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February 8, 2012

Office of Pesticide Programs, (OPP)
Regulatory Public Docket (7502P),
Environmental Protection Agency,
1200 Pennsylvania Ave. NW.,
Washington, DC 20460–0001

Re: Pyrethrins/Pyrethroid Cumulative Risk Assessment;
Docket Number: EPA–HQ–OPP–2011–0746

Dear Sir/Madam:

Beyond Pesticides and the undersigned groups would like to thank you for this opportunity to comment on the cumulative risk assessment conducted for the pyrethroid class of chemicals. As the agency is aware over last couple decades this class of chemicals has come to replace the older organophosphate insecticides and has made its way into the top 10 commonly used pesticides in the U.S. Pyrethroids have a wide range of uses from agriculture to turf, mosquito and residential uses. In accordance with the Food Quality Protection Act (FQPA), EPA has completed a cumulative risk assessment for pyrethrins/pyrethroids and recently published its conclusions. We would like to present to the agency our comments on the assessment and its conclusions.

There are several major concerns and flaws plaguing this cumulative assessment, which therefore does not meet the regulatory burden in fully evaluating synthetic pyrethroids' effect on public and environmental health. We are troubled that EPA's analysis and conclusions allow the expanded use of synthetic pyrethroids, despite the known adverse effects associated with exposures and the high degree of uncertainty associated with multiple adverse endpoints. The most egregious conclusion of this assessment is the reduction of the FQPA safety factor from 10x to 3x for children under six years of age and 1X for persons over six years old, including pregnant women. Given that some members of this chemical class are probable carcinogens and endocrine disruptors, and may suppress the immune system, endpoints that EPA has not sufficiently taken into consideration, it is not appropriate for the agency to reduce the FQPA safety factor at this time. The agency further states that cumulative estimated risks from

existing pyrethroid uses are not of concern, and that there is sufficient room in the pyrethroid cumulative 'risk cup' to support consideration of new pyrethroids and new uses. The agency violates its statutory duty under the "unreasonable adverse effect" provision of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 USC § 136a(c)(5)(c), in welcoming the proliferation of this class of insecticides when it has been shown to be associated with a host of acute and chronic health problems, and the contamination of homes and terrestrial and aquatic environments. Not fully evaluated in the assessment is the rise of insect resistance to the chemicals, inevitable with elevated use and exposure.

To comply with its standards, the agency must revisit and reassess its cumulative risk assessment and address the shortcomings highlighted below:

Retain the FQPA 10x Factor

The purpose of the FQPA margin of safety factor is "to protect infants and children, taking into account the potential for pre- and post-natal toxicity." 21 USC §346a (b)(2)(C). It is known that children face unique hazards from pesticide exposure.[1] According to the cumulative assessment, the agency has reviewed data to assess the health risks of pyrethroids to children. These data included reproductive, developmental and developmental neurotoxicity studies. In complement to this data, physiologically-based pharmacokinetic (PBPK) modeling data submitted by an industry task force will be reviewed sometime in 2013.[2] In the meantime, the agency concludes that the previous 10X safety factor should be reduced to 1X for persons over 6 years of age and to 3X for infants less than 6 years, as it believes "current available data on pyrethroids are sufficient to reduce the 10x FQPA safety factor."

Current available data that document exposures and adverse effects in the young and do not justify a reduction in the safety factor, despite EPA's calculations:

A study by Shafer et al.,[3] a paper which looked at issues of mode of action and age-dependent and developmental neurotoxicity as related to risk decisions under the FQPA, notes that there is a large age dependence to the acute toxicity of pyrethroids in which juvenile laboratory rats are at least an order of magnitude more sensitive than adults to certain pyrethroids. Previous studies have found that age related sensitivity to pyrethroids occur at higher doses. For example, cypermethrin and permethrin were 17-fold and 6-fold respectively more lethal to 8-

[1] National Research Council, National Academy of Sciences. 1993. Pesticides in the Diets of Infants and Children, National Academy Press, Washington, DC. 184-185.

[2] USEPA. 2011. Re-evaluation of the FQPA Safety Factor for Pyrethroid Pesticides. Office of Chemical Safety and Pollution Prevention. Washington DC.

[3] Shafer, T., et al. 2004. Developmental Neurotoxicity of Pyrethroid Insecticides: Critical Review and Future Research Needs. *Environ Health Perspect* 113:123–136

day old rats compared with adults[4], due to incomplete development of the enzymes which catalyze the metabolism of pyrethroids in the liver of young animals which is a a widely accepted hypothesis. However, Shafer et al. point out that age-dependent differences in pyrethroid neurotoxicity have not been thoroughly studied at the lower end of the dose–response relationship (sublethal doses), concluding that "decisions related to the FQPA could be strengthened by additional studies comparing the relative susceptibility of differential sensitivity between young and adult animals, particularly at sublethal doses." Thus far, studies looking at sublethal effects on the young have been lacking.

Fenvalerate and cypermethrin given to pregnant and nursing rats resulted in pups with significant increases in the levels of dopamine and muscarinic receptors of striatal membrane, with effects being more pronounced in lactationally exposed pups. Those prenatally exposed to fenvalerate had significant decreases in the activity of brain monoamine oxidase and Na+, K(+)-ATPase and a significant increase in acetylcholinesterase. The authors conclude that exposures to these pyrethroids disturb dopaminergic and cholinergic pathways which are more pronounced during the "growth spurt" period in the young and may lead to a functional delay in brain maturation.[5]

Another study[6] suggests that neonatal exposure to permethrin or cypermethrin induces long-lasting effects after developmental exposure in juvenile rats, leading to changes in open-field behaviors, striatal monoamine levels, and increased oxidative stress. Lower dopamine and a reduction of blood glutathione peroxidase content were also observed.

