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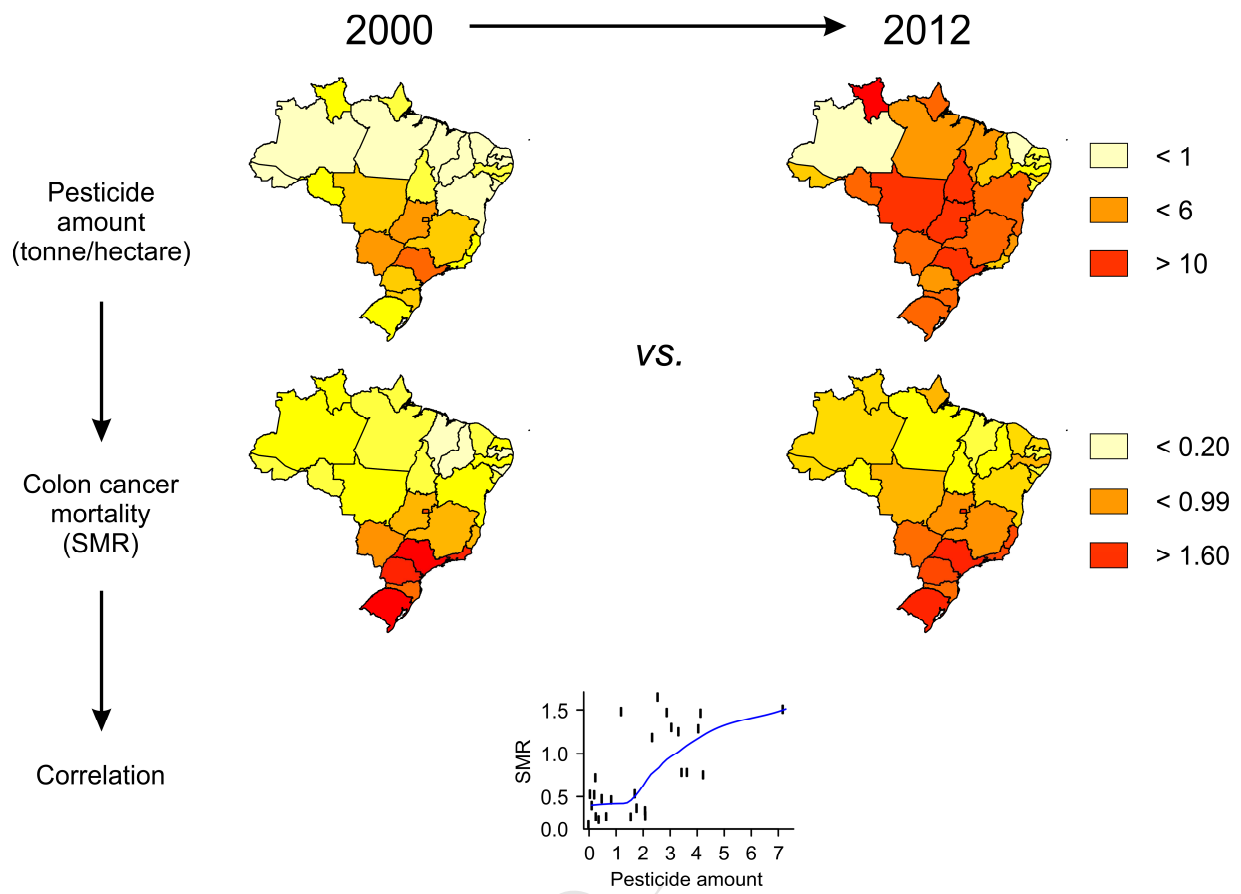
Increased exposure to pesticides and colon cancer: Early evidence in Brazil

Francis L. Martin, Edson Z. Martinez, Helga Stopper, Sergio Britto Garcia, Sergio Akira Uyemura, Vinicius Kannen

1 **Increased exposure to pesticides and colon cancer: early evidence in Brazil**

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15 **Running title:** Pesticide and colon cancer

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**ABSTRACT**

Environmental factors may increase colon cancer (CC) risk. It has been suggested that pesticides could play a significant role in the etiology of this malignancy. As agriculture is one of the mainstays of the Brazilian economy, this country has been the largest pesticides consumer worldwide. The CC burden is also increasing in Brazil. Herein, we examined data from the Brazilian Federal Government to determine whether CC mortality and pesticide consumption may be associated. Database of the Ministry of Health provided CC mortality data in Brazil, while pesticides use was accessed at the website of Brazilian Institute of Environment and Renewable Natural Resources. The CC mortality in the Brazilian states was calculated as standard mortality rates (SMR). All Bayesian analysis was performed using a Markov chain Monte Carlo method in WinBUGS software. We observed that colon cancer mortality has exhibited a steady increase for more than a decade, which correlated with the amount of sold pesticides in the country. Both observations are concentrated in the Southern and the Southeast regions of Brazil. Although ecological studies like ours have methodological limitations, the current dataset suggests the possibility that pesticide exposure may be a risk factor for colon cancer. It warrants further investigation.

**1. Introduction**

Colon cancer (CC) has afflicted humans for millennia. Chronic exposure to certain environmental factors appears to be the key to better understanding the etiology of this malignancy (David and Zimmerman, 2010). Over-nutrition and sedentary lifestyle may also be responsible for up to 75% of cancers today (Nebert and Dalton, 2006; David and Zimmerman, 2010). Notably, CC is one of the leading cause of cancer-related deaths (Torre et al., 2015). By 2030, developing countries are expected to exhibit a sharp increase in CC cases (Arnold et al., 2016). Also, it should be pointed out that recent epidemiological trends highlight that the CC burden is shifting towards a younger population (de Magalhaes, 2013; Siegel et al., 2014).

Cancer risk, including CC, appears to be profoundly influenced by environmental factors (Wu et al., 2016). Thus, CC etiology is complex, meaning that a multiple of environmental factors may cause this disease. One of many hazardous and carcinogenic factors promoting malignancies, pesticides have been suggested by the International Agency for Research on Cancer (IARC) to increase cancer risk in humans (Guyton et al., 2015; Guyton et al., 2016). Extensive epidemiological studies support the idea that pesticides are a risk factor for solid tumors (Parron et al., 2014). There has also been some evidence that pesticides promote CC in both humans and rodents (Soliman et al., 1997; Tellez-Banuelos et al., 2016; Hong et al., 2017). It seems feasible that pesticides contaminate human food sources (Nagao and Sugimura, 1993; Lodovici et al., 1997; Sakita et al., 2017), a fact that may be related to increased cancer risk (Arrebola et al., 2015). Another point underlying to study the relationship between pesticides and cancer

must be considered: disease incidence is increasing dramatically (Lodovici et al., 1997; Soliman et al., 1997; Agudo et al., 2009; Andreotti et al., 2010; Boccolini Pde et al., 2013; Parron et al., 2014; Arrebola et al., 2015; Carnero et al., 2015; Coggon et al., 2015; Guyton et al., 2015; Guyton et al., 2016; Tellez-Banuelos et al., 2016; Hong et al., 2017).

Furthermore, the lack of epidemiological and experimental data that accurately correlate CC incidence with detection of individual cancer initiators impairs our current ability to determine the impact of environmental factors on the CC development in humans (Tomasetti and Vogelstein, 2015). For instance, various environmental pollutants were reported to induce DNA damage and adducts, but the precise evolution of such genomic damages into mutations that promote CC remains unknown (Tomasetti and Vogelstein, 2015; Poirier, 2016). Then, it should be considered that instead of those DNA-damaging effects induced by initiators, endogenous and exogenous cancer promoters are classically determined to lead mutated cells towards clonal expansion, enabling them to collect further genomic changes by either high proliferative activity or new carcinogenic hits (Irigaray and Belpomme, 2010). Rather than binding to DNA, a cancer promoter usually activates transcriptional and epigenetic mechanisms that induce proliferation but inhibit apoptosis (Irigaray and Belpomme, 2010; Engstrom et al., 2015). Such mechanistic activity has for long been known to induce proliferation intrinsic errors leading to mutations and the development of CC (Ames and Gold, 1990; Bartkova et al., 2005; Gorgoulis et al., 2005). Interestingly, pesticides may act either as carcinogens or cancer promoters (Agudo et al., 2009; Andreotti et al., 2010; Arrebola et al., 2015; Carnero et al., 2015; Coggon et al.,

97  2015). Of note is the fact that Brazil has been the most significant consumer of

98  pesticides worldwide for years (Boccolini Pde et al., 2013). Recently, we have

99  hypothesized that pesticides could impact on the CC risk (Uyemura et al., 2017).

