

APPENDIX C

Annotated Review of Recent Studies on Pesticides Exposure & Health Effects

Exposure

Berkowitz GS, Obel J, Deych E, et al. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. *Environ Health Perspect*. 2003;111: 79-84.

Berkowitz and colleagues (2003) are conducting a prospective study on a cohort of 386 mothers and infants delivered at one hospital in New York City. This study examines exposure to *indoor* pesticides from both questionnaire data and analysis of maternal urinary metabolite levels. Although not directly relevant to a discussion of lawn and garden pesticides, some of the indoor use pesticides are also available for use outdoors. While only 46.4% of the women themselves reported that they or someone in their household had used pesticides during their pregnancy, additional data on pesticide applications from exterminators or building superintendents indicated that over 70% of these women likely had pesticide exposure during pregnancy. Analysis of urinary biomarkers of exposure indicated that concentrations for some commonly measured pesticide metabolites (e.g. TCPy a metabolite of chlorpyrifos) were higher in this sample than the median concentration found in the National Health and Nutrition Examination Study (NHANES) III. The study highlights some of the challenges to estimating pesticide exposure. Urinary metabolite levels reflect overall exposure to pesticides whether from indoor uses, outdoor uses or from food.

Fenske RA, et al. Children's Exposure to Chlorpyrifos and Parathion in an Agricultural Community in Central Washington State. *Environ Health Perspect* 2002;110:549-53.

University of Washington researchers found that while concentrations of chlorpyrifos in house dust were higher in farm worker's homes and in homes in close proximity to treated fields, the children in these households did not appear to have higher exposure since concentrations of pesticide metabolites in urine were similar for children regardless of parental occupation and proximity (Fenske et al, 2002). Although children's behaviour (e.g., play patterns, hand-washing, thumbsucking or hand-to-mouth activity) and family hygienic practices (e.g., presence of doormats, wearing work shoes and clothes indoors, laundering practices and vacuuming frequency) did not influence urinary metabolite concentrations, there were however, significantly higher chlorpyrifos metabolite concentrations in children's urine where families reported using organophosphorus (OP) pesticides in the garden. As stated above, urine measures provide an indication of the total amount of pesticides absorbed through all the possible routes of exposure. Environmental samples can only provide indications of potential exposures.

Koch D, et al. Temporal Association of Children's Pesticide Exposure and Agricultural Spraying: Report of a Longitudinal Biological Monitoring Study. *Environ Health Perspect* 2002;110: 829-833.

A separate study by the University of Washington team measured OP insecticide exposures throughout one year using biweekly urine samples of 44 young children living in an agricultural

community (Koch et al, 2002). They found that common metabolites of the OP pesticides were higher in children's urine during times when OP pesticides were sprayed in orchards in the study region. This refinement in the data collected led researchers to conclude that pesticide spraying in an agricultural region can increase children's exposure. This phenomenon was observed even for children whose parents had no work-related contact with pesticides and whose homes were not close to pesticide-treated farmland. Although it is expected that the volumes of pesticide applied to agricultural areas are greater than those that would be used around the home, the finding in the previously described studies suggests that garden OP insecticide use did significantly increase children's exposure in this rural sample as well.

Curl CL, Fenske RA, Elgethun K. Organophosphate pesticide exposure of urban and suburban pre-school children with organic and conventional diets. *Environ Health Perspect*. doi:10.1289/ehp.5754.

The University of Washington researchers have also recently published study results indicating that there were significant differences in urine measures of OP metabolites in two samples of Seattle children. Those eating mainly conventionally grown foods had levels of the most common OP metabolite that were 9 times greater than those found in children eating a diet of mainly organic produce (Curl et al, 2003). This study suggests that diet may provide an important source of the organophosphate pesticide exposures in people. Because the study did not assess urine measures for other types of pesticides it is not possible to say what the contribution to exposure from residential use pesticides was for these children. Parents of both sets of children did report using pesticides around the home although few of them reported using OP pesticides.

