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Brian Dougherty, PhD
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Re: Review of Pesticide Dose-Additivity

Dear Dr. Dougherty:

At your request, we have reviewed dose-additivity in pesticides and its potential application to development of cleanup targets for pesticides in Florida under Chapter 62-777, F.A.C. As you know, humans are exposed to pesticides in food, drinking water, residences, and other non-occupational environments due to widespread use (USEPA, 2002a). In response to a Congressional mandate to evaluate cumulative exposure and risks from pesticides, the USEPA has developed a method based upon dose-additivity to estimate cumulative risk from exposure to multiple pesticides that share the same mechanism of toxicity. The objective of our review was to determine whether this approach and the relative potency factors developed for pesticide classes could be used as an improved method to address additive risks from pesticides in soil and groundwater at contaminated sites.

In 1996, the Food Quality Protection Act (FQPA) required the USEPA's Office of Pesticide Programs (OPP) to assess human health risk from multiple exposure pathways to more than one pesticide acting through a common mechanism of toxicity (USEPA, 2002a). Chemicals that have a common mechanism of toxicity and exhibit a common toxicological outcome are said to belong to a common mechanism group (CMG). Pesticides within a CMG are considered to be available for dose additivity if they have similar dose response curves in addition to their common mechanism of toxicity. Once a CMG is identified, the toxicity of each pesticide within is evaluated and compared to the toxicity of an index chemical. The index chemical in a CMG is chosen based on an abundance of existing toxicological data (USEPA, 2003). These comparative toxicities are called relative potency factors (RPF). RPFs for a CMG are calculated by dividing the toxic potency of the index chemical by the toxic potency a given chemical in the CMG.

$$RPF = \frac{Toxic\ Potency_{[Index\ Chemical]}}{Toxic\ Potency_{[Chemical\ n]}}$$

At a site where more than one pesticide within a CMG is detected, RPFs would be used to calculate an index chemical equivalent dose (ICED). The ICED is identical in concept to the dioxin toxicity equivalents (TEQs) and refers to the quantification of pesticide concentrations based on equivalent index chemical toxicity (USEPA, 2003). ICEDs are calculated by multiplying individual chemical concentrations by their respective RPFs. The ICEDs for each chemical present within a CMG, would then be added together to express the total mixture dose in terms of an equivalent dose of the index chemical. The total ICED dose would be compared to the cleanup target level for the index chemical. This is the same process currently used for the evaluation of risk from exposure to dioxins and polyaromatic hydrocarbons (PAHs).

$$total\ ICED = \sum Concentration_i \times RPF_i$$

The OPP evaluated six groups of pesticides (organophosphates, N-methyl carbamates, triazines, chloroacetanilides, pyrethrins and pyrethroids, and thiocarbamates and dithiocarbamates) for potential human health risks to multichemical and multipathway exposures through cumulative risk assessments. They developed RPFs for organophosphates, N-methyl carbamates, pyrethrins and pyrethroids, and chloroacetanilides. We have reviewed these assessments and provide a summary below.

Organophosphates

OPP included thirty-three chemicals in the organophosphate (OP) CMG. These chemicals were assessed for their environmental uses and potential exposure routes (oral, dermal, and inhalation). OPs were evaluated based on neurotoxicity. The common mechanism toxicity is the inhibition of acetylcholinesterase via phosphorylation of acetylcholinesterase in the central nervous system (CNS) and the peripheral nervous system (PNS). For OPs, toxicity studies in the rat provided the most extensive cholinesterase activity data for all routes and both sexes. The USEPA used rabbit studies for the dermal route for five chemicals because dermal toxicity data in rats were not available (USEPA, 2002b). The selections of RPFs were based on female rat brain cholinesterase studies for several reasons: 1) brain cholinesterase relative potency estimates are similar to red blood cell cholinesterase potency estimates, but have tighter confidence intervals 2) brain cholinesterase is a direct measure of the common mechanism of toxicity, and 3) females were found to be more sensitive than males to three OPs (there was equal sensitivity in the remaining thirty). Potency determinations for the oral route are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected because this level is generally near the limit of sensitivity for determining statistically significant decreases in cholinesterase.

Methamidophos was chosen as the index chemical for OPs because it has a high quality database for the inhibition of acetylcholinesterase for the oral, dermal, and inhalation routes. Oral RPFs were calculated by dividing the BMD_{10} for methamidophos by the BMD_{10} of a given chemical in the CMG. The BMD is the preferred method for determining relative potency (USEPA, 2002b). However, unlike the database for oral toxicity, the database of OP dermal and inhalation studies with cholinesterase measurements is limited and a BMD_{10} cannot be derived for these exposure pathways. Therefore, the potency for the dermal and inhalation routes was determined using

comparative effect levels (CELs) for the inhibition of brain cholinesterase. The CEL is the dose that causes a minimum level of effect and does not involve modeling a dose-response curve. For OPs, the CEL was defined as the dose causing a maximum of 15% decrease in brain cholinesterase activity. The RPFs for the dermal and inhalation routes of exposure were calculated using a CEL, as data for these routes was limited. Dermal and inhalation RPFs were calculated by dividing the CEL for methamidophos by the CEL for a given chemical in the CMG (USEPA, 2002b). RPFs for OPs can be found in Appendix A, Table 1.

