

1 Article

# 2 Daily Intake Estimation for Young Children's 3 Ingestion of Residential Dust and Soils 4 Contaminated with Chlorpyrifos and Cypermethrin 5 in Taiwan

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11

12 **Abstract:** We estimated the daily intakes of chlorpyrifos and cypermethrin via ingestion of indoor  
13 dust and outdoor soils using the Stochastic Human Exposure and Dose Simulation Model on a  
14 probabilistic approach for Taiwan's homes. Variable information for the daily intake estimation,  
15 such as concentration, ingestion rate, body weight, was adopted from previous studies. Monte  
16 Carlo simulation was performed with 1,000,000 iterations to simulate a single daily intake, which  
17 was shown in terms of percentage of the Acceptable Daily Intake (ADI) of either insecticide. The  
18 daily intakes were minimal with a 99% probability; at 99.9th percentile, however, the total intakes  
19 leaped to 13.1% and 20.0% of the respective ADIs of chlorpyrifos and cypermethrin. The sensitivity  
20 analysis indicated that concentration was the most determinant variable. Compared to the data of  
21 daily intakes via dietary ingestion of vegetables derived from a previous study, the estimated  
22 intakes by this study were considerable at the highest percentile, which referred to insecticide  
23 residues few days after insecticide application. Consequently, the non-dietary ingestion exposure  
24 to either insecticide was negligible in most cases; nevertheless, for those with indoor insecticide  
25 applications, the daily intakes for young children could be of concern. Frequently home cleaning is  
26 recommended to reduce the exposure.

27 **Keywords:** chlorpyrifos; cypermethrin; daily intake; home environment; Monte Carlo simulation;  
28 non-dietary ingestion; SHEDS model; Taiwan

29

## 30 1. Introduction

31 Taiwan is a perennially warm and humid island where pesticides are frequently used for  
32 agriculture and vector-borne disease control. A previous report indicated that Taiwan was among  
33 the top countries around the world in pesticide consumption [1]. With such substantial  
34 consumption in quantity, residues of insecticides present in residential environments are nearly  
35 inevitable. A pilot study conducted in Taiwan has demonstrated high detection rates of chlorpyrifos  
36 and cypermethrin in house dust, reflecting frequent use of insecticides in the homes [2]. Residues of  
37 insecticides in the home environment serve as a potential health threat to young children, because  
38 their hand-to-mouth behaviors may enhance the non-dietary ingestion exposure to insecticides [3].

39 Chlorpyrifos and cypermethrin are different types of insecticides (i.e., organophosphate,  
40 pyrethroid), but both serve as neurotoxic agents to kill bugs. A number of studies have indicated  
41 that prenatal exposure to organophosphate and/or pyrethroid insecticides is associated with  
42 children's behavioral disorders or neurodevelopmental problems [4-14]; moreover, recent studies

43 have found that postnatal childhood exposure to insecticides may have similar effects [15-18],  
44 suggesting young children's susceptibility to insecticides. The childhood exposure may occur via  
45 dietary ingestion, such as consumption of fruits and vegetables contaminated with insecticides, and  
46 via non-dietary ingestion (e.g., by mouthing behaviors), which is of great concern should the  
47 environment be highly contaminated. A previous study conducting an exposure assessment of  
48 chlorpyrifos on residential surfaces for young children at 3 – 6 years old one week after insecticide  
49 application has found the dose via non-dietary ingestion to be 126 µg/kg/day [3]. Another study  
50 using a probabilistic modeling framework to estimate children's non-dietary ingestion of  
51 chlorpyrifos has indicated the daily ingested chlorpyrifos being approximately 1,000 µg/day  
52 (median value) and slightly lower than 100 µg/day (median value) within and after the first week of  
53 application, respectively [19]. These estimates that show high doses few days after insecticide  
54 application suggest that non-dietary ingestion could be an important route of exposure to pesticides  
55 for children in the residential environments.

