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Age-Related Differences in Acetylcholinesterase Inhibition Produced by Organophosphorus and *N*-Methyl Carbamate Pesticides

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1. Introduction

The concern that infants and children may be more susceptible to the toxic effects of chemicals, including pesticides, has received much attention in the scientific literature and the public media. Greater toxicity may be evident as long-term adverse outcomes, *e.g.*, neurological and IQ deficits from early exposure to lead, or else as increased toxicological effects of acute or short-term exposures. A National Academy of Science panel reported in 1993 on the scientific and regulatory issues regarding relative sensitivity of the young (National Research Council 1993). This report stressed how little is understood regarding the magnitude and mechanisms of these differences, and called for systematic research on pesticide toxicity in developing organisms. The concern that regulatory practices may not adequately protect these subpopulations further led to the passage of the Food Quality Protection Act in 1996 (FQPA, Public Law 104-170, August 1996), which required the US Environmental Protection Agency (EPA) to take extra steps to protect infants and children in the regulation of pesticides. Specifically, the FQPA instructed that "an additional tenfold margin of safety" be applied for non-cancer effects of pesticides "to take into account potential pre-and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children". Currently, the EPA Office of Pesticide Programs addresses this additional margin of safety during the risk characterization process (Lowit, 2006; US EPA, 2002). With pesticides for which direct or acute effects drive the assessment, one approach for determining this factor has often been an evaluation of relative sensitivity of young compared to adult animals (US EPA, 2006).

There are several factors impacting greater pesticide toxicity in children (Faustman *et al.* 2000). Exposures from intake of water contaminants and food residues are higher, because children take in considerably more food and water than adults on a per body weight basis (NRC, 1993). Behaviors of infants and toddlers (*e.g.*, crawling, hand-to-mouth) also increase the likelihood of coming into contact with pesticides through dust and soil. Greater exposure levels in children have been documented in children of agricultural workers, comparisons of organic and standard diets, and in numerous housing surveys (*e.g.*, Curl *et al.* 2003; Fenske *et al.* 1990; Loewenherz *et al.* 1997; Lu *et al.* 2001; Simcox *et al.* 1995). Higher

exposures, combined with immature and developing biological systems, underscore the potential for children's susceptibility to pesticides as well as other environmental factors.
Organophosphorus (OP) and *N*-methyl carbamate compounds inhibit acetylcholinesterase, the enzyme that preferentially hydrolyzes acetylcholine at cholinergic nerve terminals. This prolonged half-life of acetylcholine may cause an overstimulation of the cholinergic pathways and produce central and peripheral toxicities. Signs of acetylcholinesterase inhibition include salivation, lacrimation, gastrointestinal stimulation, muscular tremors to convulsions, ataxia: respiratory paralysis is the ultimate cause of death (reviewed in Fukuto, 1990; Pope, 2006). Many of these inhibitors are used as pesticides. The majority of OP pesticides have a long duration of inhibition due to the very slow regeneration of the enzyme (inhibition that lasts days to weeks), whereas the *N*-methyl carbamates are reactivated more quickly (minutes to hours) and thus have a much shorter time-course of toxicity (Aldridge and Reiner, 1975). While these chemicals are highly successful insecticides, their agricultural and especially household usage in the US have been somewhat curtailed due to concerns of toxicity, particularly to infants and children. They remain, however, to be widely used for agriculture in the US and throughout much of the rest of the world (US EPA, 2004).
The earliest studies describing greater toxicity in the young compared lethal doses of a number of pesticides. In many cases, but not all, the young were more sensitive than adults (Brodeur and DuBois 1963; Gaines and Linder 1986; Harbison 1975; Lu *et al.,* 1965). Using sublethal doses, many studies have also documented greater sensitivity in the young when comparing maximum-tolerated doses or else equi-effective doses producing cholinesterase (ChE) inhibition and/or behavioral changes (*e.g.*, Atterberry *et al.* 1997; Benke and Murphy 1975; Moser 1999, 2000; Moser and Padilla 1998; Pope *et al.* 1991; Pope and Chakraborti 1992; Zheng *et al.* 2000). Over the years researchers have examined potential kinetic or dynamic factors that may account for these differences (*e.g.*, Atterberry *et al.* 1997; Benke and Murphy 1975; Brodeur and DuBois 1967; Karanth and Pope 2000; Mortensen *et al.* 1998; Moser *et al.* 1998; Sterri *et al.* 1985). For most of the literature, there has been considerable variability in the ages tested, as well as different species, strain, gender, routes of administration, and vehicles. These different experimental details have not allowed direct quantitative comparisons across studies. In addition, much of this literature has focused on a relatively few pesticides that clearly demonstrate greater effects in the young compared to adults. Chlorpyrifos especially has been studied in considerable detail, perhaps more than any other ChE inhibitor. Chlorpyrifos, parathion, methyl parathion, and malathion have been repeatedly shown to produce greater toxicity in the young (*e.g.*, Benke and Murphy, 1975; Brodeur and DuBois 1963, 1967; Lu *et al.* 1965; Karanth and Pope 2000; Moser, 2000; Moser and Padilla, 1998; Pope *et al.* 1991; Pope and Chakraborti 1992; Zheng *et al.* 2000). Because of the extensive literature on these few chemicals, there is a tendency to assume that they are representative of the entire chemical class. Beyond these few pesticides, however, there is a paucity of data with which to determine the overall occurrence or the magnitude of such age-related sensitivity differences. The purpose of this review is to summarize and evaluate a number of studies of age-related differences in response to OP and carbamate pesticides.