N-Methyl Carbamates

Within the carbamate pesticides there are three distinct subgroups: N-methyl carbamates, thiocarbamates, and dithiocarbamates (USEPA, 2001b). These subgroups were evaluated separately. Thirteen N-methyl carbamates (NMCs) were assigned to the same CMG based on similar structural characteristics and a common mechanism of action. These chemicals were assessed for all potential exposure routes (oral, dermal, inhalation). NMCs were evaluated based on neurotoxicity. The common mechanism of toxicity is the inhibition of acetylcholinesterase via carbamylation of the serine hydroxyl group located in the active site of the enzyme in the CNS and PNS. Toxicity studies included in the NMC database were male and female rat brain cholinesterase inhibition studies. Potency determinations are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). In cases where male and female rats provide similar BMD_{10} estimates, EPA developed joint potency estimates (methomyl, pirimicarb, and thiodicarb). When male and female data produced statistically different results (aldicarb and carbaryl), the selections of RPFs were based on male rat studies, as males were found to have a lower BMD_{10} than females. Methiocarb and propoxur were based on male cholinesterase inhibition since they are the only data available. For n-methyl carbamates, $BMDs_{10}$ were calculated for all exposure routes. The calculation of route-specific BMDs is preferred over the use of CELs because it accounts for route-specific kinetics, which may influence potency. Oxamyl was chosen as the index chemical for oral, dermal, and inhalation RPFs since it had high quality dose-response data for all exposure routes. RPFs were calculated by dividing the BMD_{10} of oxamyl by the BMD_{10} of a given chemical in the CMG (USEPA, 2007). RPFs for NMCs can be found in Appendix A, Table 2.

Thiocarbamates and Dithiocarbamates

On August 17, 2001, OPP assessed the thiocarbamates and dithiocarbamates for a common mechanism of toxicity. Six thiocarbamates were stated to belong to a CMG based on the potential to produce a common toxic effect (neuropathy of the sciatic nerve) and the similarities in metabolism, particularly to a reactive sulfoxide intermediate. RPFs were calculated based on comparing the NOAELs of each thiocarbamate due to the lack of robust dose-response data that would support a comparison of BMD_{10} values (USEPA, 2001a). In response, the FIFRA Scientific Advisory Panel (SAP) commented there was insufficient evidence to support a common mechanism of toxicity and indicated a common metabolic product may not even exist. Therefore, on December 19, 2001, OPP produced a memorandum stating that the RPFs developed in the August 17, 2001 assessment are not appropriate for use for thiocarbamates as the evidence for a common mechanism and effect is not definitive. ,(USEPA, 2001b). Currently, USEPA dose not support the use of RPFs for thiocarbamates (USEPA, 2015).

Five dithiocarbamates (mancozeb, maneb, metiram, ziram, and thiram) were found to belong to a CMG based on the production of a common neurotoxic metabolite, carbon disulfide (EPA, 2001c). No RPFs were calculated in this document. However, on December 19, 2001, OPP produced a memorandum stating that, based on the recommendations of the SAP and comments from the public, OPP re-evaluated the data and concluded that the available evidence does not support a common mechanism for neuropathology (USEPA, 2001d). Currently, USEPA does not support the use of RPFs for dithiocarbamates (USEPA, 2015).

Triazines

OPP included five triazines (atrazine, simazine, sesethyl-s-atrazine, desisopropyl-s-atrazine, and diaminochlorotriazine) into the same CMG. Triazines were evaluated based on neuroendocrine effects. The common mechanism of toxicity involves the disruption of the hypothalamic-pituitary-gonadal axis. The hypothalamic-pituitary axis is involved in the development and maintenance of the reproductive system, bone formation, and immune, CNS, and cardiovascular functions. Therefore, disruption can lead to a variety of adverse health effects. Atrazine was chosen as the index chemical. Evaluation of endocrine-related data demonstrated potencies for chemicals in the CMG were equal or slightly less than atrazine. Therefore an RPF of 1 was used for all chemicals in the CMG (USEPA, 2006a).