56 The modeling used in the previous study [19] is the Stochastic Human Exposure and Dose  
57 Simulation Model (SHEDS) for multiple pollutants, which is a probabilistic human-activity-based  
58 physical model developed by the U.S. Environmental Protection Agency (EPA) [20]. It is designed  
59 to estimate dust and soil ingestion exposure to pollutants, with application of videographic data of  
60 children's everyday activities indoors and outdoors to indicate frequencies and types of contact  
61 with various surfaces, instead of using tracer-element-based mass balance models [21]. In addition,  
62 this strategy of modeling predicts full variability distributions of dust and soil ingestion rates for  
63 age-specific groups (e.g., preschool children), which are better than traditional single-point  
64 estimates. Coupled with Monte Carlo simulation, a method using repeated random sampling to  
65 generate simulated data, SHEDS could provide a decent estimate of non-dietary dust and soil  
66 ingestion exposure to insecticides in home environment for young children, with variability and  
67 uncertainty being considered.

68 Since Taiwan uses large quantities of pesticides every year, it is interesting to know residential  
69 exposure to insecticide residues particularly for young children. The previous studies that  
70 estimated non-dietary ingestion exposure to insecticides were all conducted short after application,  
71 mimicking worst-case scenarios. This study intended to assess the exposure on a regular basis, and  
72 to include variability and uncertainty for the outcome. Thus, we introduced the concentration  
73 profiles of chlorpyrifos and cypermethrin previously measured from residential environments by  
74 our research team [2] and the dust and soil ingestion rates for 3 – 6 year old children estimated by  
75 SHEDS [21] to Monte Carlo simulation to predict the non-dietary ingestion exposure to chlorpyrifos  
76 and cypermethrin for young children in the home environments of Taiwan. To our best knowledge,  
77 this is the first study that estimates residential exposure via non-dietary ingestion of insecticides for  
78 children in Taiwan.

## 79 2. Materials and Methods

80 The formula for ingestion of dust or soils is as follows:

81

$$\text{Daily intake} = \frac{IR \times C \times CF}{BW} \quad (1)$$

82

83 Where

84

85 IR: Ingestion rate of dust or soils (mg/day)

86 C: Concentration of insecticide in dust or soils (chlorpyrifos or cypermethrin) (µg/g)

87 CF: Conversion factor ( $10^{-3}$  g/mg)

88 BW: Body weight of children (kg)

89

90 Distributions of the above variables are listed in Table 1. Ingestion rates of dust or soils  
91 adopted herein were modeled specifically for 3 – 6 year old children using SHEDS, because of high

92 frequency of mouthing behaviors and availability of adequate exposure data for this age group [21].  
 93 Concentrations of insecticides (chlorpyrifos, cypermethrin) for indoor dust and outdoor soils,  
 94 provided by our previous work [2], could be used for calculation with ingestion rates of dust and  
 95 soils, respectively. For those dust samples under limits of detection (LOD), halves of LODs were  
 96 used in place for dose estimation. Children's body weight data were adopted from the new growth  
 97 charts suggested and developed for Taiwanese children and adolescents [22]. The dust and soil  
 98 ingestion fits a lognormal distribution, as stated by Özkaynak et al. [21]; concentrations of  
 99 insecticides from our previous study were distributed lognormally, as shown by most common  
 100 environmental data. Each of the body weight distributions for different ages on the growth charts  
 101 appears to be skewed to the right, suggesting a lognormal distribution.  
 102

103 **Table 1.** Distributions of variables used in daily intake estimation for ingestion of dust and soils

Variable	N	Mean	SD	P5	P25	P50	P75	P95	Maximum
Ingestion rate of dust (mg/day) <sup>a</sup>	1,000	26.65	36.54	0.66	4.06	10.80	28.72	100.97	901.96
Ingestion rate of soils (mg/day) <sup>a</sup>	1,000	40.96	78.29	0.15	5.26	15.34	44.85	175.60	1367.37
Indoor concentration of chlorpyrifos in dust (µg/g) <sup>b</sup>	52	2.32	15.41	< LOD	0.08	0.11	0.30	0.91	112.34
Outdoor concentration of chlorpyrifos in soils (µg/g) <sup>b</sup>	57	4.27	23.10	< LOD	< LOD	< LOD	0.11	16.19	134.60
Indoor concentration of cypermethrin in dust (µg/g) <sup>b</sup>	52	18.33	55.92	< LOD	0.11	0.37	0.83	105.79	343.27
Outdoor concentration of cypermethrin in soils (µg/g) <sup>b</sup>	57	4.29	22.32	< LOD	< LOD	< LOD	0.11	16.47	134.20
Variable	P3	P15	P25	P50	P75	P85	P97		
Body weight of 3 – 6 year old children at (kg) <sup>c</sup>	13.5	15.1	15.8	17.3	19.0	20.1	22.9		

104 SD, standard deviation; P#, #th percentile; < LOD, under limit of detection.

105 <sup>a</sup> Derived from Özkaynak et al. [21]; ingestion rate of dust is a sum of dust via hand-to-mouth and object-to-mouth  
 106 behaviors.