2. Methods

The overall aim of this chapter is to provide a retrospective analysis of ChE-inhibiting pesticides and their potential to be more toxic in the young. This laboratory is in a unique

position to provide this review, since a total of 18 pesticides have been systematically evaluated in both adult and young rats. Consistency in execution of the studies as well as the ChE assay provides confidence in the comparisons.

2.1 Study description

Over the years, this laboratory has conducted acute dose-response studies in adult and preweanling, 17-day old (postnatal day 17, PND17) Long-Evans hooded rats for a total of 10 OPs and 8 carbamates. In a few cases, PND11 rats were also included. ChE activity was measured at the time of peak acute effect, often derived from range-finding or time-course studies. Across studies, there was consistency in the general experimental design. For almost all studies, the assay for ChE activity used a radiometric procedure that is modified to minimize potential reactivation of carbamylated tissues (Johnson and Russell 1975), and modified for use in this laboratory (Moser *et al.* 2010). This aspect of the assay is critical for studies of carbamates, since reactivation of tissues during the assay process could underestimate the degree of *in vivo* inhibition. The exception was methamidophos-treated tissues, which were analyzed using an automated Hitachi 911 analyzer as previously described (Hunter *et al*., 1997). ChE activity was measured in brain and either whole blood or red blood cells (RBCs). For 7 carbamates, the ChE assays for adult rats were physically conducted in another EPA laboratory. While the brain ChE inhibition data were subsequently confirmed in this laboratory, the RBC data were not and therefore are not included here.

In almost all of our studies, behavioral evaluations were included to correlate with the biochemical changes; however, since the focus of this review is to compare ChE inhibition, that aspect of the studies will not be further described.

2.2 Data analysis

In order to make direct comparisons across dose-response curves, all data were fit to a logistic equation (Hill plot; Barlow and Blake, 1989) using SAS (version 9, Cary, NC) for estimation of doses producing 50% ChE inhibition (ED50). The ratios of ED50 values in adults compared to young rats indicate the magnitude of sensitivity differences.