100  Herein, we propose an association between increased CC mortality and

101  pesticide consumption in Brazil. This could suggest that pesticides alter the risk of

102  CC in a human population.

103

104  **2. Materials and methods**

105  *2.1. Collection of public data*

106  CC mortality (http://www2.datasus.gov.br/DATASUS/index.php?area=0205) was

107  collected from the database of the Ministry of Health. The quantity of pesticides

108  (tonnes) sold within the country was downloaded from the website of the Brazilian

109  Institute of Environment and Renewable Natural Resources

110  (http://dados.contraosagrotoxicos.org/pt_PT/dataset/comercializacao-ibama-2014;

111  http://www.ibge.gov.br/). Complementary data on pesticides and farmed land area

112  for each Brazilian state ($Km^2$) were collected from the Brazilian Institute of

113  Geography and Statistics (http://www.ibge.gov.br/).

114

115  *2.2. Statistical analyses*

116  The CC mortality in the Brazilian states was calculated as standard mortality rates

117  (SMR). Further information on SMR can be found in a previous report authored by

118  Ulm (Ulm, 1990). We determined SMR to be the ratio of observed mortality to

119  expected mortality adjusted for age and gender group. An SMR value >1 indicates

120  excessive mortality. Expected numbers of death were calculated using age and

121   gender-specific mortality rates for the Brazilian general population (assumed to be

122   the standard population). Within this approach, w(s,t,f) was the death rate for the

123   Brazilian population at the year t (t = 1 if 2000, t = 2 if 2001, and so on) considering

124   gender s (s = 1 if women and s = 2 if man) and age group f (f  = 1 if <50 y old, f = 2

125   if 50 to 59 y, f = 3 if 60 to 69 y, f = 4 if 70 to 79 y and f = 5 if ≥80 y). The expected

126   number of death for each Brazilian state p (p = 1, …, 27) in the year (t) according

127   to the gender (s) is given by:

128

$$E(p,s,t) = \sum_{f=1}^{5} w(s,t,f) \times m(p,s,t,f),$$

129

130   where m(p,s,t,f) is the number of inhabitants of the state (p) with gender (s) at the

131   year (t) and group age (f). The SMR is thus given by:

132

$$SMR(p,s,t) = \frac{Y(p,s,t)}{E(p,s,t)},$$

133

134   where $Y(p,s,t)$ is corresponding observed mortality. Spatio-temporally smoothed

135   SMR values were obtained from a Bayesian model based on the Poisson

136   distribution. This statistical model is given by:

137

138   $Y(p,s,t) \mid \mu(p,s,t), E(p,s,t) \sim Poisson\,[E(p,s,t) \times \mu(p,s,t)],$

139

140 where $\mu(p,s,t) = \exp[\alpha_0 + \alpha_{sp} + \omega(p,s,t)]$ is the parameter that describes the SMR,

141 $\alpha_0$ is an intercept, $\alpha_{sp}$ are bivariate random effects that capture spatial dependence

142 in the data ($s = 1,2$, $p = 1,\ldots,27$) and $\omega(p,s,t)$ models the longitudinal trend of

143 annual mortality rate for the federation unit $p$ and gender $s$, considering a

144 multivariate Gaussian process with a mean vector 5 x 1 with all components equal

145 to zero and a given covariance function. In the Bayesian analysis, it was assumed

146 that $\alpha_{sp}$ follows a conditionally bivariate autoregressive (CAR) structure and $\alpha_0$

147 follows a non-informative normal distribution with mean zero and a large variance.

148 Then, we verified the association between the HDI of each Brazilian state

149 and the corresponding SMR, for which a Bayesian model was fitted to the data.

150 Thus, $\mu(p,s,t)$ was replaced by:

151

152 $$\mu(p,s,t) = \exp[\alpha_0 + \alpha_{sp} + \beta_{st} x(p)],$$

153

154 where $x(p)$ is the amount of sold pesticide (measured in tonnes) recorded in each

155 Brazilian state ($p$) at the year 2000, divided by its respective total cultivated area in

156 hectares (including permanent and temporary crops) and multiplied by 1,000, and

157 $\beta_{st}$ is the corresponding effect. Credible intervals for $\beta_{st}$ that do not include zero

158 indicates a significant correlation between the amount of sold pesticide and the

159 mortality rate. Credible intervals are the Bayesian analogues to the traditional 95%

160 confidence intervals. In all Bayesian analysis, the posterior distributions were

161 simulated using a Markov chain Monte Carlo (MCMC) method in WinBUGS

162 software.

163

164    **3. Results**

165    CC has not only been suggested to be one of the commonest malignancy types in

166    Western countries (Torre et al., 2015) but also that its incidence and mortality may

167    increase throughout the next decade in developing countries (Arnold et al., 2016).

168    This notion inspired us to apply the Bayesian model to calculate SMR values for

169    CC mortality in the Brazilian population. Heatmaps revealed that mortality by CC

170    mainly occurred in the Southern Brazilian states (Figure 1 and 2).

171        Environmental factors are well-known able of increasing cancer risk (Wu et

172    al., 2016). In addition, the IARC has suggested that pesticide can promote human

173    risk of developing different types of cancer (Guyton et al., 2015; Guyton et al.,

174    2016). In developing countries, some research groups report that pesticides may

175    increase cancer incidence (Soliman et al., 1997; Fonnum and Mariussen, 2009; Yi,

176    2013; Arrebola et al., 2015). Herein, we analyzed the quantity of pesticide sold in

177    Brazil. We should note that these records were reported by the Federal

178    Government in tonnes for each state, and are the most accurate dataset available

179    to the public. To provide a better perspective of pesticide distribution in each

180    Federal unit, we rated pesticide values by the total cultivated area that was

181    officially reported for each of those Brazilian states. We observed a dramatic

182    increase in pesticide usage from 2000 to 2012 within the country, mainly in the

183    Southern, Southeast and Central-West regions of Brazil (Figure 3).

184        Next, we examined whether both events were correlated in the Brazilian

185    population. We found an increase in SMR values correlating with the amount of

186    pesticide sold by 2000 in Brazil (Figure 4 and 5). Smoothed curves fitted by loess

187    were added on each graph. Moreover, it shows 95% credible intervals for the

188    effects ($\beta_{st}$) of the amount of sold pesticide on the SMR values for each year (*t*)

189    and gender (*s*), obtained from the Bayesian spatiotemporal regression models.

190    From 2000 to 2007, the credible intervals do not contain zero, thus suggesting a

191    significant effect of the amount of sold pesticide recorded in each Brazilian state on

192    their corresponding SMR for CC (Figure 6).

193

**4. Discussion**

195    We should initially consider that some environmental chemicals damage the DNA,

196    whereas other promote the expansion of mutated cells during the development of

197    CC (Lawrence et al., 2013; Tomasetti and Vogelstein, 2015; Poirier, 2016),

198    meaning that we can no longer hypothesize that only DNA damaging compounds

199    impact on the cancer risk in humans. Indeed, it seems that the mutation rate

200    intrinsic to mitosis might be sufficient in invoking oncogenic changes in the rapidly

201    dividing colonic epithelial cell population (Bartkova et al., 2005; Gorgoulis et al.,

202    2005). This was initially observed in classical experiments of rodents exposed to

203    cancer promoters (Ames and Gold, 1990). Persistent epithelial self-renewal

204    requires precise molecular regulation of proliferation in component cells that is,

205    consequently, prey to corruption by environmental and mutational factors. It is,

206    therefore, no surprise that the majority of cancers originated in epithelial tissue are

207    due to somatic mutations that deregulate the molecular constraints on cell

208    pluripotency and proliferation (Lawrence et al., 2013; Tomasetti and Vogelstein,

209    2015; Vogelstein and Kinzler, 2015).