107 <sup>b</sup> Derived from Hung et al. [2].

108 <sup>c</sup> Derived from Chen et al. [22]; distributions between 3 and 6 years old are combined.  
 109

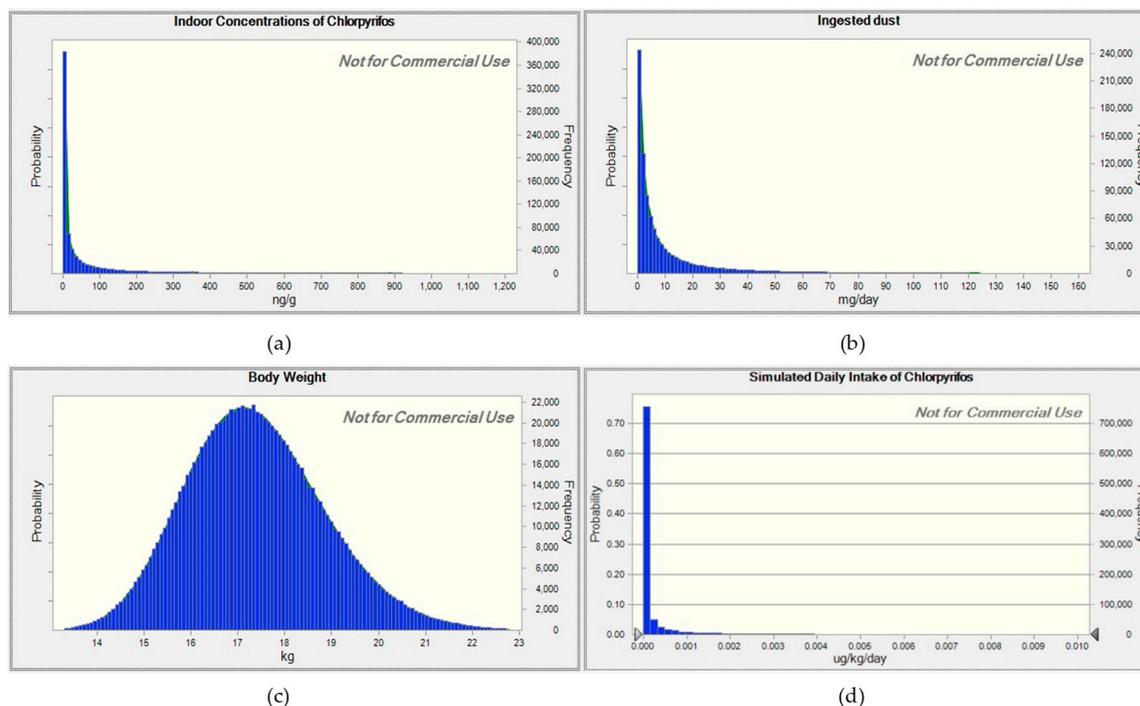
110 We applied Monte Carlo simulation as probabilistic modeling using Oracle® Crystal Ball  
 111 (Fusion Edition, Release 11.1.2.3.000), an add-on software to Microsoft® Excel 2010. The software  
 112 allows users to set up a distribution of data, instead of a value of mean or median, as input of a  
 113 variable. At each trial, data are randomly selected following the given distributions of variables to  
 114 compute an outcome value; such a trial can be repeated up to a hundred million times to derive  
 115 cumulative outcome values, which form a distribution as well with full simulated statistical  
 116 information (e.g., mean, median, standard deviation) (Figure 1). For estimation of the daily intakes  
 117 in this study, the variables of IR, C and BW were set as lognormal distributions with parameters  
 118 listed in Table 1, and doses of chlorpyrifos and cypermethrin via indoor dust and outdoor soil  
 119 ingestion were separately derived. Each simulation for dose estimation was performed with  
 120 1,000,000 iterations, and 30 replicates were completed to get better estimates.