In a study examining the relationship between prenatal exposure to indoor pesticides and infant growth and development in urban families,[7] researchers at the Mount Sinai School of Medicine found higher than expected levels of pyrethroid metabolites in sample urine (compared with previous NHANES data) which, according to the authors, may be attributed to higher exposures resulting from West Nile mosquito spray programs in the subjects' communities. Given that the half-lives of the pyrethroids in question were short, high levels of metabolites in the urine indicate continuous exposures. In this study a high percentage of women (70 percent) reported being pregnant during times of pesticide exposures. This study underscores the prevalence of prenatal exposure to pyrethroid chemicals, especially in under-represented populations.

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[4] Cantalamessa F. 1993. Acute toxicity of two pyrethroids, permethrin, and cypermethrin in neonatal and adult rats. Arch Toxicol 67:510–513.

[5] Malaviya M, Husain R, Seth PK, Husain R. 1993. Perinatal effects of two pyrethroid insecticides on brain neurotransmitter function in the neonatal rat. *Vet Hum Toxicol*, 35:119-122.

[6] Nasuti C, Gabbianelli R, Falcioni ML, Di SA, Sozio P, Cantalamessa F. 2007. Dopaminergic system modulation, behavioral changes, and oxidative stress after neonatal administration of pyrethroids. *Toxicology.* 229:194-205

[7] Berkowitz GS, Obel J, Deych E, Lapinski R, Godbold J, Liu Z, et al. 2003. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. *Environ Health Perspect* 111:79–84.

In a similar 2002 study,[8] low level concentrations of pyrethroid pesticides were frequently (47-83%) detected in pregnant minority women in New York City, indicating widespread prenatal pesticide use among minority women.

In a study conducted by researchers from the Centers for Disease Control and Prevention (CDC) in a community in the Southeastern U.S., urinary pyrethroid pesticide metabolite concentrations for children, compared to those reported in the NHANES and GerES studies, were significant and substantially higher than the general populations of the U**.** S**.** and Germany.[9]

Morgan et al. in a study with 127 preschool children[10] at their homes and daycare centers found that these children were exposed to low levels of permethrin from several sources. 67% of the children's urine samples contained permethrin metabolites with the highest recorded concentrating, 33.8 ng/mL. The authors note that the primary route of the children's exposure was through dietary ingestion, followed by indirect ingestion (hand to mouth action). Indirect ingestion as a method of exposure is also corroborated by EPA researchers in a 2011 study,[11] which demonstrated that surface concentration of pesticide residues were 'highly influential' on the dietary intake of children. In the Morgan study, permethrin residues were detected most often in the dust (100%) and hand wipe (>78%) samples.

Several studies have determined that dietary ingestion is a main source of children's exposure to pyrethroid pesticides.[12,13] A 2011 EPA study[14] found that pesticide residues were transferred from treated surfaces to foods, stating that, "[A]s long as pesticide levels are measureable on surfaces in children's eating environment, it can be concluded that transfer of pesticides to foods will take place." A Children Pesticide Exposure Study[15] found that children are continuously exposed to pyrethroid insecticides through their diets all year long, and that chronic exposure patterns are periodically modified by episodes of relatively high exposures

[8] Whyatt , R et al. 2002. Residential Pesticide Use during Pregnancy among a Cohort of Urban Minority Women *Environ Health Perspect* 110:507–514

[9] Naeher LP, et al. 2010. Organophosphorus and pyrethroid insecticide urinary metabolite concentrations in young children living in a southeastern United States city. *Sci Total Environ.* 408(5):1145-53.

[10] Morgan MK., et al. 2007. An observational study of 127 preschool children at their homes and daycare centers in Ohio: environmental pathways to cis- and trans-permethrin exposure. *Environ Res.* 104(2):266-74.

[11] Melnyk LJ, Byron MZ . et al. 2011. Pesticides on household surfaces may influence dietary intake of children. *Environ Sci Technol.* 45(10):4594-601.

[12] Schettgen T, Heudorf U, Drexler H, Angerer J. 2002. Pyrethroid exposure of the general population-is this due to diet. Toxicol Lett 134:141–145.

[13] Heudorf U, Angerer J, Drexler H. 2004. Current internal exposure to pesticides in children and adolescents in Germany: urinary levels of metabolites of pyrethroid and organophosphorous insecticides. Int Arch Occup Environ Health 77:67–72.

[14] Melnyk LJ, et al. 2011. Influences on transfer of selected synthetic pyrethroids from treated Formica to foods. J *Expo Sci Environ Epidemiol*. 21(2):186-96.

[15] Lu C., et al. 2009. The attribution of urban and suburban children's exposure to synthetic pyrethroid insecticides: a longitudinal assessment. *J Expo Sci Environ Epidemio*l. 19(1):69-78.

from residential uses. The authors concluded that the combination of the use of pyrethroid insecticides in the household, dietary intake, and seasonal differences play a significant role in predicting children's exposure to synthetic pyrethroid insecticides.

In a 2011 study[16] published in *Pediatrics,* which investigated prenatal exposure to permethrin and piperonyl butoxide (PBO) -a synergist commonly formulated with pyrethroid- and 36-month neurodevelopment, found that the synergist PBO was negatively associated with 36-month cognitive and motor development in children with a history of pre natal exposure, as measured in umbilical cord and maternal plasma.

PBPK Modeling

PBPK modeling data, which industry stakeholders have and will submit to the agency for pyrethroid review, has many useful applications that are beneficial to understanding the role of chemicals in biological systems. These models can provide relevant supplemental information for the agency's risk assessment processes. However, like most computational tools, their limitations are driven by current scientific knowledge and data inputs. Data gaps such as poorly understood characterization of some physiological processes, like the absorption process in newborns and infants, can result in models with unreliable outputs.[17] This is why modeling data, while providing useful information, should be supported by experimental data, and should supplement rather than replace experimental data.