U.S. Centers for Disease Control and Prevention (CDC). Second National Report on Human Exposure to Environmental Chemicals. Department of Health and Human Services Centers for Disease Control and Prevention. National Center for Environmental Health, Division of Laboratory Sciences, Atlanta, Georgia 30341-3724
NCEH Pub. No. 02-0716. January 2003. Accessed January 31, 2003 at:
<http://www.cdc.gov/exposurereport/default.htm>

The U.S. Centers for Disease Control (CDC) Second National Report on Human Exposure to Environmental Chemicals is the second in a long-term study assessing the general population exposure to various environmental contaminants (U.S. CDC, 2003). The Second Report presents exposure data from the National Health and Nutrition Examination Survey (NHANES) survey data collected from 1999 to 2000. Added to the organophosphate pesticides that were evaluated in serum samples in the first study (only for the year 1999) were measures of carbamate pesticides, the herbicide 2,4-D and insect repellants. The current study results indicated that chlorpyrifos levels (based on urinary TCPy) in children ages 6 to 11 were about twice as high as those for adults ages 20 and older. Levels of some dialkyl phosphate metabolites, which reflect recent exposure to several possible OP pesticides, also indicated greater exposure to OPs among those in the 6 to 11 and 12 to 19 age groups compared to adults. Only one carbamate metabolite (1-naphthol) was found in appreciable proportions of the sample and urinary levels in those 6 to 11 were comparable to findings from 1997 for a sample of children from Minnesota (Adgate et

al, 2001). 2,4-D was non-detectable in all adults and most children, however it was detected in very small amounts (1.30 µg/L and 1.00 µg/L for ages 6 to 11 and 12 to 19, respectively) in the urine of about 5% of those between 6 and 19 years of age. These results suggest that for this sample, although overall exposure to 2,4-D was negligible children and youth demonstrated detectable exposure to 2,4-D more than adults. The report cautions throughout that “finding a measurable amount of one or more metabolites in the urine does not mean that (these) levels ... cause an adverse health effect”(U.S. CDC, 2003: 173).

Adult and Childhood Cancer

Brophy JT, Keith MM, Gorey KM, et al. Occupational histories of cancer patients in a Canadian cancer treatment center and the generated hypothesis regarding breast cancer and farming. *Int. J. Occup Environ Health* 2002;8:346-353.

An exploratory case-control study of nearly 300 women with breast cancer from the Windsor-Essex region of Ontario, analysed information on occupational history of these women as part of a larger study to “screen for possible associations between any occupations and any cancers without *a priori* hypotheses” (Brophy et al., 2002: 347). Because agriculture is an important economic activity in the region and since women with breast cancer represented the largest group of participants in the study, researchers explored the relationship between breast cancer and farming as a preliminary hypothesis. Controls were chosen from among female participants with cancers other than primary, malignant breast cancer. Among women 55 years of age or younger, there were increased (but mostly non-significant) risks of breast cancer for those who had ever farmed. The odds ratio adjusted for age and education, for women under 56 was 9.05 (95% C.I. 1.06 to 77.43). The study did not determine whether women who had ever farmed were exposed to pesticides, nor could it account for other known risk factors for breast cancer such as family history and reproductive factors. Despite the study’s limitations, the researchers state that the consistency and size of the breast cancer-farming association warrants further exploration, including examining the possible role of exposure to pesticides, with “more rigorous epidemiological methods” (Brophy et al., 2002: 349).

Reynolds P, Von Behren J, Gunier RB, et al. Childhood Cancer and Agricultural Pesticide Use: An Ecologic Study in California. *Environ Health Perspect.* 2002;110:319-24.