121 For risk assessment of children's exposure to both insecticides, we followed a previous study  
 122 that expressed the estimated daily intakes as percentages of the Acceptable Daily Dose (ADI) values  
 123 for chlorpyrifos and cypermethrin [23], which were 0.01 and 0.02 mg/kg/day, in accordance with  
 124 World Health Organization (WHO) [24].

### 125 3. Results

126 The simulation results of daily intakes of chlorpyrifos and cypermethrin via ingestion of  
 127 indoor dust and outdoor soils for 3 – 6 year old children are presented in Table 2. As all variables in  
 128 the model appeared to be lognormal distributions, the simulation data were obviously accumulated  
 129 to form a lognormal distribution (Figure 1d). At the 90<sup>th</sup> percentile of the daily intake, neither  
 130 insecticide resulted in more than 0.1% of the respective ADI, indicating that the daily intake of

131 chlorpyrifos or cypermethrin for young children in the residential environment was negligible with  
 132 a probability more than 90%. The percentage of ADI increased as the percentile went up; at the P99,  
 133 the total daily intake of chlorpyrifos was raised to 1.30% of ADI (exposure to indoor dust and  
 134 outdoor soils), whereas that of cypermethrin was approximately 2.35% of ADI. In the extreme case  
 135 of P99.9, the total intakes leaped to 13.1% and 20.0% for chlorpyrifos and cypermethrin,  
 136 respectively.  
 137



138  
 139 **Figure 1.** Distributions of variables (a), (b) and (c), and result (d) for estimation of daily intake of chlorpyrifos  
 140

141 Monte Carlo simulation also conducted sensitivity analysis of modeling, determining which  
 142 variables had the greatest impact on the model. For the modeling of indoor dust ingestion, the  
 143 variable of C (concentration of either insecticide) was the one with the greatest impact, bearing a  
 144 value of contribution to variance around 82%, whereas IR (ingestion rate) only resulted in  
 145 approximately 18% and BW (body weight) had nearly zero impact (data not shown in table).  
 146 Ingestion of outdoor soils demonstrated a similar pattern with 91.4% and 8.5% for C and IR,  
 147 respectively, and no effect for BW. The sensitivity analysis indicated that concentration of  
 148 insecticide (C) was the principal factor that determined the daily intake.  
 149

150 **Table 2.** Non-dietary ingestion exposures in terms of percentage of ADI for young children

Percentile	Chlorpyrifos via indoor dust	Chlorpyrifos via outdoor soils	Cypermethrin via indoor dust	Cypermethrin via outdoor soils
P50	<0.001% (<0.001%, <0.001%)	<0.001% (<0.001%, <0.001%)	<0.001% (<0.001%, <0.001%)	<0.001% (<0.001%, <0.001%)
P75	0.002% (0.002%, 0.002%)	0.001% (0.001%, 0.001%)	0.004% (0.004%, 0.004%)	<0.001% (<0.001%, <0.001%)
P90	0.019% (0.019%, 0.019%)	0.007% (0.007%, 0.007%)	0.052% (0.052%, 0.053%)	0.005% (0.005%, 0.005%)
P95	0.079% (0.079%, 0.079%)	0.029% (0.029%, 0.029%)	0.208% (0.207%, 0.209%)	0.023% (0.023%, 0.023%)
P97.5	0.254% (0.253%, 0.255%)	0.102% (0.101%, 0.102%)	0.629% (0.627%, 0.631%)	0.080% (0.079%, 0.080%)
P99	0.884% (0.880%, 0.887%)	0.412% (0.410%, 0.414%)	2.042% (2.035%, 2.049%)	0.310% (0.308%, 0.311%)
P99.9	8.313% (8.234%, 8.392%)	4.819% (4.782%, 4.856%)	16.893% (16.745%, 17.042%)	3.155% (3.124%, 3.186%)

151 Numbers in parenthesis represent the 95% confidence intervals.

152 **4. Discussion**

153 As the sensitivity analysis shows, the estimated daily intake is mostly determined by the  
 154 variable of insecticide concentration in dust or soils (C), data of which are distributed unevenly  
 155 with the majority at the low end but few with extremely high values. The second influential  
 156 variable, ingestion rate (IR), appears to be less dispersed than C with a relative standard deviation  
 157 (RSD = SD/mean) of 1.37 (= 36.54/26.65), compared to an RSD of 6.64 (= 15.41/2.32) for C of  
 158 chlorpyrifos. The least variable with impact is body weight (BW), which results in an RSD of 0.086,  
 159 calculated from simulation modeling. It is apparent that variables with large variability turn to be  
 160 the determinant factors of simulation models, as is C in this modeling of daily intake.