The current available data, cited above, demonstrate that pyrethroids are a risk to pre- and post-natal infants. Exposures to these chemicals are high and their effects in the young have not been understood. The agency agrees that there is an increased sensitivity of juveniles to pyrethroids, but reduces the FQPA safety standard from 10X to 3X for infants younger than six years of age. Given the vast uncertainty of current developmental toxicity data and the incomplete PBPK data available, the agency has a statutory responsibility to retain the 10X safety factor for all groups, especially infants and pregnant women. The current data does show that pregnant women, especially those in low-income households, are predisposed to indoor pyrethroid exposures. Infants and children have been documented as having low to high concentrations of pyrethroid concentrations in their umbilical cord plasma and urine, with residues being detected in indoor air and dust, and surfaces. Dietary exposures are also responsible for the frequency in detections in these populations, as well as in the general public. Age-dependent differences in sensitivities are illustrated in the current scientific data and the agency acknowledges that there is increased sensitivity in the young. However, the pharmacokinetic reasons for this are still uncertain. Given the prevalence of exposure and the

[16] Horton MK et al. 2011. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. *Pediatrics*. 127(3):e699-706

[17] Khalil, F. and Läer, S. 2011. Physiologically Based Pharmacokinetic Modeling: Methodology, Applications, and Limitations with a Focus on Its Role in Pediatric Drug Development. *J. Biomedicine and Biotechnology.* Vol. 2011, Article ID 907461, doi:10.1155/2011/907461

uncertainties in the existing data and PBPK models, the agency must retain the 10X FQPA safety factor for all populations in accordance with 21 USC §346a (b)(2)(C).

National Body Burden Attributed to Pyrethroids is Pervasive

The CDC's Fourth *National Report on Human Exposure to Environmental Chemicals*[18] - the most comprehensive assessment to date of the exposure of the U.S. population to chemicals in our environment - finds that exposure continues to be widespread, specifically for permethrin, cypermethrin, deltamethrin, and/or their metabolites which were all found in greater than half of the subjects tested with levels staying relatively constant throughout the years sampled. This data also found exposures in the young (6-11 years) recorded the highest levels of pyrethroid residue in their urine for all age groups. This further highlights the continual, baseline exposure levels in the U.S. population, which should be decreased not increased, especially in children. The FQPA safety factor must be used to protect children from experiencing an increase in their pyrethroid body burden levels, protecting them from known and unknown adverse effects due to exposures.

Other Chronic End-Points Must be Considered Before Supporting New Uses

A cumulative risk assessment is the process of combining exposure (the amount of a pesticide to which an individual is exposed) and hazard (the health effects a pesticide could cause) from all substances that share a common mechanism of toxicity. Cumulative assessments are necessary since people are exposed to multiple pesticides that behave in a similar manner in the body through various exposure pathways: (air, diet, dermal absorption, etc.). According to EPA's procedures, the agency identifies a cumulative assessment group (CAG) of chemicals that are to be included in the quantification of cumulative risk needs. Several of the CAG chemicals have other serious chronic endpoints that warrant special consideration when reviewing the pyrethroid class of chemicals, although they do not fall under the scope of this cumulative assessment in regard to a common mechanism of toxicity. This is especially imperative if the agency is to recommend further uses and registrations for this class of chemicals. In the case of synthetic pyrethroids, the neurotoxicity endpoints require the agency's serious attention, as do other endpoints not included but identified as adverse health effects associated with the majority of the synthetic pyrethroids.

Pyrethroids are neurotoxic and their neurotoxic effects are well detailed in the scientific literature and by this assessment. However, consider the following Table 1. Several of the CMG pyrethroids and those not included in the CMG are associated with cancer, endocrine disruption and reproductive and developmental effects, which should be taken into consideration before the agency makes a finding to increases uses. Several studies have detailed the endocrine disrupting and reproductive effects of pyrethroids. For instance, results

[18] CDC. 2009. Fourth *National Report on Human Exposure to Environmental Chemicals. Available at* http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf

from a New Zealand study show that pyrethroid metabolites are capable of interacting with the human estrogen receptor, and thus pose a risk to human health and environmental wellbeing by adding to the overall environmental xenoestrogen load.[19] A Japanese pilot study involving men battling infertility suggested the pyrethroid exposure level and dietary habit is a significant contributor to poor semen quality.[20]

Table 1. Effects Observed in the Scientific Literature

Chemical Name	CAS No.	Reproductive Effects	Developmental Effects	Cancer	Endocrine Disruption
Allethrin	584-79-2				x
Bifenthrin	82657-04-3	x	x	x	x
Cyfluthrin	68359-37-5	x			
Cyhalothrin	68085-85-8			x	x
Cypermethrin	52315-07-8			x	x
Cyphenothrin	39515-40-7				
Deltamethrin	52918-63-5				x
Esfenvalerate	66230-04-4				
Etofenprox	80844-07-1				x
Fenpropathrin	39515-41-8				
Fenvalerate	51630-58-1	x			x
Fluvalinate	69409-94-5	x	x		x
Imiprothrin	72963-72-5				
Permethrin	52645-53-1	x		x	x
Phenothrin/Sumithrin	26002-80-2				x
Prallethrin	23031-36-9		x	x	
Pyrethrins (not synthetic)	8003-34-7		x	x	x
Resmethrin	10453-86-8	x	x	x	x
Tetramethrin	7696-12-0			x	
Tralomethrin	66841-25-6				

The following examples highlight the need for EPA to consider all the health effect endpoints associated with pyrethroids in the aggregate:

<u>Permethrin</u>

Permethrin is a type I pyrethroid mostly used in agriculture and for mosquito abatement programs, as well as for structural and residential sites. There are also some uses for headlice

[19] McCarthy AR, Thomson BM, Shaw IC, and Abell AD. 2006. Estrogenicity of pyrethroid insecticide metabolites. *J Environ Monit*. 8(1):197-202.