210        Manmade compounds (xenobiotics) can access the human body *via* multiple

211    routes, each modifying the risk of cancer (Sakita et al., 2017; Uyemura et al.,

212 2017). This requires that the increasingly large number of chemicals whose

213 cancer-causing effects remain unknown should be taken into account while

214 discussing the impact of environmental factors on CC risk (Guha et al., 2016).

215 Indeed, most pesticides might have endocrine-disrupting and metabolic effects, as

216 well as bio-accumulating in the human body (Irigaray and Belpomme, 2010; Soto

217 and Sonnenschein, 2010; Walker and Gore, 2011; Ellsworth et al., 2015; Espin

218 Perez et al., 2015; Maqbool et al., 2016). It means that whether pesticides interact

219 at low levels and may increase the risk of cancer, their activity does not need to be

220 simultaneous or continuous. Combining several exposures to different pesticides at

221 multiple time-points could, thus, induce far greater cancer-related effects than

222 single compounds in humans (Goodson et al., 2015).

223       The massive number of modern xenobiotics has made almost impossible to

224 determine what their precise impact on human cancer risk is (Bouvard et al., 2015;

225 Goodson et al., 2015). For instance, a research group analyzed 6000 human-made

226 compounds and found that 16.3% of those chemicals were pesticides, from which

227 less than 1% had been investigated in the context of cancer (Guha et al., 2016).

228 Alavanja and colleagues studied the effects of 50 commonly used pesticides in

229 56,813 pesticide applicators and found a potential relationship between exposure

230 to chlorpyrifos and aldicarb with the incidence of colorectal cancer (CRC) (Lee et

231 al., 2007). A meta-analysis study suggested that aldicarb could increase the CC

232 risk, imazethapyr may promote the cancer risk in the proximal colon region, and

233 CRC risk was probably enhanced by exposure to pendimethalin, chlorpyrifos,

234 chlordane, and toxaphene (Alexander et al., 2012). Considering the complex CC

235 etiology together with the little number of epidemiological and experimental data

236  correlating CC development with the environmental pollution by pesticides

237  becomes clear that further efforts are required to clarify this matter.

238      In Tunisia, foodstuffs containing pesticides were suggested to increase the

239  risk of breast cancer in women (Arrebola et al., 2015). Different Brazilian research

240  groups have reported high-pesticide levels in human milk in the country (Matuo et

241  al., 1992; Beretta and Dick, 1994; Dorea et al., 1997). Pesticide levels in bovine

242  milk have been reported to exceed safety standards in the Midwest region of Brazil

243  (Avancini et al., 2013). Then, public data from the Brazilian National Health

244  Surveillance Agency (Anvisa; http://portal.anvisa.gov.br/en/programa-de-analise-

245  de-registro-de-agrotoxicos-para) show that 20% of food samples analyzed

246  between 2013 and 2015 were unsafe for human use. In 2013, Meyer and

247  colleagues revealed that pesticides could be related to increased non-Hodgkin's

248  lymphoma mortality found in Brazil (Boccolini Pde et al., 2013). Koifman and

249  colleagues hypothesized that cancer-related mortality in Brazilian farm workers

250  could be related to their exposure to pesticides from 1979 to 1998 (Meyer et al.,

251  2003). Meyer and colleagues suggested that the amount of pesticides selected in

252  1985 could be related to breast, prostate, and ovarian cancer mortality ten years

253  later (Koifman S., 2002). In Martinique, pesticides increased the risk of prostate

254  cancer (Landau-Ossondo et al., 2009). In South-Korea, pesticides increased CC

255  risk (Fonnum and Mariussen, 2009; Yi, 2013). Indeed, high-pesticide serum levels

256  were detected in CC patients in Egypt (Soliman et al., 1997). In rats, pesticides

257  increased the risk of CC (Hong et al., 2017). Then, another research group

258  suggested that pesticides might increase CC risk by promoting inflammation in the

259  colon (Tellez-Banuelos et al., 2016).

260    Although there has been some evidence that pesticides could be a risk

261  factor for CC (Soliman et al., 1997; Lee et al., 2007; Fonnum and Mariussen, 2009;

262  Alexander et al., 2012; Yi, 2013; Hong et al., 2017), other limitations in studying the

263  effects of these chemicals in cancer have to be considered. Carcinogenic effects of

264  human-made pollutants usually require protracted exposure to be detectable. For

265  instance, asbestos-related effects increasing lung mesothelioma have been

266  reported to take over 63 years to develop (Hodgson et al., 2005). However, we

267  should also consider that asbestos has an established effect in promoting this type

268  of malignancy in the lungs (Hodgson et al., 2005), while the complex activity of

269  multiple pesticides in different types of cancer makes almost impossible to suggest

270  which pesticide directly increases the CC risk in the human population. Moreover,

271  other confounding factors could also have similar effects promoting CC risk. For

272  instance, dietary factors seemed to be one of the main risk factors promoting this

273  disease in humans (Sakita et al., 2017). Notably, a 10% increase in the intake of

274  ultra-processed food furthered by 10% the cancer risk in humans (Fiolet et al.,

275  2018). In Brazil, the risk of developing CRC was related to the high consumption of

276  meat (Angelo et al., 2016). Here, we should also consider that human food sources

277  have been suggested to be contaminated by pesticides in Brazil (Matuo et al.,

278  1992; Beretta and Dick, 1994; Dorea et al., 1997; Avancini et al., 2013; Uyemura et

279  al., 2017). This scenario is quite severe since some types of food with known

280  carcinogenic potential could have a more hazardous effect if they contained

281  pesticides in their composition. Indeed, we do not claim to have found that

282  pesticides cause CC mortality in Brazil, but current evidence should not be ignored

283  and requires further study.

284       Nevertheless, from our perspective, the CC mortality rates in the Brazilian

285    state Amapá, located at the North region of the country, seems to be an outlier.

286    CC-related death numbers varied from the lowest to the highest rates in the

287    country by 2005. This increase reversed over the subsequent period. Lima and

288    Queiroz analyzed the Brazilian death registry system and found that completeness

289    of death registration in this state was one of the poorest in the country (Lima and

290    Queiroz, 2014). Hence, we advise future studies to have careful consideration on

291    this matter while investigating mortality rates during this period in that Brazilian

292    state.

293

**5. Conclusion**

294

295       We believe that protracted exposure to pesticide may be a potential risk

296    factor for CC. This fact requires urgent attention from the Federal Government

297    monitoring the exposure of Brazilians to such chemicals. Whereas authorities must

298    oversee the activity of multinational agrochemical and agricultural biotechnology

299    corporations, as well as pesticide usage in agriculture, farmers should be informed

300    by awareness programs to improve their product quality without harming the

301    human population with high pesticide residue levels in the environment and food.

302

**Conflict of interest statement**

303

The authors disclose that no competing interests exist.

304

305

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306

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311

312   **Authors' role**

313   Study concept and design: VK; Acquisition of data: VK and EZM; Statistical

314   analysis: EZM; Analysis and interpretation of data: All; Drafting the first version of

315   the manuscript: FLM and VK; Critical revision of the manuscript: All; Obtained

316   funding: VK; Study supervision: FLM, EZM and VK.

317

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**Figure Legends**

**Fig.1.** Smoothed standard mortality rates for CC in the Brazilian male population in each state of the country, as calculated by the Bayesian model.

**Fig.2.** Smoothed standard mortality rates for CC in the Brazilian female population in each state of the country, as calculated by the Bayesian model.

**Fig.3.** Heatmaps show the amount of sold pesticide recorded in each Brazilian state by total cultivated area (1000 x tonne /hectare) from 2000 to 2012.

**Fig.4.** Scatterplots of the relationship in the Brazilian male population between SMR values and the amount of sold pesticide recorded in each state of the country by total cultivated area (1000 x tonne/ hectare) from 2000 to 2012.

**Fig.5.** Scatterplots of the relationship in the Brazilian female population between SMR values and the amount of sold pesticide recorded in each state of the country by total cultivated area (1000 x tonne/ hectare) from 2000 to 2012.

