 2000, Urayama KY 2007, Rudant J 2007, Menegaux F 2006]. Positive association of the risk for childhood leukemia and indoor insecticides use by parents were found in five studies with odds ratios (ORs) of 2.99 (95%CI 2.42-2.82) [Infante-Rivard1999] and 1.7 (95%CI 1.1-2.4) [Menegaux F 2006] during childhood exposure, and 2.1(95%CI 1.1-4.3) [Ma X 2002], 2.1 (95%CI 1.7-2.5) [Rudant J 2007] and1.65(95%CI 1.10-2.47) [Urayama KY 2007] during pregnancy and/or childhood exposure. Meinet et al. (2000) only found weak association of OR of 1.2 (95%CI 0.9-1.6) during childhood exposure. Ma X (2002) also showed a statistically significant elevated risk of childhood leukemia associated with the use of

professional pest control services (OR=2.8, 95% CI, 1.4-5.7) during prenatal and postnatal period. A dose-response trend was observed by Ma X (2002) for the risks of leukemia among child who had household insecticides exposure in which ORs increase from 1.5 (95% CI 0.6-3.6) to 2.4 (95%CI 1.2-5.1) as the frequency of use index increased from 1-5 to >5.

Two studies investigated the association between the risk of non-Hodgkin lymphoma (NHL) and indoor insecticide use by parents during pregnancy and/or childhood, and both found positive association with OR of 1.8 (95% CI:1.3-2.6) [Rudant J 2007] and OR up to 2.8 (95% CI:1.1-7.2) depending of the frequency of use [Meinet R 2000]. Similar association was observed when insecticides were applied by professional pest controller (OR=2.6, 95% CI, 1.2-5.7) [Meinert R 2000]. Meinet R (2000) found a statistically significant dose-response trend (*P* =0.02) between frequencies of indoor household insecticide use during childhood and the risk of childhood lymphomas, the OR increased from 1.3 (95% CI 0.6-2.8) to 2.8 (95% CI 1.1-7.2) with the frequency of use increased from 1 to >10. The household insecticide use has not been associated with the risk of Hodgkin lymphoma (HL) and solid tumors in these studies [Meinet R 2000, Rudant J 2007].

The association of childhood leukemia or lymphoma with pesticide use in garden is less consistent. Infante-Rivard (1999) reported the prenatal (1 month before pregnancy to birth) and childhood (from birth to date of diagnosis) use of herbicides and insecticides in garden, yard or on plants by owners were also associated with increased risk of acute lymphoblastic leukemia (ALL), with the ORs of 1.82 (95%CI 1.31-2.52), 1.41 (95%CI 1.06-1.86), and 2.23 (CI 0.76-6.47) for insecticides used on plant insects, herbicides use, and pesticide for slugs and snails, respectively. The associations between yard herbicide use during pregnancy or childhood and ALL and NHL were also confirmed by Rudant's study (2007) with OR of 1.5 (95%CI 1.0-2.2). In this study, garden insecticide was only linked to NHL, but not ALL, when the insecticides were used during pregnancy by mother (OR=2.3; 95% CI, 1.1-4.9). Menegaux (2006) reported garden insecticide and fungicide, but not herbicide, uses during childhood were associated with ALL, with OR of 2.4 (95%CI 1.3-4.3) and 2.5 (95%CI 1.0-6.2), respectively. A few other studies didn't find exposure to pesticides in the garden during childhood were associated with the risk of childhood leukemia or lymphoma [Ma X 2002, Meinet R 2000, Leiss JK 1995].

Case-control studies have been mainly relied on self-report of pesticide uses via interviews. However, assessment of non-occupational pesticide exposure can be more challenging since study are usually less likely to be able to report history of uses and the

name of individual pesticides than farmers or occupational pesticide applicators [Zahm SH 1997]. In order to improve the accuracy of exposure assessment, Soldin (2009) determined organonphosphate (OP) exposure by both questionnaires and urinary analysis of their metabolites. Statistically significant differences were found between children with ALL and controls for two OP metabolites, diethyldithiophosphate (DEDTP) *(P* <0.05) and diethylthiophosphate (DETP) (*P* <0.03). Although the insecticide use from the questionnaires did not correlate with the pesticide concentrations measured in urine, more case mother (33%) than controls (14%) reported using insecticides at home (P<0.02).