Researchers from the California Department of Health Services used Geographic Information System (GIS) techniques to compare data on childhood cancer incidence rates (under age 15 years) from the California Cancer Registry with detailed information on pesticide use rates from California’s Pesticide Use Registry (PUR) (Reynolds et al, 2002). In contrast with the findings of several case-control studies, this ecological study found no association between pesticide use density and overall childhood cancer incidence rates. However, childhood leukemia rates were significantly elevated (by nearly 50%) in areas with the highest use of the agricultural insecticides propargite, thiram and azinphos-methyl, although not in a dose-dependent way. The study acknowledges some important limitations. The proxy for exposure is PUR data on quantity and area of pesticide use matched with data from the cancer registry on the child’s address at the time of diagnosis of their cancer. However, given that researchers suspect the

perinatal period represents an important window of vulnerability to carcinogens that can lead to childhood cancer, the child's location at time of diagnosis is not adequate for assessing cancer risks from exposure to pesticides (Olshan et al, 2000). Also, the study does not estimate pesticide exposure from use at home or school and Reynolds and colleagues suggest, "it may be that proximity to agents used for household pest control is more important than those used in agriculture" (Reynolds et al, 2002: 323).

Ma X, Buffler PA, Gunier RB, et al. Critical Windows of Exposure to Household Pesticides and Risk of Childhood Leukemia. *Environ Health Perspect.* 2002;110(9): 955-960.

Researchers from both the University of California and California Department of Health Services conducted a small case-control study of 162 children diagnosed with leukemia between 1995 and 1999 (Ma et al., 2002). This study investigated the importance of exposure to broad types of pesticides and examined the importance of timing and location of exposure. There was a significantly elevated risk of leukemia among children whose homes had been professionally treated for pest control when their mothers were pregnant or during the first 3 years of their life. Highest risks were associated with early exposure to insecticides (especially during pregnancy) rather than exposure later in childhood. The risks increased in a dose-dependent fashion, that is, risk of leukemia was greater with greater reported frequency of insecticide use. Insecticides included products for indoor and outdoor pests control and insect repellants. There were no significant differences between cases and controls for use of flea control products. Exposure to herbicides revealed only a weak association. Odds ratios were elevated but non-significant (1.8 and 1.6) for herbicides at two exposure periods, 3 months before pregnancy and during pregnancy, respectively. Exposure to outdoor pesticides (both herbicides and insecticides) indicated only small, nonsignificant associations with childhood leukemia risks. Study results indicate that early exposure to pesticides, particularly during pregnancy, and above all, to insecticides that were applied indoors, was associated with significantly increased risks of childhood leukemia (Ma et al, 2002). These results are consistent with most other previous studies assessing associations between pesticide exposure and childhood leukemia.

Reproductive effects

Swan S, Brazil C, Drobnis EZ, Liu F, et al. Geographic differences in semen quality of fertile U.S. males. *Environ Health Perspect.* 2003;doi:10.1289/ehp5927 (Online November 11 2002).

Researchers at the University of Missouri-Columbia suggest that environmental factors, including the use of agricultural chemicals, may explain the significantly lower sperm concentration found among men in semi-rural and agricultural counties of Missouri as opposed to men in urban centres (New York, Los Angeles and Minneapolis) (Swan et al, 2002). Although all the men were fertile (having been recruited through prenatal clinics), the study authors suggest that differences in sperm quality may be predictive of reproductive function in men.

Garry VF, et al. Birth Defects, Season of Conception, and Sex of Children Born to Pesticide Applicators Living in the Red River Valley of Minnesota, USA. *Environ Health Perspect* 2002;110(3): 441-49.

A study by University of Minnesota researchers examining reproductive health outcomes in Minnesota pesticide applicators indicates that herbicides applied in the spring may be a factor in the birth defects observed and fungicides may influence determination of sex of the children in this region (Garry et al, 2002). Thus, two distinct classes of pesticides seem to have adverse effects on different reproductive outcomes. This study indicated that there were fewer live-born male children born to fungicide applicators. The results confirmed an earlier study by this group suggesting that children conceived in the spring were more likely to have birth defects than children conceived in any other season (Garry et al, 1996). One possibility is that environmental agents that are present in the spring, including herbicides, may negatively influence the rate of birth defects. Only two specific pesticides (phosphine, a fumigant and glyphosate, a herbicide) showed a significant positive correlation with adverse birth or neurodevelopmental effects. Genotoxicity has been observed in tests of phosphine, but glyphosate has not been found to be genotoxic nor neurotoxic except in high doses.