**Fig.6.** Credible intervals for the effects $\beta_{st}$ of the amount of sold pesticide on the SMR values for each year (*t*) and gender (*s*), obtained from the Bayesian spatiotemporal regression models.

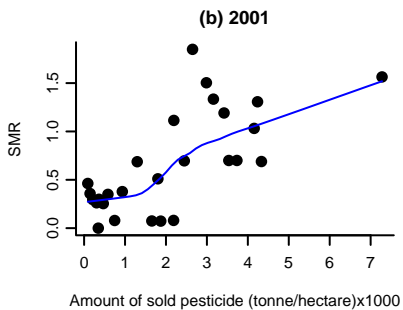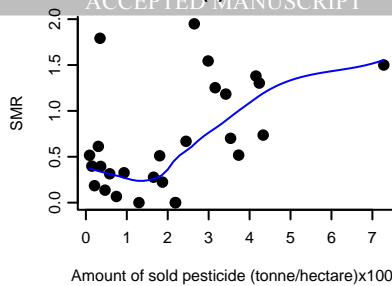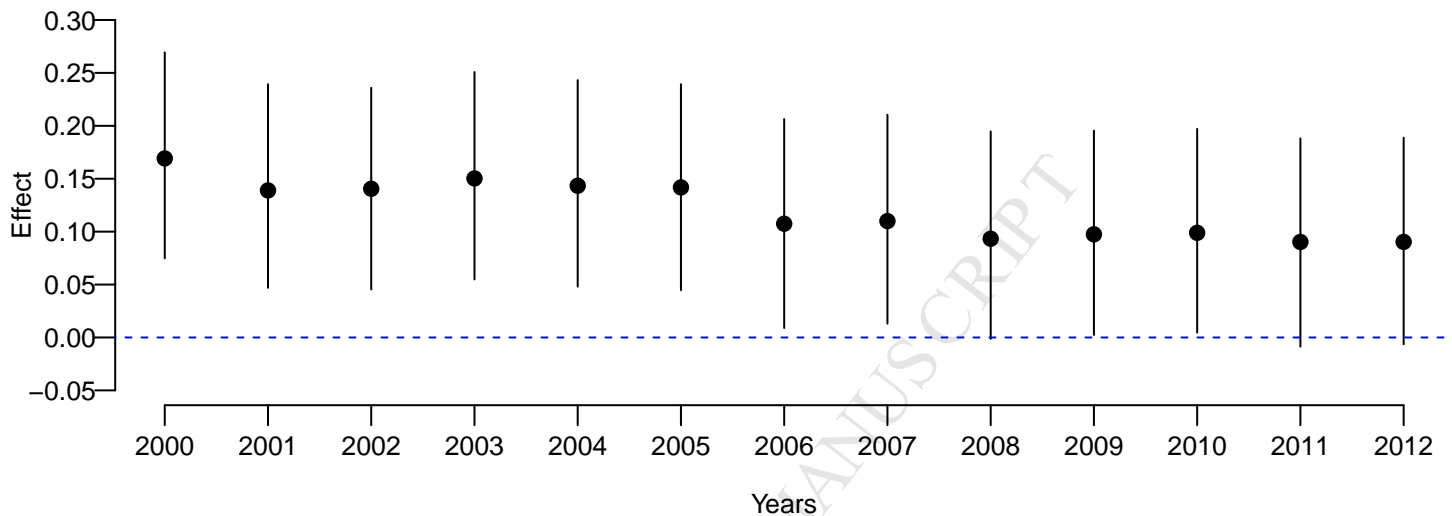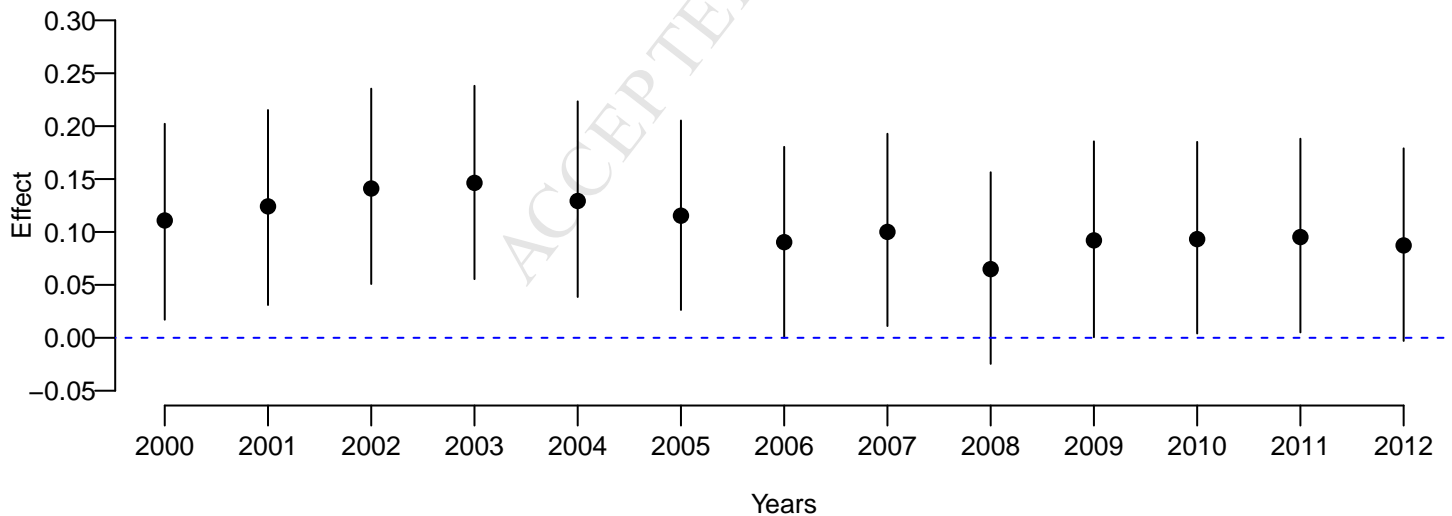| | |
|---|---|
| ☐ | Less than 0.20 |
| ☐ | 0.20 – 0.29 |
| ☐ | 0.30 – 0.39 |
| ☐ | 0.40 – 0.59 |
| ☐ | 0.60 – 0.79 |
| ☐ | 0.80 – 0.99 |
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| ☐ | 1.20 – 1.39 |
| ☐ | 1.40 – 1.59 |
| ☐ | 1.60 or more |