[20] Toshima, H., et al. 2011. Endocrine disrupting chemicals in urine of Japanese male partners of subfertile couples: A pilot study on exposure and semen quality. *Int J Hyg Environ Health*. [Epub ahead of print]

and scabies not regulated under FIFRA. Many flea and tick "spot-on" treatments for dogs also contain permethrin as their active ingredient. According to EPA, permethrin is classified as "Likely to be Carcinogenic to Humans" by the oral route based on benign tumor types (lung and liver) in the mouse and 'equivocal evidence of carcinogenicity' in the Long-Evans rats.[21] As mentioned earlier, studies have found that permethrin is more toxic to juvenile rats than to adult rats due to incomplete development of the enzymes that break down pyrethroids in the liver. Additionally, studies on newborn mice have shown that lactational exposure to permethrin may inhibit neonatal brain development.[22]

Permethrin affects both male and female reproductive systems.[23] Permethrin binds to receptors for androgen (a male sex hormone) in cells from human males.[24] It also binds to the peripheral benzodiazepine receptor, which stimulates production of testosterone.[25] In a long-term feeding study of mice, permethrin was shown to cause reduced testes weights.[26] In another study, researchers found that permethrin had significant estrogenic potency as it inhibited the binding of estradiol to the estrogen receptor.[27] Permethrin is listed as a Category 2- potential endocrine disruptor in the European Union based on the inhibition of androgen binding in vitro.[28] Permethrin was also found to have mutagenic effects in three tests with human cell cultures, resulting in an increase in chromosome aberrations, chromosome fragments, and DNA lesions.[29]

In a study investigating the effect of subchronic dermal application of permethrin and DEET - both used for mosquito control, researchers at Duke University found that subchronic dermal application of DEET and permethrin to adult rats, alone or in combination, leads to a diffuse neuronal cell death in the cerebral cortex, the hippocampal formation, and the cerebellum,

[21] USEPA. 2009. Permethrin Registration Fact Sheet. Office of Pesticide Programs, Washington DC
[22] Imamura L, H.et al. 2002. Neonatal exposure of newborn mice to pyrethroid (permethrin) expresses activity-dependent c-fos mRNA expression in cerebellum. *Archives of Toxicol*ogy 76(7): 392-397.
[23] Cox, C. 1998. Permethrin. *Journal of Pesticide Reform* 18(2): 14-20.
[24] Eil, C. and B. C. Nisula. 1990. The binding properties of pyrethroids to human skin fibroblast androgen receptors and to sex hormone binding globulin. *Journal of Steroid Biochemistry* 35: 409-414.
[25] Ramadan, A. A. et al. 1988. Actions of pyrethroids on the peripheral benzodiazepine receptor. *Pesticide Biochemistry and Physiology* 32: 106-113.
[26] Cox, C. 1998
[27] Chen, H., J. et al. 2002. *Journal of Toxicology and Environmental Health, Part A* 65(19): 1419-1435.
[28] European Comission, DG ENV. 2002. Endocrine disrupters: study on gathering information on 435 substances with insufficient data. Final Report. Available at http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#report2
[29] Surrallés, J. et al. 1995. The suitability of the micronucleus assay in human lymphocytes as a new biomarker of excision repair. *Mut. Res.* 342:43-59.

which in turn can lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.[30,31]

Permethrin is impregnated into clothing for insect repellency. Once mainly used in the military setting, impregnated clothing is now widely available to the general public. EPA considered these uses to be too minor to include in the assessment and in the past has stated that risks are negligible. One study demonstrated that permethrin levels in treated clothing did not significantly reduce after 100 launderings.[32] Persons wearing permethrin impregnated clothing have higher levels of pyrethroid metabolites in their urine.[33] EPA continues to ignore this route of exposure and potential risk. Snodgrass[34] found that fabric treated with permethrin lost the substance to the skin surface at an average rate of 0.49%/day. After 7 days about 3.2% of the available permethrin had reached the skin of exposed rabbits, with a predicted 6×10^{-4} mg/kg/day for humans. Considering the long-term use of these clothing, dermal exposures are expected to be continuous. If a person is sweating or swimming while wearing the clothing, more of the chemical will likely come off onto the skin. The longer one wears the clothes, the more permethrin will be absorbed into the body. EPA fails in its responsibility under FIFRA to fully evaluate this important exposure path, undermining its risk calculation.

Bifenthrin

Bifenthrin is also a type I pyrethroid and has various agricultural and structural uses. It has been classified as a class C carcinogen -possible human carcinogen by EPA, due to an increased tumor incidence in the male urinary bladder of mice.[35] In a recent 2011 study, bifenthrin was shown to significantly decrease the secretion of progesterone and PGE2 in granulosa cells in rat ovarian cells. [36] A similar study by the same authors also found systemic disrupting effects on the network of ovulatory gene expression patterns as well as prostaglandin synthesis in rats exposed to bifenthrin, suggesting that exposure to bifenthrin may increase the risk of ovulatory dysfunction in females.[37]