3. Results

3.1 ED50s

Doses which produce 50% inhibition were derived and compared by taking the ratio of the adult ED50 to that for the younger rat; values >1 indicate higher ED50s and therefore less sensitivity in the adults, *i.e.*, greater sensitivity in the young. For the purposes of this review, ratios ≥5-fold are considered "large", and <2-fold suggest little or no differences. These calculated ED50 values and ratios for each pesticide are listed in Table 1. In all cases, whole brain was used, whereas RBC was tested for some chemicals, and whole blood for others. As described above, adult RBC data for five carbamates are not available from this laboratory. In addition, the lowest doses used for aldicarb produced almost 70% blood ChE inhibition, and the lowest dose of methamidophos produced considerable blood ChE inhibition (40-60%), and thus dose-response curves could not be fit reasonably well. Dose-response data for adult brain ChE inhibition produced by carbofuran and carbaryl were conducted twice (McDaniel *et al.* 2007; Moser *et al.* 2010). The calculated ED50 values were essentially the same (carbaryl, 29.1 and 29.8; carbofuran, 1.06 in both), and therefore are

averaged for the purposes here. The highest dose of malathion used in adults was 500 mg/kg, and range-finding studies went as high as 750 mg/kg (unpublished); these doses produced no inhibition of brain ChE. Therefore an ED50 could not be calculated, but it is evident that the ratio would be at least 3-fold given that the ED50 value in PND17 rat pups was less than half of the doses that were ineffective in adults.

Tissue	Brain			Blood		
Pesticide/Age	Adult	PND17	Ratio	Adult	PND17	Ratio
Acephate[a,b]	14.7	14.2	1.0	20.1[1]	13.2[1]	1.5
Aldicarb[c]	0.27	0.096	2.8	-- [3]	-- [3]	
Carbaryl[d,e]	29.5[4]	32.8	0.9	6.64[2]	11.5[2]	0.6
Carbofuran[d,e]	1.06[4]	0.40	2.7	0.39[2]	0.096[2]	4.1
Chlorpyrifos[a,b]	22.6	5.29	4.3	1.72[1]	2.40[1]	0.7
Diazinon[a,b]	121	22.8	5.3	5.24[1]	8.96[1]	0.6
Dicrotophos[f]	0.75	0.31	2.4	0.45[2]	0.36[2]	1.3
Dimethoate[a,b]	21.5	17.9	1.2	15.8[1]	8.72[1]	1.8
Formetanate[d,e]	1.35	0.49	2.8	-- [3]	0.28[2]	
Malathion[a,b]	>750[3]	241	>3	494[1]	146[1]	3.4
Methamidophos[c]	1.47	1.94	0.8	-- [3]	-- [3]	
Methiocarb[d,e]	13.8	8.44	1.6	-- [3]	2.94[2]	
Methomyl[d,e]	3.86	2.74	1.4	-- [3]	1.44[2]	
Mevinphos[f]	1.04	0.29	3.6	0.27[2]	0.21[2]	1.3
Monocrotophos[f]	0.49	0.35	1.4	0.28[2]	0.35[2]	0.8
Oxamyl[d,e]	1.13	0.59	1.9	-- [3]	0.19[2]	
Phosphamidon[f]	2.55	1.40	1.8	1.34[2]	1.12[2]	1.2
Propoxur[d,e]	21.5	7.05	3.0	-- [3]	3.09[2]	

[1] whole blood
[2] RBC
[3] could not calculate
[4] Average value
[a] Moser *et al.*, 2005
[b] Moser *et al.*, 2006
[c] Moser, 1999
[d] McDaniel *et al.*, 2007
[e] Moser *et al.*, 2010
[f] Moser, 2011

Table 1. ED50 values (mg/kg) for brain and blood ChE inhibition for all pesticides in adult and PND17 rats, with the ratio calculated as adult:PND17. Blood assays involved RBC for some, and whole blood for other chemicals.

ED50 values obtained in PND11 rat pups are presented in Table 2; adult values in this table are taken from Table 1. For carbaryl and carbofuran, but not dicrotophos, the ratios of brain ED50 values were greater, indicating more sensitivity, in the PND11 rat compared to PND17.

Overall, it is clear that while the young are much more sensitive to some of these pesticides, there are no such differences with others. This is illustrated in Figure 1, showing brain ChE dose-response data for both ages for diazinon (brain ratio >5) and acephate (brain ratio=1).