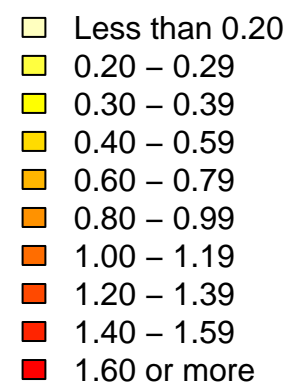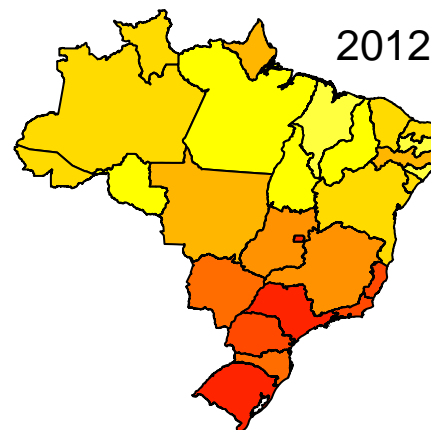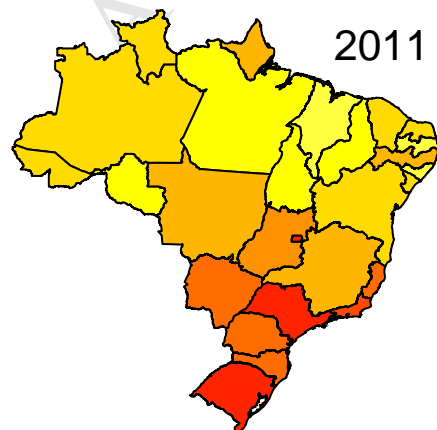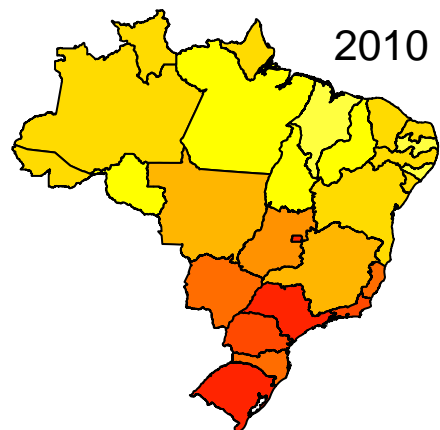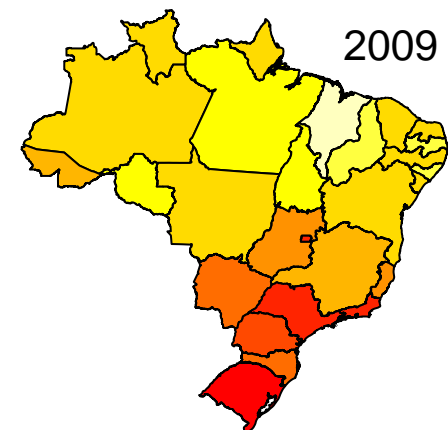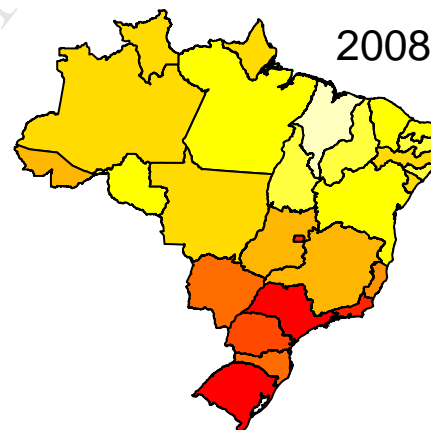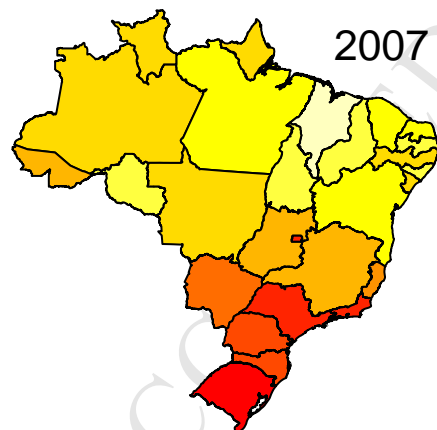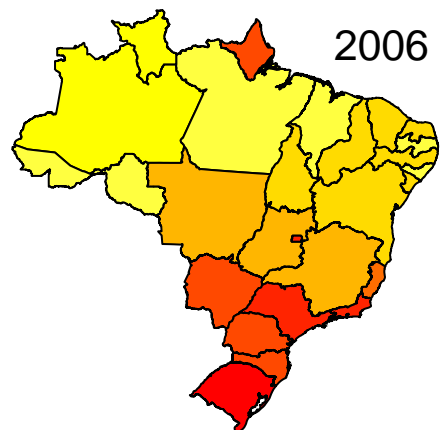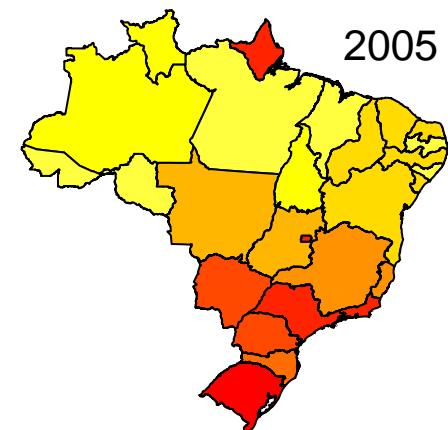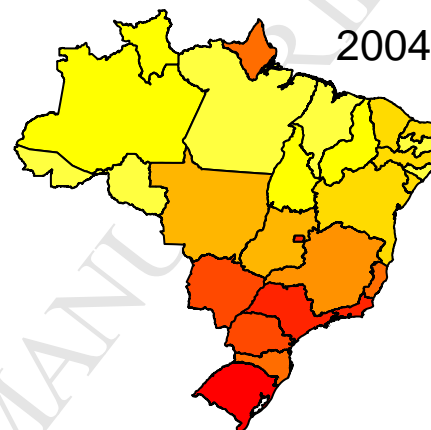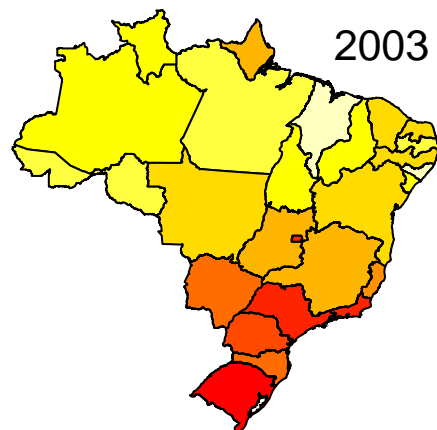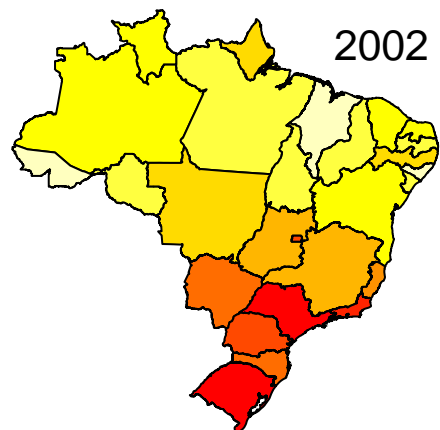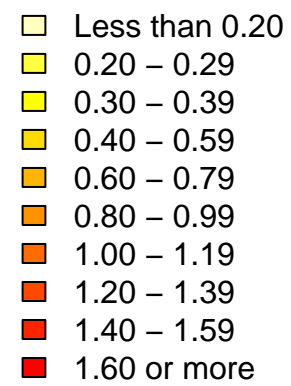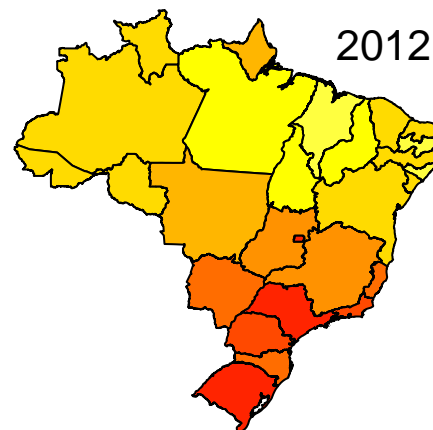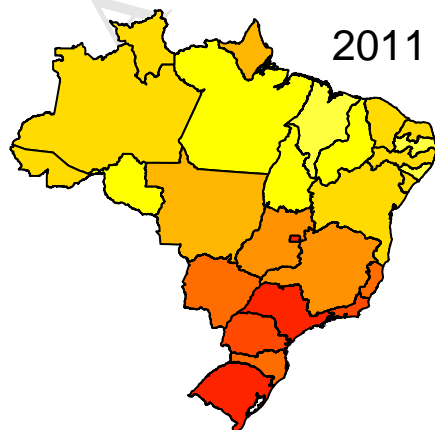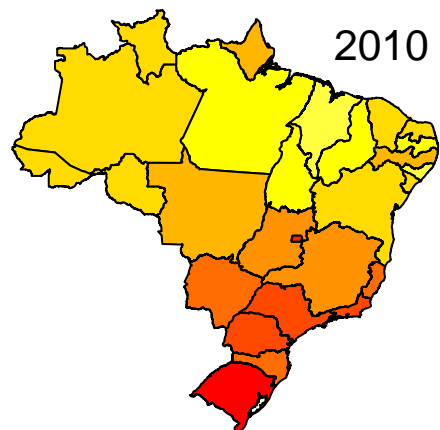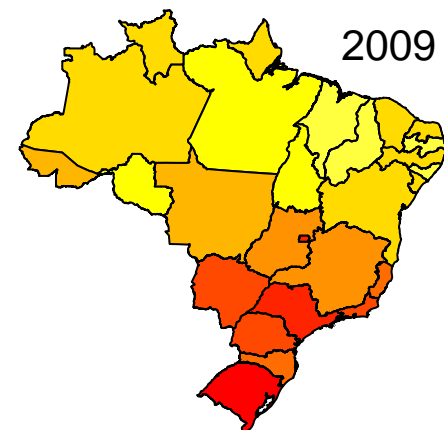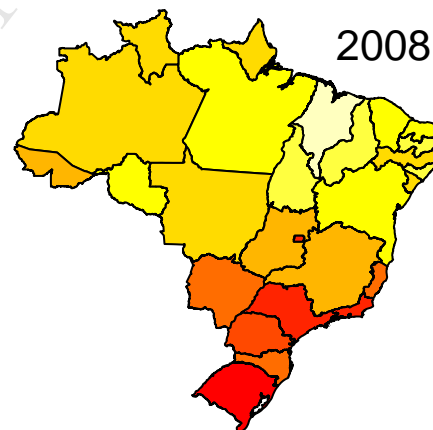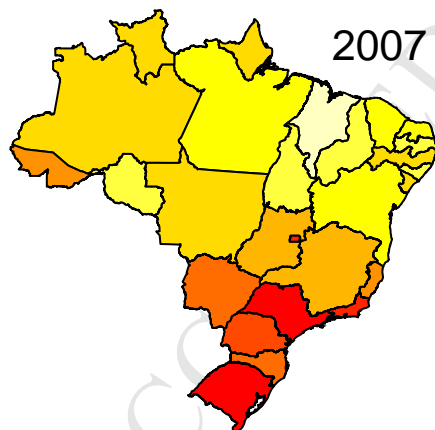