The association between the genetic polymorphism and childhood ALL risk associated with pesticide exposure were investigated in two studies; however, the results are not conclusive. Genetic polymorphism is best described as the phenomenon in which variations of gene(s) existed in a sub-group of people in the population affect their abilities in metabolizing toxic chemicals. In a case-only study conducted by Infante-Rivard (1999), the interaction OR between CYP1A1 polymorphisms and pesticide exposure were increased among carriers of CYP1A1m1 and CYP1A1m2 mutations when their mothers during pregnancy or the child had exposed to indoor insecticides, with interaction ORs of 5.02 (95%CI, 1.00-25.09) and 4.31 (95%CI, 0.90-20.56), respectively. Since this is a case-only study, the results did not give us direct estimation of the effect of the exposure nor the genotype on risk of ALL. In another case-control study, Urayama (2007) reported a statically significant increased risk of ALL associated with four MDR1 SNPS,1236TT, 2677TA/TT/AA, and 3435TT genotypes, as compared to the respective homozygous wild-type genotypes, with interaction OR of 40.35 (95%CI, 3.00-542.60), 6.01 (95%CI, 1.12-32.23) and 8.86 (95%CI, 1.35-58.03), respectively. However, this association was only observed in a small subgroup of non-Hispanic White hyperdiploid ALL, but not in ALL among all race/ethnicities combine, or in non-Hispanic White and Hispanic children only. More studies are needed to investigate on the interaction between genetic polymorphism and pesticide metabolism in body and effect on childhood cancer.

Childhood brain tumor (CBT)

Increased risks of CBT associated with household pesticide exposure in mothers during pregnancy were reported in two studies. Prenatal exposure of herbicide from residential use has shown an elevated risk of childhood astrocytoma by 2 folds (OR=1.9; 95% CI, 1.2-3.0), but not primitive neuroectodermal tumors (PNET) [Shim 2009]. Prenatal exposure to pesticides treating flee/tick also showed an increase risk for CBT (OR=1.7;

95%CI, 1.1-2.6), in particular for children ages 0-4years old (OR=2.5; 95%CI, 1.2-5.5) [Pogoda JM 1997]. Elevated risk was also observed during childhood exposure. David (1993) reported the home pesticide use for nuisance pests (roaches, ants, spiders and mosquitoes) during childhood (from seven-month to diagnosis) showed significant elevated ORs for CBT, 3.4 (95%CI, 1.1-10.6) [Davis 1993]. In addition, the use of garden insecticides, carbaryl and diazinon, and yard herbicides during childhood (from birth to diagnosis) also showed significant elevated risk for CBT, with ORs of 2.4 (95%CI, 1.1-5.6), 4.6 (95%CI, 1.2-17.9) and 3.4 (95%CI, 1.2-9.3), respectively [Davis 1993]. However, the association between garden pesticides use and CBT was not confirmed by other studies [Leiss 1995, Pogoda JM 1997].

The interplay of pesticide exposure, genes, and the effect on CBT was reported by Nielsen (2005, 2010). The results indicated that constitutive genetic variations could influence pesticide metabolism in children. Strong interactions between genetic polymorphism of OP detoxification enzymes and insecticide treatment at home during childhood were observed in Nielsen's 2 studies. Nielsen (2005) first reported the strong association between CBT risk among children with *PON1*$_{\_108T}$ carriers, but not *PON1*$_{\_Q192}$ carriers, and with OR of 2.6 (95% CI, 1.2-5.5) for home pesticide uses during pregnancy and childhood [Nielsen 2005]. In next study, the authors reported the risk of CBT increased per PON1$_{-108T}$ allele (OR=1.8, CI1.1-3.0) and FMO1$_{_9536A}$ allele (OR=2.7, 95% CI,1.2-5.9) among children exposed to pesticides during childhood. The result indicated that insecticides (likely OP and carbamate insecticides) exposure during childhood might increase the risk of brain tumor in children with reduced ability to metabolized OP and carbamate insecticides.