Tissue	Brain			RBC		
Pesticide/Age	Adult	PND11	Ratio	Adult	PND11	Ratio
Carbaryl[a,b]	29.5[1]	18.1	1.6	6.64	9.36	0.7
Carbofuran[a,b]	1.06[1]	0.18	5.9	0.39	0.090	4.3
Dicrotophos[c]	0.75	0.43	1.7	0.45	0.40	1.1

[1] Average value
[a] McDaniel *et al*., 2007
[b] Moser *et al*., 2010
[c] Moser, 2011

Table 2. ED50 values (mg/kg) for brain and RBC ChE inhibition for three pesticides in adult and PND11 rats, with the ratio calculated as adult:PND11.

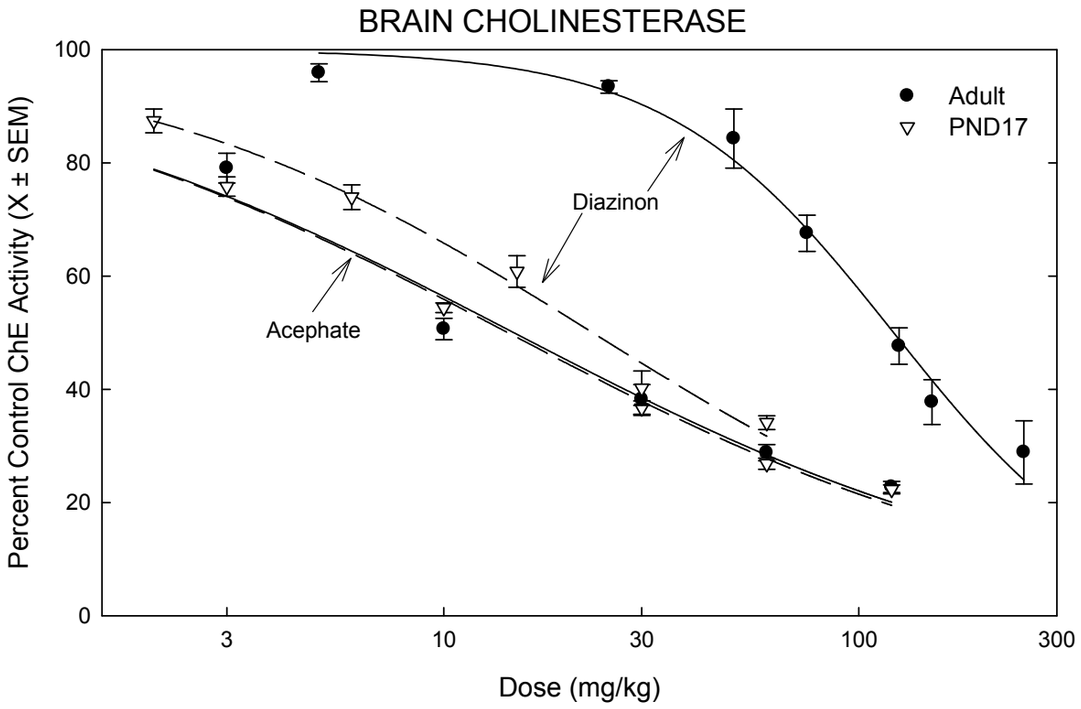

Fig. 1. Brain ChE inhibition in adult and PND17 rats treated with either acephate or diazinon. Data presented as percent control (X±SEM)

For most pesticides where data are available, there were less obvious age differences in blood ChE inhibition, with ratios <2 on this measure for all except carbofuran and malathion: this was true for both PND17 and PND11 ages. Finally, even where brain ChE was more sensitive, in many cases the blood ChE inhibition was similar.