161 The simulation modeling indicates that the daily intake of chlorpyrifos or cypermethrin is  
 162 minimal for the most occasions, suggesting that pesticide contamination in Taiwan's home  
 163 environments may not need to worry. The concentration profiles, adopted from our previous study  
 164 [2], monitored pesticide concentrations in residential environments using composite sampling. By  
 165 definition, a composite sample refers to "a physical mix of individual sample units or a batch of  
 166 unblended individual sample units that are tested as a group;" in such a way, the sample is "as  
 167 homogenous as possible" [25]. That is, the concentration profiles built by composite samples were  
 168 actually groups of mean insecticide concentrations of homes, implying concentrations higher than  
 169 mean values certainly occurring in "hot spots," such as rooms after application of insecticides. Thus,  
 170 our focus should lie on those estimates on the high end (e.g., P99, P99.9), the occurrence of which  
 171 may be sporadic but needs attention to be paid to.

172 Even at P99 or P99.9, the estimate daily intake of chlorpyrifos or cypermethrin is considered  
 173 safe, because the predicted results (<20% of ADI) are lower than ADI suggested by WHO [24].  
 174 Nevertheless, let us not forget that non-dietary ingestion is not the only route of exposure to  
 175 insecticides; dietary ingestion of vegetables or agricultural produce is a major route of insecticide  
 176 exposure. A Chinese study analyzing 2,083 vegetables for chlorpyrifos and cypermethrin in  
 177 Zhejiang Province has completed a risk assessment for daily intakes of both insecticides via dietary  
 178 ingestion on a probabilistic approach [23], providing valuable data for comparison with ours of  
 179 non-dietary ingestion (Table 3). Because those vegetables are also commonly consumed in Taiwan  
 180 and the regulations for pesticide residues are similar, we assume that the data of risk assessment  
 181 could be used as replacement of dietary ingestion exposure to insecticides in Taiwan. As seen in  
 182 Table 3, with a 99% probability dietary ingestion exposure to either insecticide outweighs  
 183 non-dietary ingestion exposure by a large margin; at P99.9, however, the ratio of dietary to  
 184 non-dietary ingestion exposure shrinks to 3.06 for chlorpyrifos and 1.30 for cypermethrin,  
 185 suggesting that home environment highly contaminated with insecticides may contribute  
 186 considerable doses to daily intakes for young children, compared to that via dietary ingestion.

187  
 188 **Table 3.** Comparison of non-dietary and dietary ingestion exposures in terms of percentage of ADI

Percentile	Chlorpyrifos via non-dietary ingestion	Chlorpyrifos via dietary ingestion <sup>a</sup>	Cypermethrin via non-dietary ingestion	Cypermethrin via dietary ingestion <sup>a</sup>
P50	<0.001% (<0.001%, <0.001%)	1.39% (1.35%, 1.42%)	<0.001% (<0.001%, <0.001%)	1.67% (1.64%, 1.70%)
P75	0.003% (0.003%, 0.003%)	NA	0.004% (0.004%, 0.004%)	NA
P90	0.026% (0.026%, 0.026%)	15.52% (15.35%, 15.70%)	0.057% (0.057%, 0.058%)	10.55% (10.44%, 10.67%)
P95	0.108% (0.108%, 0.108%)	NA	0.231% (0.230%, 0.232%)	NA
P97.5	0.356% (0.354%, 0.357%)	24.07% (23.69%, 24.47%)	0.709% (0.706%, 0.711%)	15.94% (15.68%, 16.19%)
P99	1.296% (1.290%, 0.887%)	29.03% (28.43%, 29.66%)	2.352% (2.343%, 2.360%)	19.09% (18.70%, 19.52%)
P99.9	13.095% (13.016%, 13.248%)	40.16% (38.39%, 42.41%)	20.048% (19.869%, 20.228%)	26.07% (24.87%, 27.42%)

189 NA, not available.

190 Numbers in parenthesis represent the 95% confidence intervals.

191 <sup>a</sup> Data for 2 – 6 years old in the whole province of Zhejiang, derived from Yuan et al. [23].

