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Response to Commentary on “Agricultural exposures and gastric cancer risk in Hispanic farm workers in California” (Mills, P.K., and Yang, R.C., *Environmental Research* (2007) 104, 282–289)

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To the Editor,

The representative of the Dow Chemical Company and the pesticide manufacturers suggest that the results of our study “Agricultural exposures and gastric cancer risk in Hispanic farm workers in California” (Mills and Yang, 2007) were hampered by lack of data on internal dose of the pesticides which were identified in our paper as being associated with increased gastric cancer, that the airborne route of exposure to 2,4-D is unlikely, and that our previous analysis of organophosphate metabolites in farm worker children was flawed (Burns, et al. 2007)

The half-life of 2,4-D in soil is about 1–2 weeks and 1–3 weeks in water (Extension Toxicology Network (ETN). 1996. Pesticide information profile for 2,4-D (http://extoxnet.orst.edu/pips/24_d.htm)). 2,4-D is also an indoor air toxin and has been found in 63% of sampled homes in one study (Rudell R, et al., 2003) and in 94.6% of carpet dust samples of homes in close proximity to crops where herbicides had been sprayed (Ward MH, et al. 2006). After lawn application of 2,4-D, indoor air levels and levels on floors, tables and windowsills have been shown to increase (Nishioka M et al. 2001) and 2,4-D is adsorbed onto dust and both ingestion and inhalation of this dust may result in internal depositions of the parent compound or its derivatives. Geometric mean levels of 2,4-dichlorophenol, a metabolite of 2,4-D, were found to be 1.80 micrograms/liter among Mexican Americans aged 6 to 59 years in the National Health and Nutrition Examination Survey, which was twice as high as in non-Hispanic whites (Centers for Disease Control and Prevention, National Center for Environmental Health, 2003) Although we suggested that inhalation is one potential route of exposure to 2,4-D, chlorophenoxy compounds including 2,4-D are also easily absorbed in the gastrointestinal tract (Kohli JD, 1974) and dermal absorption tends to be minimal (Arnold EK, 1989). Although the average residence half-life of 2,4-D in humans is between 13 and 39 hours, it is also longer with large doses and prolonged exposure (Keller T, 1994) as frequently occurs in farm workers.

The issue of internal dose was not addressed in our study, which relied upon the California Department of Pesticide Regulation Pesticide Use Reports for information on pounds of active ingredients of 2,4-D (and other chemicals) applied on the same crops, at the same time and in the same location where the study participants were employed. We found that, among the stomach cancer patients in our study, 42% had at least some (non-zero pounds) of potential exposure to 2,4-D compared to 33% in the controls. Among those patients with some amount

of exposure, an average of 349 pounds of 2,4-D was applied in those crops during the time the workers were present compared to an average of 135 pounds among controls. Although we did not report on “internal dose” resulting from such experiences in the farm workers, there are data demonstrating that concentrations of urinary 2,4-D among farmers increase to above the 95th percentile of the reference range after applications of the herbicide on their farms and perhaps more importantly, the levels of 2,4-D in the urine of applicator’s children sometimes exceeds the reference range (<1 to 1.8 microgram per liter). (Barr JR, et al., 1999).

The thrust of our paper concerning levels of urinary metabolites of organophosphate pesticides (Mills and Zahm, 2001) was the *relative* level of urinary metabolites in the children of farm workers compared to the farm worker parents themselves. In that study we demonstrated that levels of detection of dimethylphosphate (DMP) in urine were 44% in children (compared to 33% in adults) and levels of detection of dimethylphosphorothionate (DMTP) were 33% in the children compared to 28% of the adults.

Among our previous papers cited by Burns et. al., in which we used the same exposure assessment approach, our findings linking 2,4-D exposure to non-Hodgkin’s lymphoma in these same farm workers (Mills PK, 2005) were consistent with other several other studies of 2,4-D and lymphoma risk in the U.S. (Hoar SK, 1986; Zahm SH, 1990), in Canada (McDuffie HH, 2001) and in Europe (Hardell L, 1994; Persson B, 1993). In addition, our findings concerning prostate cancer in these farm workers that noted positive associations with the organochlorine chemicals lindane and heptachlor (Mills and Yang, 2003), were consistent with positive findings concerning organochlorine chemicals and prostate cancer in the Agricultural Health Study (Alavanja M, et al. 2003). Despite our lack of internal dose information, the consistency of our finding with the findings of others, the presence of measurable levels of 2,4-D in the air and dust of homes in close proximity to agricultural fields where this herbicide has been applied, the presence of 2,4-D metabolites in urine of farmers and their children, the continued widespread use of 2,4-D (and other chemicals) in California, and the fact that the chemicals were applied at the same location and time as when workers were present, gives us confidence in our conclusions.

Finally, lessons learned from historical efforts to limit exposure to carcinogens in tobacco smoke, for example, indicate that prevention strategies are not to be delayed until the carcinogenic constituents of a given exposure (e.g. tobacco smoke) are demonstrated in human biological specimens; the decision to remove the handle of the Broad Street Pump occurred long before the identification of the *Vibrio cholerae* in drinking water as the causative agent for cholera. The precautionary principle suggests that prudent avoidance be exercised to reduce harm, before definitive data allow the identification of a potential toxin in the human environment.

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