Pyrethrins and Pyrethroids

OPP included a total of 15 naturally occurring pyrethrins (including pyrethrins I and pyrethrins II) and synthetic pyrethroids that belong to the same CMG. The common mechanism grouping is based on 1) shared structural characteristics, 2) shared ability to interact with the voltage-gated sodium channels, which results in disruption of membrane excitability in the nervous system, and 3) neurotoxicity characterized by two different toxicity syndromes. OPP's CMG science policy paper (USEPA, 2011a) discusses how behavioral responses, particularly in the rat, can be used as sensitive indicators of pyrethroid toxicity. Rat behavior studies from Weiner et al. (2009) and Herberth (2010) were selected for benchmark dose modeling. A BMD_{20} was calculated based on a 20% change from controls. Behavioral data tends to have a higher level of variability compared to other biomarkers of toxicity. Due to the high variability and smaller sample size of the pyrethrin behavioral data, the BMD_{20} is the lowest dose for which a significant change can be detected from control values. It is consistent with the threshold used in other pyrethroid behavior studies (USEPA, 2011b). Deltamethrin was chosen as the index chemical because it has the most robust database of guideline and literature studies and is of sufficient quality to minimize error and uncertainty in cumulative risk assessments. RPFs for pyrethrins and pyrethroids can be found in Appendix A, Table 3.

Chloroacetanilides

OPP included two pesticides (alachlor and acetochlor) in the same CMG. Both compounds produce nasal olfactory epithelium tumors in rats by a common mechanism including cytotoxicity of the olfactory epithelium, followed by regenerative cell proliferation of the nasal epithelium, and neoplasia if cytotoxicity and proliferation are sustained. Additionally, both compounds produce thyroid follicular cell tumors in rats by UDPGT induction, increased TSH, alterations in T3/T4 hormone production, and thyroid

hyperplasia (USEPA, 2006b). Because tumor development for these chemicals has a non-linear mode of action, tumor incidences were used to derive NOAELs for nasal tumors in male and female rats. Alachlor was chosen as the index chemical (EPA, 2006b). The RPF was calculated using the ratio of the NOAEL for alachlor to the NOAEL for acetochlor. The RPF for acetochlor can be found in Appendix A, Table 4.

For chemicals that share a common mechanism of toxicity, and where comparative potency data are available, we consider dose-additivity to be the best approach for determining combined risks. The analyses conducted above for pesticides were scientifically rigorous and subject to extensive peer review, including review by outside experts (namely, the FIFRA Scientific Advisory Panel). We recommend that the FDEP consider using dose-additivity and the RPFs (ICEDs) developed by the USEPA when evaluating risks and developing cleanup goals for organophosphate pesticides, N-methylcarbamates, triazines, pyrethrins and pyrethroids, and chloroacetanilides. In addition to a significant improvement in how additive risks are addressed for these contaminants, this approach will make it possible to include a number of pesticides for which cleanup targets do not currently exist in Chapter 62-777, F.A.C.

Please let us know if you have any questions regarding the pesticide RPFs presented in this letter.

Sincerely,

Leah D. Stuchal, Ph.D.

Hannah M. Neeley, MPH

Stephen M. Roberts, Ph.D.

References:

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USEPA (2003) *Developing Relative Potency Factors for Pesticide Mixtures: Biostatistical Analysis of Joint Dose-Response*. United States Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development, Cincinnati, OH.

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USEPA (2006b) *Cumulative Risk from Chloroacetanilide Pesticides*. United States Environmental Protection Agency, Office of Pesticide Programs, Health Effects Division, Washington, DC.

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Appendix A

Table 1: Organophosphate Relative Potency Factors

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyridos-methyl	0.005		
Diazinon	0.01		
Dichlorvos	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	0.003
Methamidophos*	1.00	1.00	1.00
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	0.82
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	0.087

* Index Chemical

Table 2: N-Methyl Carbamate Relative Potency Factors

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Aldicarb	4.00		
Aldicarb sulfone	3.44		
Aldicarb sulfoxide	3.68		
Carbaryl	0.15	0.71	0.51
Carbofuran	2.4		
3- and 5-Hydroxycarbofuran	2.4		
Formetanate HCL	2.18		
Methiocarb	0.18	0.09	0.62
Methomyl	0.67		
Oxamyl*	1.00	1.00	1.00
Pirimicarb	0.02		
Propoxur	0.11	0.03	0.18
Thiodicarb	0.89		

* Index Chemical

Table 3: Pyrethroid (Including Pyrethrins) Relative Potency Factors

Chemical	Oral RPF
Allethrin	0.11
Bifenthrin	1.01
Cyfluthrin	1.15
Lambda-Cyhalothrin	1.63
Cyphenothrin	0.15
Cypermethrin	0.19
Deltamethrin*	1.00
Esfenvalerate	0.36
Fenpropathrin	0.50
Tau-Fluvalinate	1.00
Imiprothrin	0.02
Permethrin	0.09
Prallethrin	0.10
Pyrethrins	0.02
Resmethrin	0.05

* Index Chemical

Table 4: Chloroacetanilide Relative Potency Factors

Chemical	Oral RPF
Alachlor*	1.00
Acetochlor	0.05

* Index Chemical