ESA SME Report (January 2018)
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During December (2017) I spent two days at EPA OPP headquarters in Crystal City, VA. I had arranged meetings with Health Effects Division (HED) and Biopesticides staff to discuss issues of interest to ESA constituencies, including the chlorpyrifos registration decision and regulation of biopesticides, such as *Wolbachia*. In addition, I attended staff meetings with Registration Division and BEAD (Biological and Economic Analysis Division) staff about herbicide issues, spray nozzles technology, pesticide resistance terminology and management and relationships to label language, and efficacy of neonicotinoid treated seeds. The latter meetings with RD and BEAD staff were joined by Weed Science Society of America (WSSA) SMEs Michael Barrett (University of Kentucky; stepping down) and Greg Kruger (University of Nebraska; newly appointed).

Summary of Meeting Regarding the Chlorpyrifos Risk Management Decision

EPA has been reviewing the registration of chlorpyrifos during the last 15 years after its registration was renewed in the early 2000s. One concern has been several prospective epidemiological studies suggesting a positive correlation between excretion of urinary metabolites associated with OP use (and more specifically chlorpyrifos via analysis of the urinary metabolit trichloropyridinol, TCP) and mental development in children. EPA HED decided to use a novel approach for assessing the risk of chlorpyrifos from dietary exposure, which is the remaining main route of consumer exposure.

EPA used a PBPK (Physiologically Based Pharmacokinetic) model to reverse engineer the urinary TCP metabolite data from one epidemiological (epi) study into a whole body dose. At the same time, HED used the results of the regression modeling from the epi study to define a toxicologically relevant endpoint that led to a revised benchmark dose (or POD, point of departure) for characterizing risk. As a result of this novel technique (i.e., using a PBPK model combined with an epidemiological study), the risk of chlorpyrifos exposure, especially among infants and children, significantly exceeded EPA's established levels of concern (LOCs).

On the basis of the revised risk assessment for chlorpyrifos, some scientists within HED were recommending cancellation of the product registrations. However, the decision to not follow HED's recommendations and leave chlorpyrifos registrations intact was made by EPA Director Scott Pruitt. When I asked about this decision making role, I was told that having the EPA Director make these kinds of decisions was not routine.

I inquired about the use of epidemiology with HED staff and whether this procedure, as opposed to relying on rodent studies, was going to be used in the future. I was told that the epidemiology studies are fraught with problems, such as lack of access to raw data, experimental design, interpretations of data, reliance on relative risk as opposed to absolute risk. I was concerned about pyrethroid insecticides that are now receiving more attention by epidemiologists, especially because they are now arguably the number one used indoor insecticide class. However, HED staff assured me that the epidemiological data is not robust enough and furthermore, the decision to continue to use those kinds of data would be made at a higher level within the division.

Other problems that were revealed in the discussion about chlorpyrifos were the values of trichloropyridinol reported in the urine. The LODs (Limits of Detection) and LOQs (Limits of Quantitation) needed further validation, especially because many urine sample had concentrations reported somewhere in between the LOD and LOQ. Thus, the relationship between exposure and effect becomes more uncertain.

The bottom line is that the decision not to cancel the registration of chlorpyrifos was made at the highest levels in the agency, an unusual action in OPP. On the other hand, much uncertainty by the scientific staff was expressed about the epidemiology data and concentrations of metabolites in the urine. However, the staff thought that PBPK modeling was on sound footing. At this time, no plans seem to exist to recreate the new chlorpyrifos assessment method and map it on to other insecticides, such as the

pyrethroid class. Finally, HED staff reiterated that they did not have any intentions of getting rid of OP insecticides but they were obliged to manage the risk associated with exposure.