Perera F, Rauh V, Tsai WY, Kinney P, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multi-ethnic population. Environ Health Perspect. 2003;doi:10.1289/ehp5742 (Online October 31, 2002).

A team from the Columbia Center for Children's Environmental Health, Columbia University is the first to evaluate the effects of prenatal exposure to chlorpyrifos among 263 urban, minority women (African-American and Dominican) (Perera et al., 2002). Eighty-five percent of the women reported that pesticides were used at some time during their pregnancy. Chlorpyrifos was the most frequently detected pesticide, however, there were a number of other pesticides found in plasma samples of these women. Prenatal exposure to chlorpyrifos was an important determinant of birth outcome being associated with significantly decreased birth weight and birth length in the offspring of these mothers. Since 2001 all residential use products containing chlorpyrifos have been phased out in Canada and the U.S..

Cavieres MF, Jaeger J, Porter W. Developmental toxicity of a commercial herbicide mixture in mice: I. Effects on embryo implantation and litter size. *Environ Health Perspect.* 2002;110: 1081-85.

Laboratory research conducted at the University of Wisconsin examined the developmental effects from exposing pregnant mice to a commercial mixture of lawn chemical herbicides including 2,4-D, mecoprop and dicamba (Cavieres et al., 2002). Sets of mice were exposed either from preimplantation to the end of organogenesis or solely during organogenesis. Different groups of mice were exposed to one of four doses (very low, low, intermediate and high) of the herbicide mixture diluted in water. Cavieres et al (2002) found that there was a significant effect of dose on litter size with an approximate 20% reduction in number of pups for all doses during pregnancy. The magnitude of the litter size effect appeared also to vary with season of exposure. The dose-response relationship demonstrated a nonlinear, to some extent U-shaped curve with lowest exposure doses associated with greatest reductions in litter size. This does not fit with currently accepted models for dose-response although such U-shaped patterns have been found in studies looking at various effects from other substances. The researchers are not able to say which of the three pesticides or formulants in the mixture might be contributing to the effects observed. While the toxicological literature has either not reported

developmental effects or only effects at high, acute doses from exposure to the individual pesticides, the authors suggest that their findings plus those of two epidemiological studies warrant further studies of effects from mixtures of pesticides and other chemicals.

Lamb JC, Neal BH, Ginevan ME. Review of paper entitled “Developmental toxicity of a commercial herbicide mixture in mice: I. Effects on embryo implantation and litter size.” Unpublished manuscript submitted to ITFII for 2,4-D. Blasland, Bouck & Lee, Inc. November 15, 2002.

A review of the above paper by Cavieres and colleagues (and of Cavieres’ doctoral dissertation upon which the paper is based) was recently requested and circulated by the Industry Task Force II for 2,4-D. The reviewers are toxicologists from an independent environmental engineering consulting firm. They report sufficient concern with aspects of the study’s methodology as to “call for a retraction of this paper from publication” (Lamb et al, 2002: 1). A major criticism concerns data in the dissertation that is not reported in the paper and that changes a previously non-significant result to one showing statistical significance regarding litter size difference among treatment groups. The reviewers’ point out other methodological flaws such as improperly combined data from different study designs, inadequate assessment of endpoints, weakly explored or overstated conclusions regarding effects of seasonality and the shape of the dose-response curve. If these comments are accurate, they have serious implications for the scientific merit of the paper and the validity of its conclusions.

Other health effects

Sweet, L. Is there a temporal association between agricultural pesticides spraying and asthma hospitalizations in Prince Edward Island (PEI)? PEI Health and Social Services. Unpublished presentation, March 20, 2002, Sackville NB.

A recent study by Health & Social Services, Prince Edward Island could not demonstrate a temporal relationship between asthma symptoms and agricultural pesticide use on PEI. The study summarized asthma morbidity by days spent in hospital and by admissions, discharges or separations due to asthma. According to Health Canada analyses, indices of asthma morbidity are generally higher among the Atlantic Provinces compared to the rest of Canada (as cited by Sweet, 2002). Peak pesticide spraying in PEI is from July to mid-September. From 1984 to 1988 however, asthma hospital admissions were highest in April and September and lowest in July. There was therefore no obvious temporal association between the patterns in asthma hospitalizations and agricultural pesticide spraying in PEI. The researchers conclude that while the findings do not disprove an etiological association between pesticide exposure and asthma, “there is not enough evidence to support any further research into any possible association between pesticides spraying and asthma morbidity on PEI” (Sweet, 2002: 4).