[30] Abou-Donia. 2001. Subchronic dermal application of *N*,*N*-diethyl- *m* toluamide (DEET) and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum. *Experimental Neurolo*gy 172(1):153-71.
[31] Abu-Qare ,AW and Abou-Donia, MB.2003. Combined exposure to DEET (N,N-diethyl-m-toluamide) and permethrin: pharmacokinetics and toxicological effects. *J Toxicol Environ Health B Crit Rev*. 6(1):41-53.
[32] Faulde, M and Uedelhoven, W. 2006. A new clothing impregnation method for personal protection against ticks and biting insects. *International J Medical Microbiology.* 296(1): 225-229
[33] Rossbach, B. et al. 2010. Uptake of permethrin from impregnated clothing. *Toxicology Letters.192(1): 50-55*
[34] Snodgrass, H. 1992. Permethrin transfer from treated cloth to the skin surface: Potential for exposure in humans. *J of Toxicology and Environmental Health.* 35(2).
[35] EXTOXNET. Pesticide Information profile: Bifenthrin. Available at http://extoxnet.orst.edu/pips/bifenthr.htm
[36] Liu J, et al. 2011. Enantioselective endocrine-disrupting effects of bifenthrin on hormone synthesis in rat ovarian cells. *Toxicology*. 290(1):42-9.
[37] Liu, J. et al. 2011. Disrupting effects of bifenthrin on ovulatory gene expression and prostaglandin synthesis in rat ovarian granulosa cells. *Toxicology*.282(1-2):47-55.

Cypermethrin

Also classified by EPA as a possible human carcinogen, cypermethrin also has use patterns similar to its chemical cousins. This pyrethroid can reduce the androgen receptor levels and the serum levels of testosterone, induce impairments of the structure of seminiferous tubules and spermatogenesis in the male rat.[38] One study saw fertility significantly reduced in male rats, reduction in the implantation sites in females mated with exposed males, and a significant reduction in the number of viable fetuses for females impregnated by the exposed males.[39] Testicular sperm counts as well as daily sperm production were significantly decreased in these exposed males. Disruption of estrous cycle in female rats has also been observed.[40] In another study investigating the estrogenic activity of cypermethrin, it was discovered that cypermethrin exhibits significant estrogenic activity in the MCF-7 human breast carcinoma cell line.[41] Numerous studies document the endocrine disrupting activities of cypermethrin, especially in males.

About two million pounds of permethrin and one million pounds of cypermethrin[42] have been applied annually, which account for the major uses of pyrethroids. Uses of bifenthrin and deltamethrin have volume of use statistics that are similar. While the bulk of the uses are in agriculture, uses in mosquito control programs, gardens, and home insect products are on the rise, giving way to increased human and pet exposures. The 2010 report of the National Poison Data System logged over 24,000 incidents involving unintentional pyrethroid human exposures, with close to 6,000 being exposures to children under 6 years of age.[43]

Since the most widely used synthetic pyrethroids (permethrin, bifenthrin, cypermethrin) share common adverse chronic endpoints not included in this cumulative assessment, the agency is compelled to evaluate their cumulative impact, under FIFRA, before supporting new uses as a class of chemicals. The agency is wrong to recommend an expansion of uses without sufficiently evaluating ***all*** the chronic endpoints associated with this class. Further, new use patterns and exposures are not justified for this class of chemicals given the serious chronic effects associated with it. Supporting the proliferation of this class of pesticides without the full set of data on chronic effects poses an unreasonable adverse risk to the public and constitutes a

[38] Hu JX, et al. 2011.Toxic effects of cypermethrin on the male reproductive system: with emphasis on the androgen receptor. *J Appl Toxicol*. doi: 0.1002/jat.1769.

[39] Elbetieha A,et al. 2001. Evaluation of the toxic potentials of cypermethrin pesticide on some reproductive and fertility parameters in the male rats. *Arch Environ Contam Toxicol*.41(4):522-8.

[40] Sangha GK, et al. 2011. Toxicological effects of cypermethrin on female albino rats. *Toxicol Int*. 18(1):5-8.

[41] Jin M et al. 2010. Estrogenic activities of two synthetic pyrethroids and their metabolites. *J Environ Sci (China)*. 2010;22(2):290-6.

[42] US EPA, Office of Prevention, Pesticides and Toxic Substances, Reregistration Eligibility Decisions (REDs), Interim REDS (iREDs) and RED Factsheets. http://www.epa.gov/pesticides/reregistration/status.htm.

[43] 2010 Annual Report of the American Association of Poison Control Centers ' National Poison Data System (NPDS): 28th Annual Report. Available at http://www.aapcc.org/dnn/Portals/0/2010%20NPDS%20Annual%20Report.pdf

compliance failure with 21 USC §136a(c)(8).

Pyrethroids Put Pets At Risk

While this is a cumulative risk assessment as it pertains to human health, the agency cannot ignore the impact of pyrethroids on pets, especially when determining that there is sufficient room in the pyrethroid cumulative 'risk cup' to support consideration of new pyrethroids and uses.

Pyrethroids such has cyphenothrin, permethrin, phenothrin are neurotoxicants that can also affect the central nervous systems of pets like dogs and cats. Pet incidents involving this class of chemicals are significant. Clinical signs in small animals during pyrethroid toxicosis vary but are generally attributable to neural dysfunction.[44] In laboratory rats, pyrethroids cause a syndrome consisting of aggressive sparring, increased sensitivity to external stimuli, and fine tremors progressing to whole-body tremor and prostration.[45,46] In general, cats are highly sensitive to permethrin and inappropriate or accidental application of these products could be fatal. Though they are mostly used on dogs, even small amounts of permethrin spot-on products can cause severe clinical signs in cats.[47] As mentioned before, members of this class of chemicals are also possible carcinogens (permethrin), endocrine disruptors (cyphenothrin, permethrin) and may cause reproductive effects (permethrin).[48]

Children and adults alike, while playing and stroking pets, will come into contact with these chemicals, which lead to dermal exposures. Human oral exposures can also occur through hand-to-mouth transfer after petting treated animals.[49] One study detected residues on gloves worn while petting treated dogs for five minutes, with high concentrations detected up to 24 hours after application.[50] Human exposures to these toxic pesticides, via pet expsoures, can give rise to acute and chronic symptoms explained above. While the agency has looked at human exposures from pets, the agency must not forget that an expansion of pyrethroid uses will also affect pet health. In light of already high pet incident reports, EPA must re-evaluate its support for an expansion on pyrethroid uses.