192

193 The comparison in Table 3 also indicates that daily intake of dietary ingestion of either  
194 insecticide raises gradually as the percentile goes up, unlike that of non-dietary ingestion remaining  
195 at very low levels until reaching the highest percentile. As discussed before, the estimation of daily  
196 intake is mostly determined by insecticide concentration; thus, the difference between the two  
197 ingestion routes is probably due to much smaller variability for insecticide residues in vegetables  
198 than that in dust or soils. Yuan et al. [23] reported the maximum concentrations of either insecticide  
199 in vegetables to be  $<10 \mu\text{g/g}$ , whereas the environmental data used in this study showed the highest  
200 levels above  $100 \mu\text{g/g}$  (Table 1). This fact can be reasonably explained because insecticide  
201 application for vegetable farming is regulated, meaning that residues of insecticides are supposedly  
202 kept under the standards, and variability of the distribution of insecticide residues is limited. In  
203 contrast, concentrations of insecticides in dust may be largely different, from none to extremely  
204 high levels. For instance, an indoor application of insecticides could sustain much higher levels than  
205 that of residues in vegetables for weeks [3, 19]. Even though the ingestion rate of dust is minimal  
206 compared to that of vegetables, the estimated daily intake of dust/soil ingestion is as significant as  
207 that of vegetable ingestion in a home environment that is highly contaminated with insecticides.  
208 Therefore, for homes with need of indoor applications of insecticides, the daily intakes for young  
209 children should not be overlooked, particularly for the first few days after application.

210 The trend that dietary ingestion is the major route of insecticide exposure with non-dietary  
211 ingestion catching up at the high percentiles is in support of the work of Xue et al. [26], which used  
212 EPA's SHEDS-multimedia model to estimate pyrethroid intakes for 3 – 5 years old. They  
213 estimated the doses for the general population and specifically for people with pyrethroid use in  
214 the homes (i.e., residential use population), and found that exposure via non-dietary ingestion  
215 prevailed over that via dietary ingestion above the 95<sup>th</sup> and 75<sup>th</sup> percentiles for the general  
216 population and residential use population, respectively. The difference between our result and  
217 theirs is that the estimated daily intakes of non-dietary ingestion from this study do not top that of  
218 dietary ingestion of vegetables at any chance, indicating that the residential concentrations of  
219 insecticides in Taiwan were lower than those measured from American homes. This is supported  
220 by a comparison of pyrethroid concentrations in dust among various studies made in our previous  
221 study [2], which shows the lowest median ( $0.37 \mu\text{g/g}$ ) and P75 values ( $0.83 \mu\text{g/g}$ ) for Taiwan's home  
222 environments. Despite the slight difference between this work and other western studies,  
223 non-dietary ingestion exposure to insecticides could be considerable as the environmental levels are  
224 elevated. Frequent home cleaning is recommended to reduce insecticide residues as well as the  
225 intakes for young children.

226 The environmental data used herein comes from a pilot study, and may not fully reflect the  
227 distribution of insecticide residues in Taiwan's houses. In southern cities and counties of Taiwan,  
228 insecticide applications are more frequently conducted than that in other parts of the island for  
229 vector control (e.g., dengue fever) during the warm and hot months, and the residential insecticide  
230 concentrations are expected to be elevated; therefore, the non-dietary ingestion exposure to  
231 insecticides could be of special concern in those homes with 3 – 6 year old children.

## 232 5. Conclusions

233 Concentrations of residential insecticide residues are the major determinant factor of the  
234 estimation of daily intake via non-dietary ingestion for young children. The daily intake is rarely of  
235 concern until the environment is highly contaminated with insecticides (e.g., after an indoor  
236 application). It is estimated that the occurrence of such a contamination could bring the intake of  
237 non-dietary ingestion exposure close to that of dietary ingestion exposure in the homes of Taiwan,  
238 and the total intake would approach the recommended ADI. Frequent home cleaning is necessary  
239 for homes with need of insecticide applications to lower the exposure of young children.  
240

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245 Lih-Ming Yiin contributed to study design, performed data analysis and wrote the manuscript.  
246 **Conflicts of Interest:** The authors declare no conflict of interest.  
247