Meeting with EFED (Environmental Fate & Effects Division) Staff:

Along with the WSSA SMEs, I met with EFED staff to discuss the development of a webinar for spray drift management of glyphosate. The particular concern was the fate of the Monarch butterfly based on recent literature (and public concerns) that has suggested intense use of Roundup herbicide in HR engineered crops was "wiping" out milkweed species, and thus reducing good habitat for Monarch larvae. Although EFED staff seemed unconvinced of a problem with use of Roundup and the fate of the Monarch, they were responding to a commitment to addressing the issue by managing spray drift. The concern was movement of Roundup via drift into nearby non-crop areas where milkweed might be growing.

Meeting with BEAD Staff

One issue that has been recurring was the desire of BEAD staff to "unify" the myriad definitions associated with pest resistance phenomena among the entomologists, weed scientists, and plant pathologists. A list of terms and uses observed in the literature were developed by the staff, and the SMEs were asked to review this list to determine if common ground ground could be forged in use of terms and their definitions.

Another topic of discussion related to resistance was whether product label language could be standardized for resistance management. The inclusion of mode of action information was becoming more standardized and agreement existed that such information is a good idea. Issues of how to present it were briefly discussed. Also, interest in a system for reporting resistance was raised. Presently, resistance observations are partly handled through the auspices of the industry action committees, IRAC (Insecticide Resistance Action Committee), HRAC (Herbicides), and FRAC (Fungicides). For example, IRAC partly funds the Insecticide Resistance Database hosted by Michigan State University.

One other item of potential interest was brought up. BEAD staff were interested in knowing more about the efficacy of various droplet sizes when insecticides and fungicides are sprayed. The agency is seeking some empirical information. This issue of droplet size is important because pesticide spray drift is presently one of the vexing issues the agency has to deal with and droplet size control is one best management practice for reducing non-target exposure (i.e., bigger droplets less prone to drift). In a related manner, the issue of wind speed effects on drift came up with regard to product label language permitting spraying in a wind of 15 mph or less. The question revolved around whether this cutoff was too high and if it should be removed from older labels. Again the agency was seeking empirical data on drift at different wind speeds.

Finally, the agency continues interest in empirically understanding the relationship between neonicotinoid seed treatments and yields. The agency somewhat butt heads with the USDA owing to differences in benefits assessment regarding neonicotinoid-treated soybean seeds. Unclear was the position of the agencies about treated corn seeds. I pointed out that seed treatments were historically always used on corn. However, I also informed the staff about a 2017 article by Krupke et al. that addressed the issue of efficacy, showing no significant yield benefit from using seed treatments.

Meeting with Biopesticides Division (BD) Staff:

Issues discussed included the Zap mosquito population management product utilizing *Wolbachia* to cause sterile matings, the Oxitech gene drive technology, and Bt. Regarding *Wolbachia*, EPA explained how an experimental use permit (EUP) was established for testing the product. Basically, the EUP defines a release point for the mosquitoes and considers the expected dispersal distance of the mosquitoes. Pertinently, the regulated active ingredient is the *Wolbachia* itself with the mosquito being considered analogously to a carrier product.

Based on an FDA memorandum, EPA was now expected to take over the registration and approval of the Oxitech gene drive based technology for mosquito population management. One issue

that EPA has with the Oxitech mosquito population management system is the environmental enzymatic degradation of the protein marker.

I raised the issue with BD staff about the EFSA document that seemed to question the safety of Bt toxins. I shared the EFSA document and letters written "in protest" by ESA members. EPA BD does not seem to have any concerns about Bt based on the EFSA position. They pointed out that every batch of Bt manufactured for use as a microbial insecticide spray must be tested for pathogenicity/toxicity by direct injection into mice. They seemed to downplay the one possible food contamination incident that putatively led to consumer illness as being relevant to Bt risk assessment.

For Future Information Regarding Pesticide Re-Registration Reviews:

The 2018 Registration Review schedules for conventional pesticides, antimicrobials (disinfectants), and biopesticides can be found at URL https://www.epa.gov/pesticide-reevaluation/registration-review-schedules.