Other childhood tumor

Existing literature on association between pesticide exposure and other types of childhood cancer are limited. One study reported a slight increased risk of Wilms tumor among children whose mothers reported home insecticide use during pregnancy or during childhood period (OR=1.4; 95% CI, 1.0-1.8) [Cooney MA 2007]. In another study, a modest association was observed between neuroblastoma in children and home pesticide use (mainly for ants and roaches), garden herbicide use and garden insecticide use by home owners during pregnancy or childhood period with ORs of1.6 (95% CI, 1.0-2.3), 1.9 (95% CI, 1.1-3.2) and1.3 (95% CI, 0.7-2.3), respectively [Daniel JL 2001]. Garden herbicide or insecticide use was also more strongly associated with neuroblastoma among children

diagnosed after 1 year old (OR=2.2; 95% CI, 1.3-3.6) than under 1year old. Yard treatment (most likely herbicide, 2,4-D) during childhood was found strongly associated with the risk of childhood soft tissue sarcomas (OR around 4) [Leiss 1995]. More studies are needed to confirm these risk associations.

Neurological development

The potential effects of pesticide exposure on children, in particular the neurodevelopmental health, are of interest to the society and the regulatory agencies. A growing number of studies investigating potential neurodevelopmental toxicity from long-term, low-level exposure during gestational and early postnatal period suggested organochlorine and OP exposure in early life, especially prenatally, may have adverse effects on children's neurodevelopment [Engel SM 2007,2011, Rauh VA 2006, 2012, Marks AR 2010, Bouchard MF, 2011, Grandjean P 2006]. However, most studies either lacked the specific information of the source of pesticide exposure, or focused on exposure related to occupation or agriculture where relatively higher doses of pesticide are used than residential places. One long-term follow-up study on evaluating cognitive behavior of children (6-12 years old) who have experienced hospitalization for acute OP poisoning before age three found that subtle but significant (p<0.05) impairment on verbal learning and the difficulties in retraining and controlling their motor behaviors [Kofman O 2006]. However, the study is limited by small sample size.

There are a few studies exploring the association between indoor pesticide use during prenatal exposures and neurodevelopment of infants. In a cohort study of 1980 subjects, Llop (2013) found indoor insecticide spray during pregnancy was associated with decrement in psychomotor development (β=-1.9; 95% CI:-3.4 - -0.5) in infants ages 11-23 months. Similar result was reported in a New York City cohort study in which prenatal exposure to chlorpyrifos was associated with decreased cognitive and psychomotor development at age 36 months [Lovasi GS 2011]. Chlorpyrifos was the most heavily used insecticide by pest control operators at the NYC public housing development, but it has been banned for residential use by EPA since early 2000 [Landrigan PJ 1999]. Very few studies have evaluated the potential neurological effects as a result of pyrethroids uses. In a cohort study of 348 subjects, Horten et al. (2011) found a negative association between prenatal exposures to piperonyl butoxide (a pyrethoid synergist) measured in personal air within home during pregnancy and delayed mental development in infants at age 36 months (OR=1.32; 95%CI 1.06-1.66), but not with permethrin, a commonly used pyrethroids in

indoor application. However, these associations became less consistent between indoor pesticide use during postnatal exposures and neurodevelopment [Engel SM 2011, Bouchard MF, 2011, Lovasi GS 2011]. More studies are needed to further confirm the association between indoor or residential pesticide exposure and the potential negative health effect on neurodevelopment in children.

Asthma

Very few epidemiological studies reported the association between pesticide exposure and respiratory health in children [Salameh PR 2003, Karpeti AM 2004, Merchant JA 2005, Liu B 2012]. A cross-sectional study demonstrated an association between chronic respiratory disease and any pesticide exposure at home, outside home, and parental occupational exposure in Lebanon children, with OR of 2.47 (95% CI 1.52-4.01) [Salameh PR 2003]. However, a correlation study conducted in New York City, NY showed that application of pyrethroids in the residential areas was not associated with increase in asthma exacerbations (RR =0.78; 95% CI 0.8-1.04) that requires emergency care at the population level, including children aged younger than15 [Karpeti AM 2004]. Available studies on chronic pesticide exposure and respiratory health in children are very limited.

POLICY IMPLICATION SYNTHESIS

From the regulatory perspectives, most of the pesticides that are legally registered and therefore used in the U.S. were eventually banned or restricted their uses. Pesticides, such as organocholorine (such as DDT), organophosphate (such as chlorpyrifos), and several carbamates (such as carbofuran), fell into this category. The driving force behind this phenomenon is the identification of the harms of those pesticides to ecological and/or human health after a period of uses. This list of pesticides banned for use in other countries is longer than in US because of the different perspectives of human health risk associated with the same pesticides. For instance, atrazine, a very commonly used herbicide as of today in US has been banned in European Union because of the reproductive hazards, specifically the birth defects.