248 **References**

- 249 1. 2005 Environmental Sustainability Index, Benchmarking National Environmental Stewardship. Available  
250 online: [http://archive.epi.yale.edu/files/2005\\_esi\\_summary\\_for\\_policymakers.pdf](http://archive.epi.yale.edu/files/2005_esi_summary_for_policymakers.pdf) (accessed on 14 May  
251 2018).
- 252 2. Hung, C.C.; Huang, F.J.; Yang, Y.Q.; Hsieh, C.J.; Tseng, C.C.; Yiin, L.M. Pesticides in indoor and outdoor  
253 residential dust: a pilot study in a rural county of Taiwan. *Environ Sci Poll Res* (under review).
- 254 3. Gurunathan, S.; Robson, M.; Freeman, N.; Buckley, B.; Roy, A.; Meyer, R.; Bukowski, J.; Liroy, P. J.  
255 Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. *Environ Health*  
256 *Perspect* **1998**, 106, 9-16.
- 257 4. Andersen, H.R.; Debes, F.; Wohlfahrt-Veje, C.; Murata, K.; Grandjean, P. Occupational pesticide exposure  
258 in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age.  
259 *Neurotoxicol Teratol* **2015**, 47, 1-9.
- 260 5. Bouchard, M.F.; Chevrier, J.; Harley, K.G.; Kogut, K.; Vedar, M.; Calderon, N.; Trujillo, C.; Johnson, C.;  
261 Bradman, A.; Barr, D.B.; Eskenazi, B. Prenatal exposure to organophosphate pesticides and IQ in  
262 7-year-old children. *Environ Health Perspect* **2011**, 119, 1189-1195.
- 263 6. Eskenazi, B.; An, S.; Rauch, S. A.; Coker, E. S.; Maphula, A.; Obida, M.; Crause, M.; Kogut, K.R.; Bornman,  
264 R.; Chevrier, J. Prenatal exposure to DDT and pyrethroids for malaria control and child  
265 neurodevelopment: the VHEMBE cohort, South Africa. *Environ Health Perspect* **2018**, 126, 047004. doi:  
266 10.1289/EHP2129.
- 267 7. Eskenazi, B.; Marks, A.R.; Bradman, A.; Harley, K.; Bart, D.B.; Johnson, C.; Morga, N.; Jewell, N.P.  
268 Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children.  
269 *Environ Health Perspect* **2007**, 115, 792-798.
- 270 8. Gunier, R.B.; Bradman, A.; Harley, K.G.; Kogut, K.; Eskenazi, B. Prenatal Residential Proximity to  
271 Agricultural Pesticide Use and IQ in 7-Year-Old Children. *Environ Health Perspect* **2017**, 125, 057002. doi:  
272 10.1289/EHP504.
- 273 9. Marks, A.R.; Harley, K.; Bradman, A.; Kogut, K.; Barr, D.B.; Johnson, C.; Calderon, N.; Eskenazi, B.  
274 Organophosphate pesticide exposure and attention in young Mexican-American children: the  
275 CHAMACOS study. *Environ Health Perspect.* **2010**, 118, 1768-74. doi: 10.1289/ehp.1002056.
- 276 10. Harari, R.; Julvez, J.; Murata, K.; Barr, D.; Debes, F.; Bellinger, D.C.; Grandjean, P. Neurobehavioral deficits  
277 and increased blood pressure in school-age children prenatally exposed to pesticides. *Environ Health*  
278 *Perspect* **2010**, 118, 890-896. doi: 10.1289/ehp.0901582.
- 279 11. Roberts, J. R.; Karr, C. J. Pesticide exposure in children. *Pediatrics* **2012**, 130, e1765-1788.
- 280 12. Muñoz-Quezada, M.T.; Lucero, B.A.; Barr, D.B.; Steenland, K.; Levy, K.; Ryan, P.B.; Iglesias, V.; Alvarado,  
281 S.; Concha, C.; Rojas, E. Neurodevelopmental effects in children associated with exposure to  
282 organophosphate pesticides: a systematic review. *Neurotoxicology* **2013**, 39, 158-168.
- 283 13. Fluegge, K.R.; Nishioka, M.; Wilkins, J.R., 3rd. Effects of simultaneous prenatal exposures to  
284 organophosphate and synthetic pyrethroid insecticides on infant neurodevelopment at three months of  
285 age. *J Environ Toxicol Public Health* **2016**, 1, 60-73.
- 286 14. Furlong, M.A.; Barr, D.B.; Wolff, M.S.; Engel, S.M., Prenatal exposure to pyrethroid pesticides and  
287 childhood behavior and executive functioning. *Neurotoxicology* **2017**, 62, 231-238.
- 288 15. Viel, J.F.; Rouget, F.; Warembourg, C.; Monfort, C.; Limon, G.; Cordier, S.; Chevrier, C., Behavioural  
289 disorders in 6-year-old children and pyrethroid insecticide exposure: the PELAGIE mother-child cohort.  
290 *Occup Environ Med* **2017**, 74, 275-281.