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[44] Valentine WM, 1990. Toxicology of selected pesticides, drugs, and chemicals. Pyrethrin and pyrethroid insecticides. Vet Clin North Am Small Anim Pract ;20(2):375-82.

[45] Cantalamessa, F. 1993. Acute toxicity of two pyrethroids, permethrin, and cypermethrin in neonatal and adult rats. Arch Toxicol (1993) 67:510-513 Archives of

[46] Sutton, N.M. et al. 2007. Clinical effects and outcome of feline permethrin spot-on poisonings reported to the Veterinary Poisons. J. Feline Med & Surgery,9(4): 335-339

[47] Richardson, J. 2000. Permethrin Spot-On Toxicoses In Cats. *The Journal of Veterinary Emergency and Critical Care*

[48] Beyond Pesticides' Factsheets available at

[49] CDPR. 2009. Fipronil [CASRN: 120068-37-3] Materials for the July 28-29, 2009 Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP). California Department of Pesticide Regulation

[50] Jennings KA, Canerdy TD, Keller RJ, Atieh BH, Doss RB, Gupta RC. 2002. Human exposure to fipronil from dogs treated with frontline. Vet Hum.Toxicol. 44(5):301-3.

Increased Pyrethroid Use Can Worsen the Problem of Insect Resistance

Studies are increasingly finding a reduction in the efficacy of pyrethroid use against the pests they are commonly used to control. Several species of mosquitoes have been demonstrated to exhibit reduced mortality to the application of pyrethroid chemicals. The *Aedes aegypti mosquito, for instance, which is becoming increasingly resistant to chemical controls, has demonstrated high levels of resistance to* deltamethrin. One study found that the knock-down effect and mortality for these mosquitoes by deltamethrin and synergized pyrethrins when applied by thermal-fogging was greatly reduced.[51] Other species have been found to be resistant to several pyrethroids, including cyfluthrin, lambda-cyhalothrin, alpha-cypermethrin, deltamethrin, permethrin.[52,53] Resistance has been observed in other insects like aphids, brown planthopper (*Nilaparvata lugens), housefly (Musca domestica* L.), corn earworm and German cockroach, *Blattella germanica* (L.)[54,55,56, 57]

However, the reported incidents of bedbug resistance that are currently occurring nationwide is most alarming. Romero at al. found extremely high levels of resistance to deltamethrin and lamda-cyhalothrin in populations collected from human dwellings in Kentucky and Ohio.[58] Resistance to deltamethrin has also been observed in New York City.[59] Stink bugs have also become increasingly immune to pyrethroid treatments.[60,61] In light of these growing pyrethroid resistant insect populations, all of which are known to the agency, it seems that the invitation for more pyrethroid uses and registrations is quite misguided and will result in higher exposures than the agency has anticipated. Insect resistance comes about when the same product(s) are used repeatedly, i.e. overuse and/or misuse of pesticides and continual selection pressure is

[51] Marcombe, S. et al. 2009. Reduced Efficacy of Pyrethroid Space Sprays for Dengue Control in an Area of Martinique with Pyrethroid Resistance. *Am J Trop Med Hyg.* 80(5): 745-751

[52] Chandre, F et al. 1999. Pyrethroid cross resistance spectrum among populations of Anopheles gambiae s.s. from Cote d'Ivoire. *J Amer. Mosquito Control Ass*. 15(1):53-9

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[55] Farnham, A. W. 1973. Genetics of resistance of pyrethroid-selected houseflies, *Musca domestica* L. *Pesticide Science*, 4: 513–520. doi: 10.1002/ps.2780040410

[56] Atkinson, T. et al. 1991.Pyrethroid Resistance and Synergism in a Field Strain of the German Cockroach (Dictyoptera: Blaitellidae) *J Economic Entomology.* 84(4):1247-1250(4)

[57] Hopkins, B. W. and Pietrantonio, P. V. 2010. Differential efficacy of three commonly used pyrethroids against laboratory and field-collected larvae and adults of *Helicoverpa zea* (Lepidoptera: Noctuidae) and significance for pyrethroid resistance management. *Pest Management Science*, 66: 147–154.

[58] Romero, A. et al. 2007. Insecticide Resistance in the Bed Bug: A Factor in the Pest's Sudden Resurgence? *J Medical Entomology* 44(2):175-178.

[59] Sup Yoon, K. et al. 2008. Biochemical and Molecular Analysis of Deltamethrin Resistance in the Common Bed Bug (Hemiptera: Cimicidae). *J Medical Entomology* 45(6):1092-1101.

[60] Snodgrass, J. Adamczyk J., and Gore, J. 2005. Toxicity of Insecticides in a Glass-Vial Bioassay to Adult Brown, Green, and Southern Green Stink Bugs (Heteroptera: Pentatomidae). J *Economic Entomology* 98(1):177-181.

[61] Allen, K.C. et al. 2010. Susceptibilities of tarnished plant bug and stink bug nypmps to various insecticides. USDA ARS. http://ddr.nal.usda.gov/dspace/handle/10113/44372

placed on the target pest leading to the development of resistance.

Inevitably, an increased use of pyrethroids will only serve to exacerbate the pest resistance problem at a time when the agency should be focusing on alternative pest management strategies to minimize the onset of resistance, while safeguarding public health. There is great concern that pests that may be of public health concern, such as mosquitoes and bedbugs, will increase their resistant populations, leading to greater economic, environmental, and public health costs. The agency must therefore go back and reevaluate its conclusions from this cumulative risk assessment and recognize that increased pyrethroid use has broader implications when it comes to pest management and human health.

