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Down on the Farm

BY FRANK MIRER

In March, *The New York Times* and other news outlets reported that EPA administrator Scott Pruitt had decided not to ban the insecticide chlorpyrifos (CPF), against the recommendations of the agency's staff. (The *Times* article has numerous links worth following, including to regulatory documents.) CPF, an organophosphate (OP) insecticide, is presently the most used insecticide in the United States, according to EPA. I've looked into the science and history of CPF to see if there's more to the story than just the heavy hand of authority squelching the scientific staff at EPA.

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My initial interest in toxicology, spurred by Rachel Carson's *Silent Spring*, was concern about pesticides. My post-doctoral project compared potency of parathion and methyl parathion. I got to the postdoc from a PhD project on organophosphate ester hydrolysis. Recently I've sidelined myself from pesticides, except for reading ingredients on stuff used by the exterminator attacking cockroaches in my apartment. Relatively new developments in pesticides illuminate concerns beyond farms. However, I confess to being a "Sunday driver" regarding regulatory precedents for pesticides—it wasn't easy for me to navigate EPA databases. This article is written for industrial hygiene practitioners who are similarly challenged.

Pesticides—insecticides, fungicides, rodenticides, herbicides, and antimicrobials—are regulated under the Federal Insecticide, Fungicide and Rodenticide Act and the Food Quality Protection Act. Pesticides must be registered with EPA, with considerable data supplied to support registration, and approved as not posing an "unreasonable risk to public health." By law, registration must be renewed every 15 years, which is much more scrutiny than is required for chemicals regulated under the Toxic Substances Control Act or by OSHA.

CHLORPYRIFOS RISK ASSESSMENT

First registered as a pesticide in 1965, CPF has a considerable history of restrictions on its use. In 1999, EPA negotiated a "voluntary" withdrawal of CPF's registration, which amounts to a prohibition, for residential use, based on concern for developmental effects. By 1999, as demonstrated by a Google Scholar search, hundreds of peer-reviewed papers were available that observed developmental effects in laboratory, toxicity by non-anti-cholinesterase mechanisms, and environmental contamination. EPA's publication of re-registration in 2000 didn't clearly state the evidence for the negotiated de-registration of home use, and left the previous risk characterization mostly in place.

The 2006 registration eligibility decision also left the same characterization in place. The risk assessment supporting the 2006 registration generated an acute reference dose of 5 x 10^{-3} mg/kg/day, a chronic RfD of 3 x 10^{-4} mg/kg/day, and a chronic population average dose (including children and women of childbearing age) of 3 x 10^{-5} mg/kg/day. (These reference doses, all for oral exposure, were removed from the EPA Integrated Risk Information System in 2011.) In 2007, the National Resources Defense Council petitioned EPA to revoke all registrations, then litigated to compel a response. Multiple missed EPA-promised deadlines for responding to the petition were recorded from 2011 to 2017.

The risk assessment for CPF incorporated in EPA's November 2016 proposal to revoke the registration was supported by hundreds of pages of analysis and reviewed multiple times by a pesticide advisory committee of scientists, independent of EPA. The proposal applied the RfDs to a series of exposure scenarios, including occupational exposures in agriculture (which have the highest exposure and the most risk), people exposed on golf courses, and runoff into water supplies. Protective measures proposed for agricultural workers seemed weak, based on personal protective equipment, and without any enforcement regime. The EPA pesticide program concluded that CPF exposures exceeded safe levels in aggregate, and that registration should be withdrawn.

Scott Pruitt disagreed. EPA's 2016 proposal was repudiated by the agency's 2017 statement denying NRDC's petition, putting an end to EPA's commitment to act before the legally required re-registration in 2022. NRDC has appealed this decision.

BASIS FOR REGULATION

EPA's assessment of organophosphate insecticides is driven by acetylcholinesterase (AChE) inhibition only. AChE functions to stop excitation of a nerve after an impulse has been transmitted. EPA designates the dose that causes 10 percent AChE inhibition as a "point of departure" (POD) for calculating the reference dose. The dispute over the reference tolerances is whether the uncertainty factor should be 10 (a default value for human variability) or 10 x 10 (or more) as required by the Food Quality Protection Act.