- 291 16. Viel, J.F.; Warembourg, C.; Le Maner-Idrissi, G.; Lacroix, A.; Limon, G.; Rouget, F.; Monfort, C.; Durand,  
292 G.; Cordier, S.; Chevrier, C. Pyrethroid insecticide exposure and cognitive developmental disabilities in  
293 children: The PELAGIE mother-child cohort. *Environ Int* **2015**, *82*, 69-75.
- 294 17. van Wendel de Joode, B.; Mora, A.M.; Lindh, C.H.; Hernandez-Bonilla, D.; Cordoba, L.; Wesseling, C.;  
295 Hoppin, J. A.; Mergler, D. Pesticide exposure and neurodevelopment in children aged 6-9 years from  
296 Talamanca, Costa Rica. *Cortex* **2016**, *85*, 137-150.
- 297 18. Yu, C.J.; Du, J.C.; Chiou, H.C.; Chung, M.Y.; Yang, W.; Chen, Y.S.; Fuh, M.R.; Chien, L.C.; Hwang, B.;  
298 Chen, M.L. Increased risk of attention-deficit/hyperactivity disorder associated with exposure to  
299 organophosphate pesticide in Taiwanese children. *Andrology* **2016**, *4*, 695-705.
- 300 19. Zartarian, V.G.; Ozkaynak, H.; Burke, J.M.; Zufall, M.J.; Rigas, M.L.; Furtaw, E.J., Jr. A modeling  
301 framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue  
302 contact and nondietary ingestion. *Environ Health Perspect* **2000**, *108*, 505-514.
- 303 20. USEPA. Stochastic Human Exposure and Dose Simulation (SHEDS) to estimate human exposure to  
304 chemicals. Available online: [https://www.epa.gov/chemical-research/  
305 stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure](https://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure) (accessed on 23 April  
306 2018).
- 307 21. Özkaynak, H.; Xue, J.; Zartarian, V.G.; Glen, G.; Smith, L. Modeled estimates of soil and dust ingestion  
308 rates for children. *Risk Anal* **2011**, *31*, 592-608.
- 309 22. Chen, W.; Chang, M.-H., New growth charts for Taiwanese children and adolescents based on World  
310 Health Organization standards and health-related physical fitness. *Pediatr Neonatol* **2010**, *51*, 69-79.
- 311 23. Yuan, Y.; Chen, C.; Zheng, C.; Wang, X.; Yang, G.; Wang, Q.; Zhang, Z. Residue of chlorpyrifos and  
312 cypermethrin in vegetables and probabilistic exposure assessment for consumers in Zhejiang Province,  
313 China. *Food Control* **2014**, *36*, 63-68.
- 314 24. FAO/WHO. Pesticide residues in food 2006, Joint FAO/WHO Meeting on Pesticide Residues. Available  
315 online: [http://www.fao.org/fileadmin/templates/agphome/documents/Pests\\_Pesticides/JMPR/  
316 JMPRrepor2006.pdf](http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/JMPRrepor2006.pdf) (accessed on 30 April 2018).
- 317 25. USEPA. EPA Observational Economy Series, Volume 1: Composite Sampling. Available online:  
318 <https://www.epa.gov/sites/production/files/2016-03/documents/comp-samp.pdf>. (accessed on 1 May  
319 2018).
- 320 26. Xue, J.; Zartarian, V.; Tornero-Velez, R.; Tolve, N.S., EPA's SHEDS-multimedia model: children's  
321 cumulative pyrethroid exposure estimates and evaluation against NHANES biomarker data. *Environ Int*  
322 **2014**, *73*, 304-311.