Proliferation of Pyrethroid Registrations Will Lead to Increased Environmental Contamination

Pyrethroids have very low water solubility and high adsorption coefficients, meaning they tend to bind strongly to soil and other organic matter. With half-lives ranging from two weeks to over a year,[62] pyrethroids tend to persist in the environment. Monitoring studies carried out in California have found widespread contamination of both surface water/suspended sediment and stream bed sediment. Even though they mostly accumulate in sediment, pyrethroids may also desorb from sediment to re-enter the water column. [63] Studies out of California's Department of Pesticide Regulation find that 60% of samples collected in four agricultural regions in the state had detectable pyrethroids in either water or sediment.[64] Additionally, within the state, detection of cyfluthrin and cypermethrin is typical to urban areas, and lambda-cyhalothrin is typical to agricultural areas, while bifenthrin and permethrin are characteristic of both urban and agricultural areas.[65] In Illinois, pyrethroids have a 95% detection rate in urban areas,[66] and, in Montana, bifenthrin, permethrin, and allethrin have been detected in sediment most frequently.[67] This trend has been supported by research out of the U.S. Geological Survey

[62] CDPR. 2004. Study 224: A Preliminary Assessment of Pyrethroid Contamination of Surface Waters and Bed Sediments in High Pyrethroid-Use Regions of California. Environmental Monitoring Branch. CA Department of Pesticide Regulation.

[63] Fojut, T.L. and Young, T.M. 2011. Desorption of pyrethroids from suspended solids. E*nviron Toxicol Chem.* 30(8):1760-6.

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[65] Ng, C.M. et al.2008. Patterns of Pyrethroid Contamination and Toxicity in Agricultural and Urban Stream Segments. S*ynthetic Pyrethroids: Occurrence and Behavior in Aquatic Environments,* (Gan, J, et al., Eds.) pp 355–369. American Chemical Society

[66] Ding, Y., Harwood, A. D., Foslund, H. M. and Lydy, M. J. (2010), Distribution and toxicity of sediment-associated pesticides in urban and agricultural waterways from Illinois, USA. Environmental Toxicology and Chemistry, 29: 149–157.

[67] Schmidt , C. 2010. Sediment Pyrethroid Sampling in Irrigation Canal/Ditch System, Missoula, Montana. Montana Department of Agriculture

(USGS).[68,69] In a year-long study monitoring residential runoff, pyrethroids were detected in every sample collected with bifenthrin found at 73ng/l in water samples and 1211ng/g in sediment,[70] making it the most frequently detected pyrethroid, with cypermethrin and cyfluthrin following respectively. In regions were pyrethoids have been detected, bifenthrin has been identified as the dominant contributor to sediment toxicity accounting for 50-85% of predicted toxicity units[71] and is the main contributor to the mortality of benthic organisms in sediments.

Pyrethroids are toxic to aquatic organisms, even at low and environmentally relevant concentrations.[72] Pyrethroid exposure can reduce biological fitness in fish by reducing growth, impairing behavior and increasing susceptibility to predation, as well as inducing cell apoptosis and causing immune system disruption.[73,74] In a study looking at the sublethal effects of bifenthrin on larval fish, researchers noticed an impairment of swimming performance, significant down-regulation for gene coding and an induction of endocrine responses evident from significant up-regulation of vitellogenin and down-regulation of insuline-like growth factor transcripts.[75] Another study found that exposure to deltamethrin at very low doses, resulted in induced oxyradical production in fish[76] which can lead to oxidative damage in tissue. Algal species have also been shown to be sensitive to pyrethroid exposures, as well as plankton.[77,78,79]

[68] US Geological Survey. Are Pyrethroid Insecticides in Our Streams? Available at http://toxics.usgs.gov/highlights/pyrethroids.html

[69] Hladik, M.L., and Kuivila, K.M., 2009, Assessing the occurrence and distribution of pyrethroids in water and suspended sediments. J Agricultural and Food Chemistry, 57(19): 9079-9085.

[70] Weston, D.P. Holmes, R.W, Lydy, M.J. 2009. Residential runoff as a source of pyrethroid pesticides to urban creeks. *Environmental Pollution*.157(1): 287-294.

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[72] Brander, S. M., Werner, I., White, J. W. and Deanovic, L. A. 2009. Toxicity of a dissolved pyrethroid mixture to *Hyalella azteca* at environmentally relevant concentrations. *Environ Toxico Chem.* 28: 1493–1499.

[73] Floyd EY, et al. 2008. Acute, sublethal exposure to a pyrethroid insecticide alters behavior, growth, and predation risk in larvae of the fathead minnow (Pimephales promelas). *Environ Toxicol Chem.* 27(8):1780-87.

[74] Jin Y, et al. 2011. Embryonic exposure to cypermethrin induces apoptosis and immunotoxicity in zebrafish (Danio rerio). *Fish Shellfish Immunol.* 30(4-5):1049-54.

[75] Beggel, S. et al. 2011. Changes in gene transcription and whole organism responses in larval fathead minnow (Pimephales promelas) following short-term exposure to the synthetic pyrethroid bifenthrin. Aquat Toxicol. 105(1-2):180-8

[76] Varanka Z et al. 2002. Influence of the polyphenolic tannic acid on the toxicity of the insecticide deltametihrin to fish. A comparative study examining both biochemical and cytopathological parameters. Acta Biol Hung. 53(3):351-65.

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[78] Medina, M., et al. 2004. Effects of cypermethrin on marine plankton communities: a simulated field study using mesocosms. *Ecotoxicol Environ Saf*. 58(2):236-45.

[79] Wendt-Rasch L., et al. 2003. Effects of metsulfuron methyl and cypermethrin exposure on freshwater model ecosystems. Aquat Toxicol. 63(3):243-56.