The problem with the default approach is that multiple studies in children—three major studies and seven lesser studies cited in the 2016 registration document—observed adverse neurobehavioral outcomes associated with increased OP exposure. A study by researchers at Columbia University observed increased pervasive developmental disorder diagnoses at 3 years, and reduced measures of intelligence by 7 years, associated with increased measures of CPF exposure. Studies by Mt. Sinai and the University of California-Berkeley observed similar associations. These findings appeared at levels where no AChE depression was observed.

Medline also identified hundreds of publications of adverse neurobehavioral outcomes in laboratory studies of OPs, many without substantial AChE inhibition. In my view, the carcinogenicity findings for other OPs discussed below add to this concern—we don't know what pathways the OPs are affecting beyond AChE.

EXTRAPOLATION

The EPA approach to establishing a reference dose (RfD) or reference concentration (RfC) in the Integrated Risk Information System seems different than that used for OP pesticides. Both the IRIS approach and the pesticide approach select a target health effect and then identify a No Observed Adverse Effect Level as a point of departure. This dose is then divided by uncertainty factors for population variability, extrapolation from animal to man, and for extrapolation from short-term to chronic exposure. For IRIS, a default UF of 10 was originally assumed for each, although there is a continuing and somewhat successful campaign by industry to reduce these to 3. Alternatively, a Benchmark Dose may be calculated, a statistical NOAEL equivalent to a 1 in 10 risk rate to which the UFs will be applied. For pesticides, the dose causing a 10 percent inhibition of AChE is the POD, the population variability UF is assumed to be 10, and typically another factor of 10 is added as a "safety" factor required by the FQPA. There is no UF for acute to chronic.

CARCINOGENIC POTENTIAL

New to assessment of the health effects of pesticides are results from the Agricultural Health Study (**https://aghealth.nih.gov**). The AHS—a collaboration of the National Cancer Institute, the National Institute of Environmental Health Sciences, NIOSH, and EPA—had enrolled, and is now following, the health of 89,000 farmworkers, pesticide applicators, and their families in Iowa and North Carolina. The AHS and other large studies identified increased rates of certain cancers associated with exposures to several OP pesticides, although not chlorpyrifos.

The elevated cancer risks observed in the epidemiological studies for OP pesticides such as malathion, diazinon, and glyphosate could be used to extrapolate to population exposure levels beyond agriculture. Even if EPA were to continue to discount these findings (as the agency's Pesticide Office now seems disposed to do), we could have an authoritative statement of the upper range of risk. Among organophosphates, malathion and diazinon were classified by the International Agency for Research on Cancer as Group 2A (probably carcinogenic) based on observed excesses with some dose response, while parathion and tetrachlorvinphos were classified as 2B (possibly carcinogenic) based on laboratory studies.

LESSONS FOR PROFESSIONAL PRACTICE

Scientifically, I was most interested in a body of knowledge that OP pesticides have toxic potential well beyond AChE inhibition. It's logical that these OP agents could phosphorylate and thereby inactivate receptors beyond AChE, and thereby have a wider range of effects. I was somewhat surprised that OPs are still widely used in large quantities, not supplanted by new agents.

The policy lesson is more difficult. As practitioners, we generally rely on authoritative bodies for conclusions about toxic potential and toxic potency (evaluation criteria). There is a majority opinion, maybe a consensus, that CPF causes adverse developmental effects in people at levels of exposure permitted by EPA. What are we supposed to do when the evaluation of the most used pesticide is determined by industry representatives? Maybe the answer for professional practice is to measure exposures down to those levels, and to propose control measures, starting with agricultural workers.

RESOURCES

EPA: A Review of the Reference Dose and Reference Concentration Processes, **http://bit.ly/rfdrfcprocesses** (PDF, December 2002).

EPA: Chlorpyrifos Revised Human Health Risk Assessment, **http://bit.ly/cpfriskassessment2016** (November 2016).

The New York Times: "E.P.A. Chief, Rejecting Agency's Science, Chooses Not to Ban Insecticide," **http://bit.ly/rejectcpfban** (March 2017).