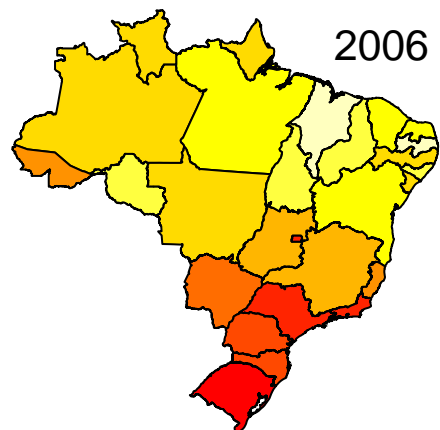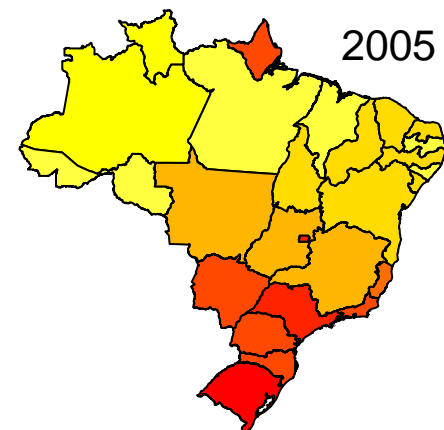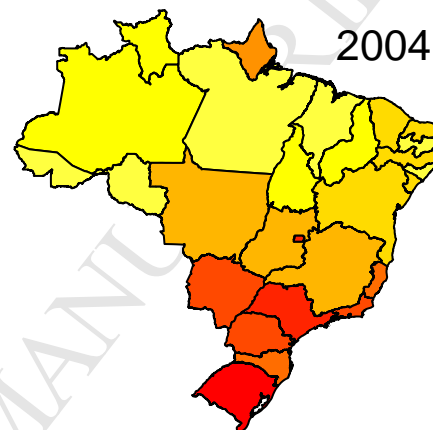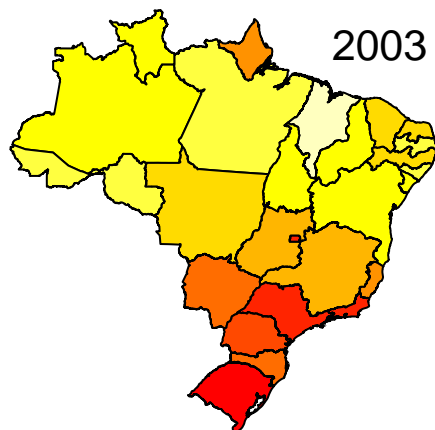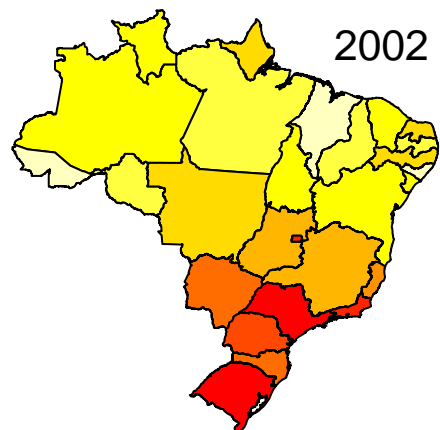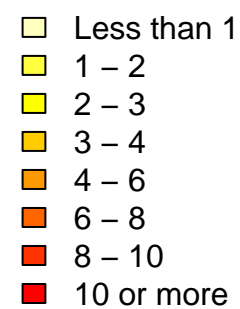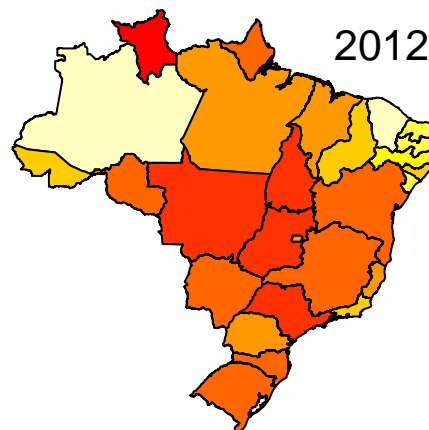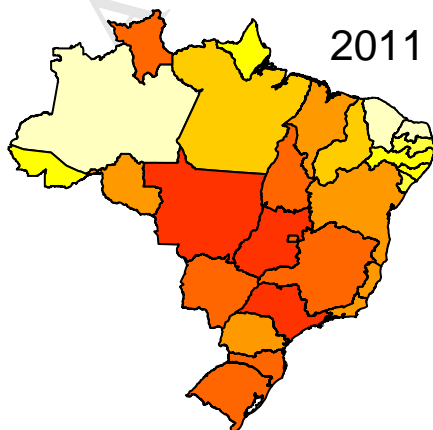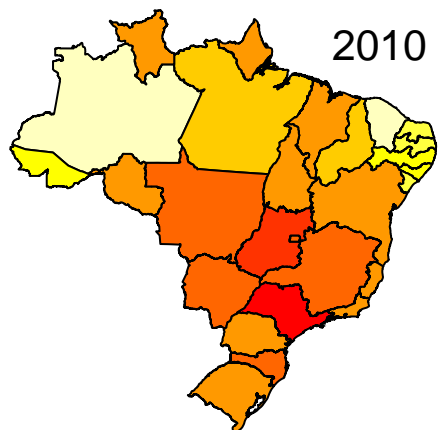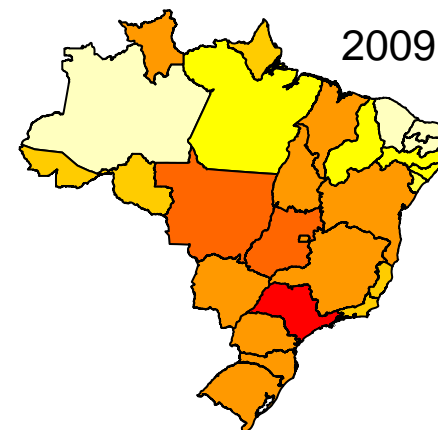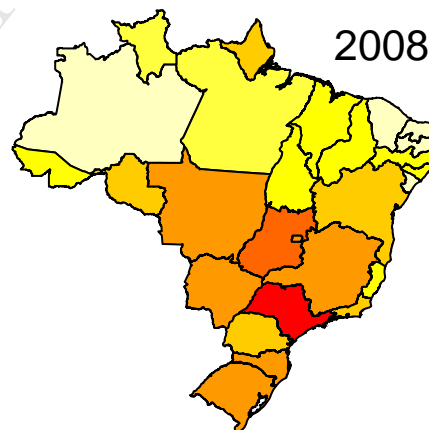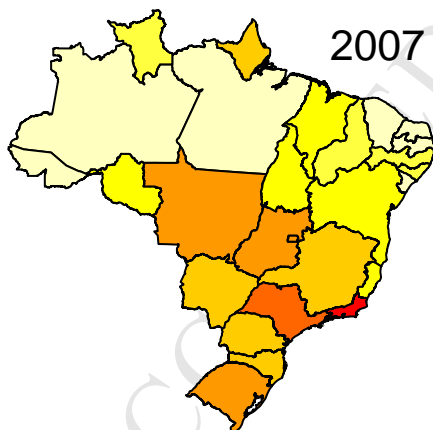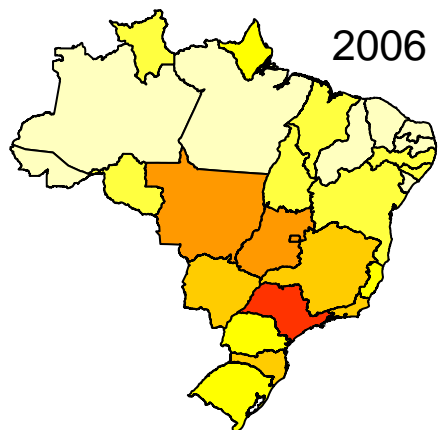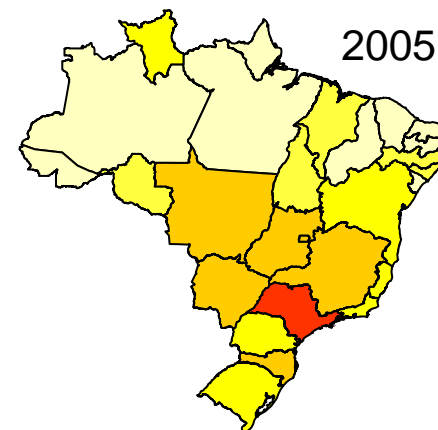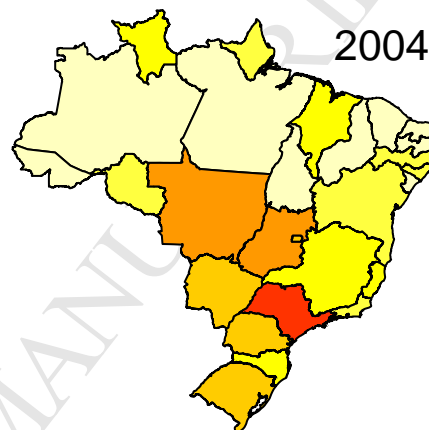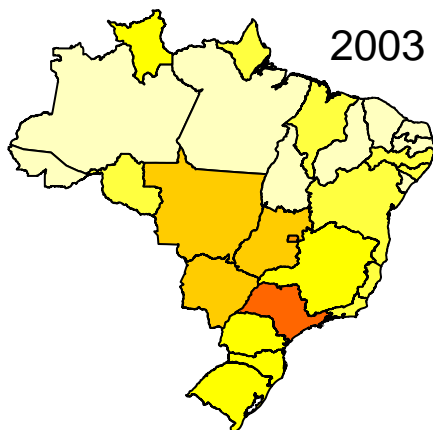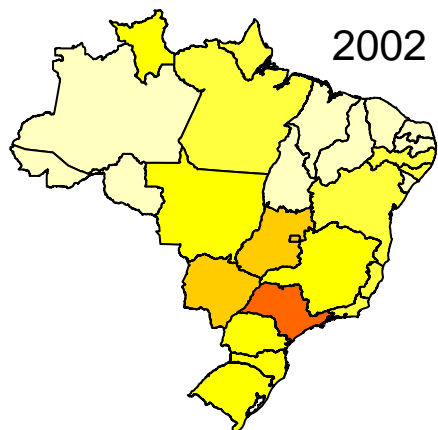