3.2 Summary

Table 3 summarizes and bins the adult:PND17 ratios from Table 1 by chemical class. A comparison of ED50s for brain ChE inhibition revealed that slightly more than a quarter of the pesticides showed increased sensitivity in the young of 3-fold or greater, slightly less showed about 2- to 3-fold greater sensitivity, and fully half of the pesticides showed

essentially no marked differences (<2-fold) in sensitivity. With both carbamates and OPs, half of the tested chemicals had low ratios (<2-fold), but there were more OPs producing relatively large age differences than carbamates. OPs with the largest ratios were diazinon, chlorpyrifos, mevinphos, chlorpyrifos, and malathion, and carbamates were propoxur and carbofuran. In contrast to brain, many ED50 values for blood ChE inhibition showed little or no differences (<2-fold) between ages. For the two pesticides that showed greater age differences in blood values, there was one from each chemical class.

Tissue	Brain ChE ratio			Blood ChE ratio	
Chemical/Bin	<2	2.0-2.9	≥3	<2	>3
Combined	9	4	5	9	2
OPs	5	1	4	8	1
Carbamates	4	3	1	1	1

Table 3. Grouping of adult:PND17 ratios from Table 1. There were 10 OPs (brain for all, whole blood or RBC for 9) and 8 carbamates (brain for all, RBC for 2).

Similar grouping for the adult:PND11 ratios was not reasonable due to the low number of pesticides tested. However, of these three, the highest ratio for both brain and blood ChE inhibition was observed with carbofuran, a carbamate.

4. Discussion

4.1 Organophosphates

The majority of the literature in this area has addressed chlorpyrifos, parathion, methyl parathion, and malathion. The data presented here for chlorpyrifos and malathion further support previous findings of juvenile sensitivity, and in general show similar magnitudes of differences. In this study, the ratio of brain ChE ED50s for chlorpyrifos was 4.3, similar to the 5-fold difference in maximally tolerated dose (MTD) at PND17 (Moser and Padilla 1998). While others have reported somewhat greater MTDs and LD10s in younger rats (PND7, MTD ratio 6.2-fold, LD10 ratio 9.1-fold; Pope *et al.* 1991; Zheng *et al.* 2000), they found the ratio of brain ED50 values at PND7 to be less (2.2-fold; Pope and Liu 1997) than reported here for older rat pups. In our data, RBC ChE inhibition was not greater in the pups, in contrast to other reports of juvenile sensitivity of around 4-fold (Pope *et al.* 1991; Zheng *et al.* 2000). The reason for these tissue-dependent differences in ChE inhibition ratios is unclear.

The only dose-response studies for malathion that could be found in the literature measured lethality. The greatest difference in LD50 values, 27.5-fold, was measured in newborn rats (Lu *et al.* 1965). As the pups matured, the LD50 ratios decreased, being measured at 7.2-fold in PND12, 4-4.5-fold in PND14-18, and 2.2-fold in weanling rats (Brodeur and DuBois 1963; Lu *et al.* 1965). Our difference of 3-fold or greater for ChE inhibition agrees well with these values, despite the different endpoints.

The ratios presented here are generally in agreement with the few available studies for a few other OPs. Acephate showed little to no differences in sensitivity, as was reported for lethality (Gaines and Linder 1986). Likewise, methamidophos showed no differences in terms of lethality or MTDs (Gaines and Lindner, 1986; Moser, 1999), agreeing with the similar brain ChE inhibition obtained here. While our data report increased sensitivity of 3.6-fold in PND17 rats with mevinphos, an earlier study showed only a 1.5-fold difference in

LD50s in PND23 rats (Brodeur and DuBois, 1963). No other dose-response data with which to compare point estimates could be found for the remaining OPs.

It is important to note that while we have not studied parathion or methyl parathion, ratios of sensitivity differences from the literature range from around 8-fold in newborn to PND7 rats, to less than 2-fold in weanling pups (Benke and Murphy, 1975; Brodeur and DuBois, 1963; Harbison, 1975; Pope and Chakraborti, 1992). This information could add two more OP pesticides to the group that show sensitivity ratios >3-fold at approximately PND17; however, they are not added to Table 1 or 3 since we did not test those pesticides in this laboratory.