Additionally, pyrethroids can also threaten sensitive and listed species, like salmon. Measurable levels of pyrethroids have been documented in the Pacific Northwest,[80,81] where bifenthrin is identified as the 'pyrethroid of greatest concern' with regard to aquatic life toxicity, consistent with other studies. Based on this toxicological data and the prevalence of pyrethroid contamination, especially bifenthrin, increased uses of this class of chemcials should not be recommended. This will only serve to exacerbate the contamination levels currently seen in various states and put undue toxicological stress on already sensitive species and on an already fragile environment.

Proliferation of Pyrethroids Will Impact Sensitive Honey Bees and Other Beneficial Pollinators

Honey bees are the most economically important pollinators in the world, according to a recent United Nations report[82] on the global decline of pollinator populations. Unfortunately honey bee (*Apis mellifera* L) populations across the globe have been suffering the impacts of environmental contamination. Several pesticides classes have been identified for further study on their impacts on honey bee health and that of other beneficial insects. Pyrethroids are highly toxic to the honey bee. Some have proposed that the honey bee's olfactory receptor neurons, which are responsible for inter-individual communication, are affected by pyrethroid exposures. Tetramethrin and permethrin have been found to induce abnormal prolongation of open sodium channel configuration and binds at this site to inevitably modify neuronal excitability.[83] A similar study of exposed bees (in vivo and in vitro) found that bifenthrin, deltamethrin, and flauvalinate greatly suppress neuronal excitability, reduce the peak sodium currents, and inhibit the steady-state inactivation in sodium channels.[84] Another study examining the effects of sublethal pyrethroid concentrations on honeybees found that bifenthrin and deltamethrin significantly reduces bee fecundity, decreases the rate at which bees develop to adulthood, and increases their immature periods.[85] Several field and laboratory studies using deltamethrin have consistently documented decreases in foraging activity and activity at the hive entrance after exposure.[86,87,88]

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[80] Weston, D.P. et al. 2011. Pyrethroid insecticides in urban salmon streams of the Pacific Northwest. *Environ Pollut*. 159(10):3051-6.

[81] NMFS. Endangered Species Act Section 7 Consultation Biological Opinions. NOAA National Marine Fisheries Service.

[82] UNEP. 2010. UNEP Emerging Issues: Global Honey Bee Colony Disorder and Other Threats to Insect Pollinators. Available at http://www.unep.org/dewa/Portals/67/pdf/Global_Bee_Colony_Disorder_and_Threats_insect_pollinators.pdf

[83] Kadala A, et al. 2011. A use-dependent sodium current modification induced by type I pyrethroid insecticides in honeybee antennal olfactory receptor neurons. *Neurotoxicology*. 32(3):320-30.

[84] Zhou, T. et al. 2011. Effects of pyrethroids on neuronal excitability of adult honeybees *Apis mellifera. Pesticide Biochemistry and Physiology*. 100(1):35–40.

[85] Dai, P.L. et al. 2010. Effects of sublethal concentrations of bifenthrin and deltamethrin on fecundity, growth, and development of the honeybee Apis mellifera ligustica. *Environ Toxicol Chem*. 29(3):644-9.

[86] Decourtye A, et al. 2004. Effects of imidacloprid and deltamethrin on associative learning in honeybees under semi-field and laboratory conditions. *Ecotoxicol Environ Saf.* 57(3):410-9.

Honey bees and other non-target insects are exposed to pesticides in the fields they pollinate and by drift that has left the application site. Ground and aerial pyrethroid applications, especially those for mosquito control, result in in-situ and off-site exposures. Pyrethroids, due to their toxicity to bees, are thought by some researchers to be a contributing factor in the significant collapse of honey bee colonies referred to as Colony Collapse Disorder. Introducing greater amounts of pyrethroids into potential honey bee foraging habitat will likely result in additional hive losses with corresponding adverse effects to agriculture and the environment. It is clear that EPA has not thought about the broader implications of its risk assessment conclusions. The agency's assessment of the health of honey bees and their economic importance should lead it to reconsider its decision to encourage new pyrethroid uses.

Conclusion

Beyond Pesticides and the undersigned believe that further uses of pyrethroid chemicals will put public and environmental health at risk. The EPA's cumulative risk assessment, while addressing the neurotoxic mechanisms associated with pyrethroids, overlooked a host of other chronic endpoints also associated with their use and known to the agency, including endocrine disruption, since the agency still has not implemented its endocrine disruptor screening program. Thus, the conclusions reached by the agency are flawed. Reducing the 10X safety factor to 1X and 3X is misguided given the uncertainties that surround infant and children's exposures, the impacts on pregnant women and the fact that age-dependent sensitivities do exist. We believe that the highest range of protection should be set in place for these vulnerable populations. Additionally, the support for new and increased uses of pyrethroids as a result of the agency finding "sufficient room in the pyrethroid cumulative risk cup" is inadvisable. The agency failed to adequately consider the ecological impacts of this decision. Due to these short-comings, we request that the agency reconsider its cumulative risk assessment and its conclusions in order to lend credibility to risk assessment process and its mission to protect human and environmental health.

We appreciate the agency's attention to this critical matter of synthetic pyrethroid use and look forward to revisions of the cumulative risk assessment to ensure a full and adequate review.

Sincerely,

Beyond Pesticides

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[87] Dechaume Moncharmont FX. et al. 2003. Statistical analysis of honeybee survival after chronic exposure to insecticides. Environ Toxicol Chem. 22(12):3088-94.

[88] Badiou A, and Belzunces LP. 2008. Is acetylcholinesterase a pertinent biomarker to detect exposure of pyrethroids? A study case with deltamethrin. *Chem Biol Interact*. 175(1-3):406-9.