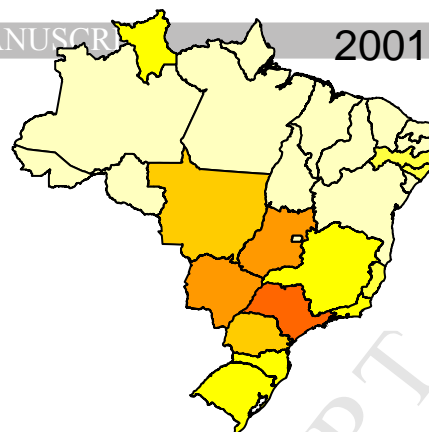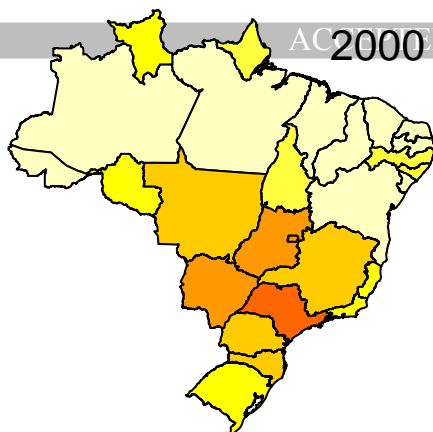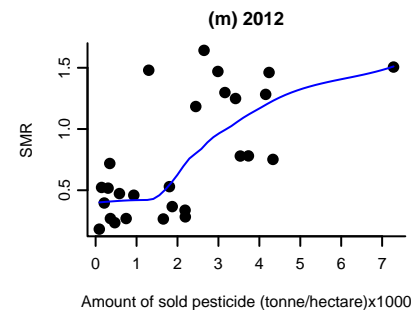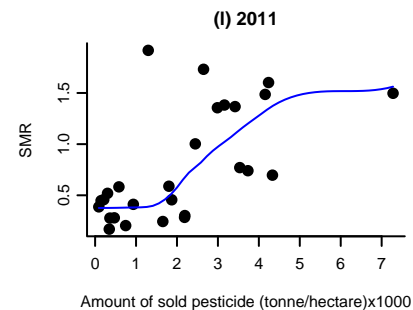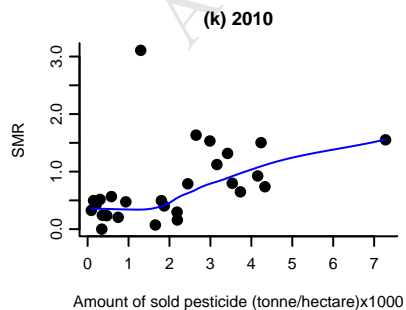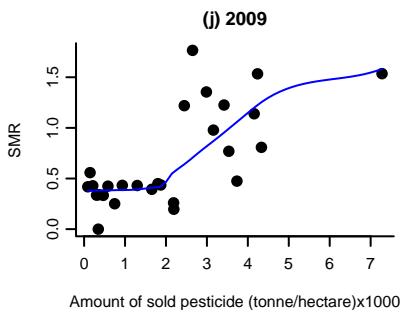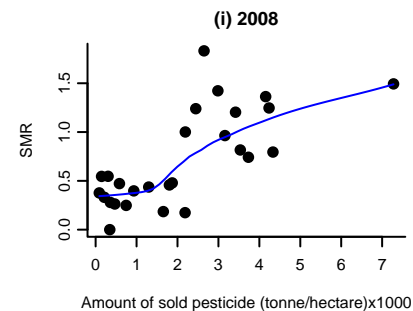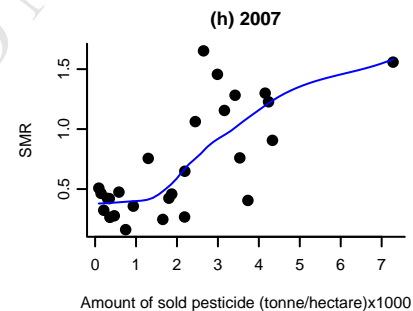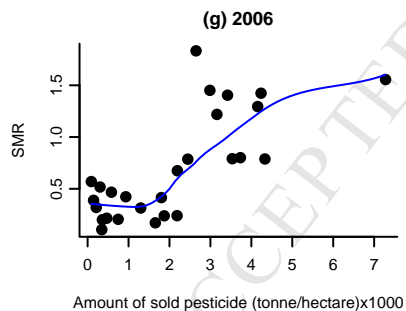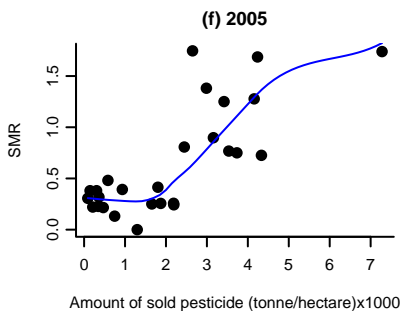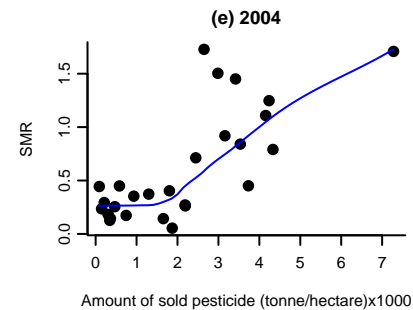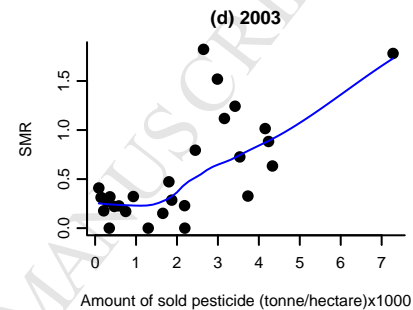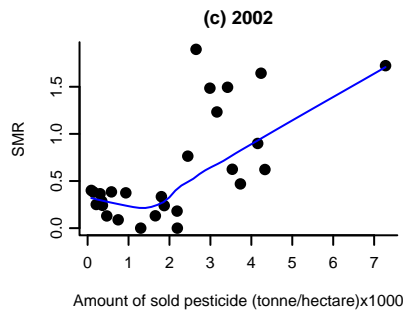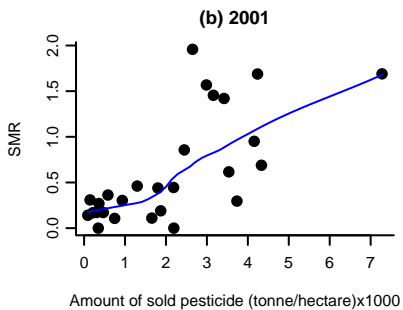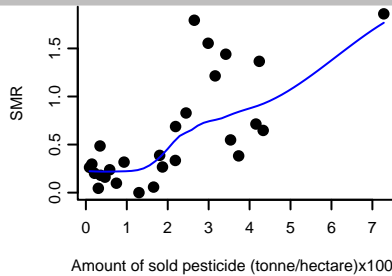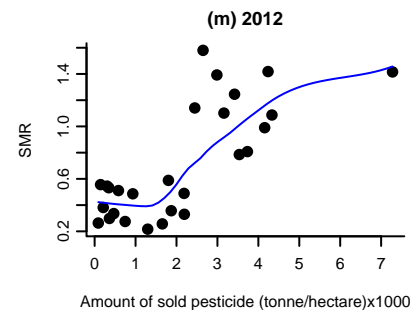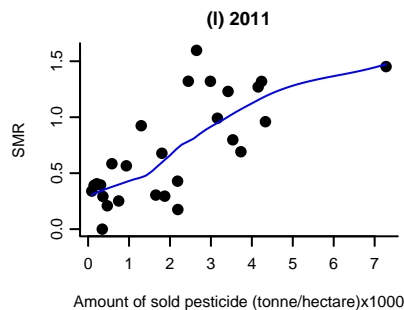