Major Reviews

Garabrant DH & Philbert MA. Review of 2,4-Dichlorophenoxyacetic Acid (2,4-D) epidemiology and toxicology. *Crit Rev Toxicol.* 2002;32:233-57.

Garabrant and Philbert (2002) conducted an updated review of the toxicological and epidemiological literature on 2,4-D at the request of the Industry Task Force II for 2,4-D. This review focused on research produced between 1995 and 2001. Animal studies of reproductive toxicity from exposure to 2,4-D suggest that 2,4-D in any of its forms is not teratogenic unless doses exceed the pregnant mother's ability to excrete the chemical. Notably, dogs appear to be more sensitive to 2,4-D because their renal excretion mechanisms are more readily saturated at lower doses compared to other test animals. Human studies of reproductive toxicity from exposure to 2,4-D alone are limited and the authors stated they could not locate any studies published since 1991. [Of note, this review did not evaluate studies that included exposure to 2,4-D and other pesticides, but only studies examining effects from exposure to 2,4-D alone. For example it did not review the recent study by Arbuckle and colleagues (2001) that indicated modestly increased risks for spontaneous abortion with exposure to 2,4-D among other pesticides.] Garabrant and Philbert report that recent studies and a review of genotoxic and mutagenic potential of 2,4-D and its forms in animals or cell cultures all reported negative findings and "add to the weight of evidence that 2,4-D does not have genotoxic/mutagenic potential *in vitro* and *in vivo*" (2002: 237). In addition, recent studies of oncogenicity (cancer-causing potential) in rats and mice did not find an oncogenic effect from exposure to 2,4-D. Similarly, mild neurotoxic effects (typically transient muscle spasm and weakness or retinal degeneration) in animal studies have been observed only with high-level, acute or chronic exposure. These exposures typically are enough to produce other systemic toxicity because renal excretion is overloaded and the blood-brain barrier is compromised. While there have been some human studies suggesting an association between exposure to 2,4-D and a range of neurologic effects, these have largely been cases of acute poisoning or those occupationally exposed to phenoxy herbicides which include 2,4,5-T and its dioxin contaminants. They report that animal studies involving neurologic effects from 2,4-D have involved doses that are far higher than those expected in the environment or in the workplace except via accident or spills.

Garabrant and Philbert provide a lengthy review of the studies of cancer risk from 2,4-D exposure in humans. Cohort studies of workers in pesticide manufacture or of pesticide applicators generally provide more reliable information on exposure. Garabrant and Philbert note, however, that few studies provide information on the cancer risks [particularly for soft tissue sarcoma (STS), non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD)] of workers appreciably exposed to 2,4-D. Other studies involve cohorts where exposure was mainly to phenoxy herbicides other than 2,4-D, including those with considerable contamination by TCDD, a strong carcinogen. (They state that the manufacturing process for 2,4-D or MCPA does not produce TCDD contamination.) Garabrant and Philbert conclude that the cohort studies suggest that 2,4-D exposed cohorts were either not at increased risk for these cancers or that the estimated risks were low. Garabrant and Philbert review the series of case-control studies examining risks for STS, NHL or HD with exposure to phenoxy herbicides. Often the studies had inadequate assessment of exposure to 2,4-D or were unable to control for confounding exposures (such as to other pesticides like OPs). Garabrant and Philbert conclude that the case-control studies do not provide evidence of associations between STS or HD and 2,4-D exposure and that evidence of an association between NHL and 2,4-D exposure is conflicting and

inconclusive overall. Similarly, case-control studies of canine malignant lymphoma and 2,4-D exposure have not provided reliable evidence of a causal relationship.

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