4.2 Carbamates

There are many fewer studies of juvenile sensitivity in carbamate toxicity. Besides our studies on ChE inhibition, the literature has only provided lethality data. Methomyl and carbaryl were not more sensitive to lethality in post-weaning (3-6 weeks of age) rats (Brodeur and DuBois, 1963; Gaines and Lindner, 1986). We observed essentially no differences in PND17 rats with either pesticide, but younger rats (PND11) were 1.6-fold more sensitive with carbaryl. We had previously reported about 2-fold more sensitivity with aldicarb for lethality and MTDs, similar to the 2.4-fold difference in ChE brain inhibition (Moser, 1999).

As part of an ongoing pesticide registration process by the EPA Office of Pesticide Programs, manufacturers have submitted comparative ChE studies in which inhibition in adult and PND11 rats is measured following acute and/or short-term repeated exposures. These data were modeled to calculate values that inhibit 10% brain ChE. While most of the studies are not available in the peer-reviewed literature, summaries are reported in the carbamate cumulative risk assessment document (US EPA, 2007). Sensitivity ratios based on these values for formetanate and carbofuran were similar to those obtained here for ED50 values, but the >3-fold ratios for methomyl and oxamyl were greater than those reported here. Some of these discordant results may be due to differences in levels of effect (10% vs 50%), age (PND11 vs PND17), as well as other experimental factors (*e.g.*, rat strain, ChE assay, etc.). Values for carbaryl and aldicarb were calculated using the same data presented here, so it is not surprising that the sensitivity ratios are similar for those carbamates.

4.3 Kinetics

Considerable evidence suggests that immature detoxification mechanisms in the young account for much of the reported age-related differences in sensitivity (*e.g.*, Atterberry *et al.* 1997; Benke and Murphy 1975; Chanda *et al.* 1997; Mendoza 1976; Mortensen *et al.* 1996; Sterri *et al.* 1985). All of these chemicals are detoxified through a combination of P450 microsomal enzymes, carboxylesterases, and/or A-esterases, but the metabolic patterns differ greatly (Chambers *et al.*, 2010). For some chemicals such as chlorpyrifos, sensitivity in young rats has been directly correlated with maturing carboxylesterase and A-esterase systems (Chanda *et al.* 1997,. 2002; Karanth and Pope 2000; Mortensen *et al.* 1996; Moser *et al.* 1998). In addition to chlorpyrifos, esterase detoxification, determined *in vivo* and/or *in vitro*, is known to be important for diazinon, mevinphos, malathion, and propoxur (*e.g.*, Cashman *et al.* 1996; Cohen and Murphy 1971, 1974; Gupta and Dettbarn 1993; Gupta and Kadel 1990; Main and Braid 1962; Moser and Padilla, 2011; Padilla *et al.* 2000, 2004; Poet *et al.* 2003; Walker and Mackness 1987). These chemicals all showed ≥3-fold increased sensitivity in the

young. Using *in vitro* tests, measurements of esterase (carbarylesterase, A-esterase) detoxification have also revealed good concordance between juvenile sensitivity and degree of esterase detoxification (Moser and Padilla, 2011; Padilla *et al.* 2000, 2004). Extrapolation of these findings suggest that the chemicals most dependent on esterases for detoxification will be more toxic to the young, and that screening for this can be predictive of juvenile sensitivity.

In these studies, the magnitude of age-related differences in sensitivity did not correlate with potency. Juvenile sensitivity was notable for malathion, the least potent (highest ED50) of the chemicals tested, as well as for aldicarb, the most potent. While a highly potent pesticide may produce more environmental risk, it may not necessarily be more toxic to the young.

4.4 Considerations

The ratios presented here may not be quantitatively exact or fixed. For example, point estimates depend on the curve-fitting model used. The logistic function was used here for all pesticides instead of chemical-specific models, even though the latter may fit better specific shapes of the dose-response curves. These different models may produce different estimates, and similar but different ratios. In a previous report (Moser *et al*., 2010), we used a four-parameter logistic model to fit the adult, PND17, and PND11 data for carbaryl and carbofuran. Most of the ratios were essentially the same as what is reported here, the largest discrepancy being the carbofuran brain, where the PND11 comparison is 5.9 here, and reported as 5.3 previously (Moser *et al*., 2010). Here we have also only compared 50% inhibition values, but the choice of this level could also impact the ratios, especially where the curves may not be parallel.