As newer pesticides are being introduced to replace those obsolete chemicals, the lack of epidemiological studies to investigate their links to adverse health outcomes is entirely conceivable. Neonicotinoid insecticides are the perfect example. While several neonicotinoids (such as imidacloprid) are the most widely used insecticide in the world, there is essentially no epidemiological research associated with those pesticides. However, several recent toxicological studies may have shed light on its potential adverse health outcomes. For instance, neonicotinoids are known to selectively target insects' nicotinic acetylcholine receptors (nAChRs) and therefore were thought to pose less toxicity in mammals. However, recent data have shown that imidacloprid can change the membrane properties of neurons (Li et al. 2009), diminish sensorimotor performance, and elevate glial fibrillary acidic protein expression in the motor cortex and hippocampus of neonatal rats observed after in utero exposure at the sub-lethal levels (Dawson et al. 2010). Imidacloprid and other neonicotinoids have also been shown to agonize human α4β2 nAChR subtypes in which the α4β2 and α7 subtypes of nAChR in the developing brain are involved in neuronal proliferation, migration, differentiation, apoptosis, synapse formation, and neural-circuit generation (Shen et al. 2010). It has been shown that transient but essential expression of nAChRs during the perinatal stage has great importance for brain development (Kimura-Kuroda et al. 2012), and it is likely that neonicotinoids could affect these processes by the activation of nAChRs. Those toxicological studies will no doubt be used as the foundation for future epidemiological research.

Although epidemiological research is relatively limited in identifying the link between pesticide uses in residential, school ground, or parks and adverse health outcomes in young

children, the current scientific findings suggest the associations of pesticide exposure and several common childhood diseases. While the research community is working toward a better understanding of pesticide exposure and its association with disease etiology in children, there are several reasons that warrant an immediate action on the public policy implementation to mitigate the possible adverse heath outcome.

First of all, the association of residential pesticide exposure and childhood cancers is significant enough that merits a practical and effective intervention on reducing pesticide uses in the environment that children are often present. This is where the public health precautionary principle should be exercised. Secondly, more and more pesticides, both quantities and the numbers of pesticides, are being used in agriculture, residential environment, for cosmetic landscaping and public health purposes. This upward usage trend is partially due to the results of excessive use of pesticides. When the targeted organisms, such as bugs, weeds, or microorganisms, develop resistant to those pesticides, more and more pesticides are being used hoping to overwhelm the resistant phenomenon. This vicious cycle only further worsens the resistant problem, and therefore prompts more pesticide uses. Lastly, the changes of climate pattern in recent years may increase the survivals of many pests in the environment that requires chemical-base eradication. West Nile virus infestation is just one of the examples. It is therefore foreseeable that overall pesticide uses in the society will only be increasing. While some pesticide usages are legitimate and likely needed, some usages are deemed unnecessary and should be eliminated, or at least reduced in order to protect children's health.

"The Risk Cup" concept as used by US EPA's interim decision logic might be a good guidance for managing health risks as a result of pesticide exposure at the individual level (http://www.epa.gov/PR_Notices/pr97-1.html). The Risk Cup is essentially equal to the Reference Dose (RfD) of a specific pesticide at the level of exposure that a person could receive every day over a seventy-year period without significant risk of a long-term or chronic non-cancer health effect. While US EPA's intention of using the Risk Cup concept is for the purpose of approving new pesticide usage registration under the consideration that the Risk Cup for certain pesticides at the individuals is not "full", it actually undermines the core value of the "Risk Cup" concept which is analogical to the 1996 Food Quality Protection Act (FQPA). FQPA calls for assessing pesticide exposure and health risk based on aggregate and cumulative manners for pesticides that pose similar toxicological health endpoints. In the layman language, the law mandates that we shall regulate the same

pesticide from all possible exposure pathways that individuals could encounter, and then sum all pesticides that cause the same toxicological endpoints in humans. While the implementation of FQPA is at a very slow pace since 1996, the Risk Cup concept provides a practical and reasonable health risk management tool for protecting public health. The question to ask is “If the objective of the public policy is to take precautionary steps to prevent from chronic diseases caused by pesticides, what individuals or government should do to eliminate unnecessary pesticide exposures in order to ensure that we never fill up the Risk Cup?”

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