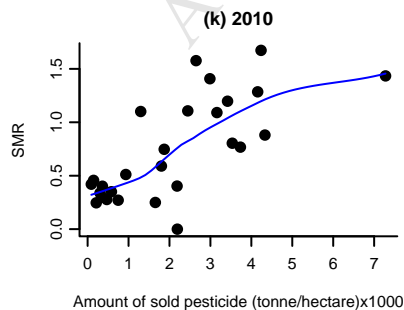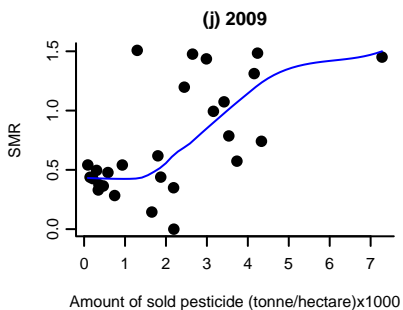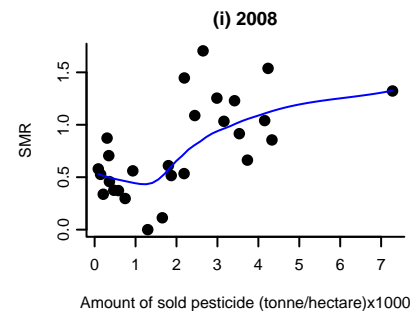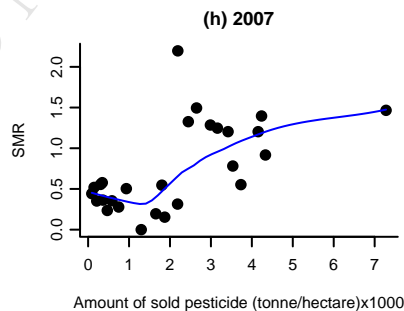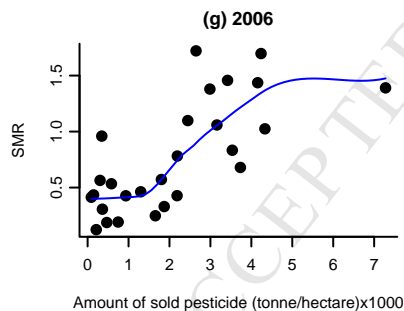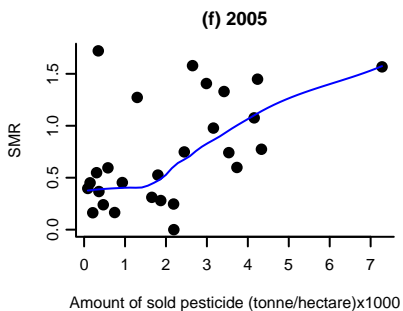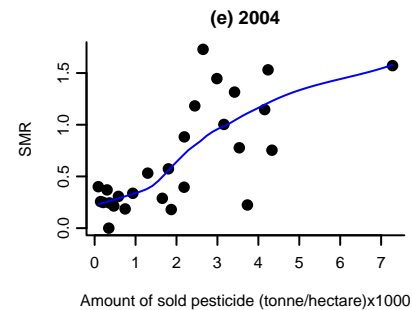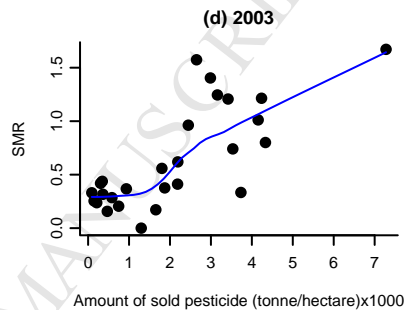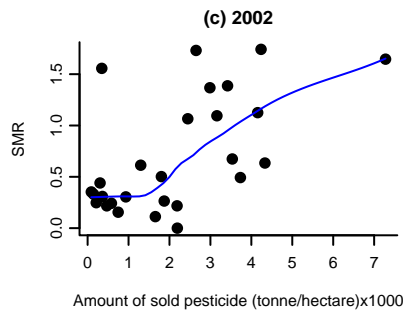
**(a) Male**

**(b) Female**

**Highlights**

- Human exposure to xenobiotics occurs worldwide, largely;

- Pesticides may promote cancer risk;

- Brazil is the world major pesticides consumer;

- Colon cancer (CC) mortality is steadily increasing in Brazil;

- We found CC mortality and pesticide levels may be correlated events in Brazil.