The age of the pups is an important factor. Progressively decreasing sensitivity from birth to weaning has been demonstrated for several pesticides, and may correlate with maturing esterase detoxification as described in section 4.3. Similar evidence is presented here, since for carbaryl and carbofuran, the brain ChE ratios were greater in PND11 pups compared to PND17. On the other hand, dicrotophos ED50 values for PND11 pups were slightly higher than for PND17, resulting in somewhat lower ratios in the youngest rats.

The interpretation of the magnitude of age differences in terms of "large" or "small" is relative. For example, even a 5-fold difference, which is considered here as a "large" difference, is less than a 10-fold uncertainty factor for intraspecies variability. On the other hand, a 5-fold difference is clearly larger than 2-fold, allowing the pesticides to be directly compared. Furthermore, as mentioned above, these ratios depend on the age at testing. Finally, it is important to note that these ED50 values are based on administered dose in mg/kg. Considering the large differences in body weight, on a total dose level, the differences are greater. For example, for chlorpyrifos the ED50 values for adult and PND17 brain ChE inhibition are 22.6 and 5.3 mg/kg, respectively (Table 1). Given an average weight of 330g for adults, and 28 g for PND17 pups, the total doses administered average about 7.5 mg for adults and 0.15 mg for pups, which is a 50-fold difference in intake. Thus, these differences in sensitivity can be considered several different ways.

5. Conclusions

Generalizing these data along with other literature reports leads to a conclusion that relatively large age-related differences are evident more often with OP pesticides, whereas

carbamates showed more moderate differences. However, fully half of both classes of chemicals showed essentially no age differences. These outcomes are mostly chemical-specific, and therefore assumptions that the young are always more sensitive to ChE inhibition are incorrect. For children's health, logic would dictate the use of pesticides showing less juvenile sensitivity. This retrospective analysis informs estimation of the likelihood for age-related differences in sensitivity for acute cholinesterase inhibition.

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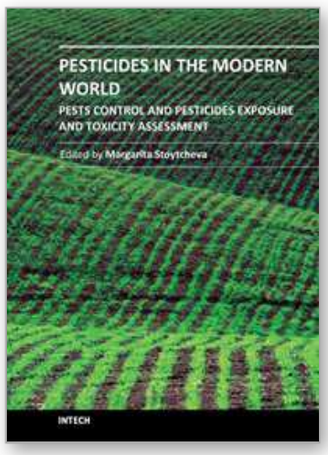

Pesticides in the Modern World - Pests Control and Pesticides Exposure and Toxicity Assessment

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The present book is a collection of selected original research articles and reviews providing adequate and up-to-date information related to pesticides control, assessment, and toxicity. The first section covers a large spectrum of issues associated with the ecological, molecular, and biotechnological approaches to the understanding of the biological control, the mechanism of the biocontrol agents action, and the related effects. Second section provides recent information on biomarkers currently used to evaluate pesticide exposure, effects, and genetic susceptibility of a number of organisms. Some antioxidant enzymes and vitamins as biochemical markers for pesticide toxicity are examined. The inhibition of the cholinesterases as a specific biomarker for organophosphate and carbamate pesticides is commented, too. The third book section addresses to a variety of pesticides toxic effects and related issues including: the molecular mechanisms involved in pesticides-induced toxicity, fish histopathological, physiological, and DNA changes provoked by pesticides exposure, anticoagulant rodenticides mode of action, the potential of the cholinesterase inhibiting organophosphorus and carbamate pesticides, the effects of pesticides on bumblebee, spiders and scorpions, the metabolic fate of the pesticide-derived aromatic amines, etc.

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